BMJ Open

Asthma does not increase the risk of neurodegenerative dementia: A nested case-control study using a national sample cohort

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-030227
Article Type:	Research
Date Submitted by the Author:	05-Mar-2019
Complete List of Authors:	Choi, Hyo Geun; Hallym University, Min, Chanyang Oh, Dong Jun; Asan Medical Center, University of Ulsan College of Medicine Kim, So Young
Keywords:	Asthma < THORACIC MEDICINE, Dementia < NEUROLOGY, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

Asthma does not increase the risk of neurodegenerative dementia: A nested case-control study using a national sample cohort

So Young Kim, MD[1], Chanyang Min, PhD[2,3], Dong Jun Oh, MD[4], Hyo Geun Choi, MD[2,5]

[1]Department of Otorhinolaryngology-Head & Neck Surgery, CHA Bundang Medical Center, CHA University, Seongnam, Korea

[2]Hallym Data Science Laboratory, Hallym University College of Medicine, Anyang, Korea

[3]Graduate School of Public Health, Seoul National University, Seoul, Korea

[4]Department of Internal medicine, Soonchunhyang University College of Medicine, Seoul

[5]Department of Otorhinolaryngology-Head & Neck Surgery, Hallym University College of Medicine, Anyang, Korea

Running title: Asthma and dementia

***Correspondence:** Hyo Geun Choi

Department of Otorhinolaryngology-Head & Neck Surgery, Hallym University Sacred Heart Hospital, 22, Gwanpyeong-ro 170beon-gil, Dongan-gu, Anyang-si, Gyeonggi-do, 14068 Republic of Korea

Tel: 82-31-380-3849

Fax: 82-31-386-3860

Email: pupen@naver.com

Key words: Asthma; dementia; Risk factors; Cohort studies; Epidemiology

Abstract

Objectives: This study investigated the risk of neurodegenerative dementia following asthma.

Design: A nested case-control study

Setting: The ≥ 60-year-old population was selected from the Korean Health Insurance Review and Assessment Service - National Sample Cohort from 2002 through 2013.

Participants and Interventions: The 11,442 dementia participants were matched with 45,768 control participants for age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia. Asthma was classified using ICD-10 codes (J45 and J46) and medication history. Dementia was identified based on ICD-10 codes (G30 and F00).

Primary and secondary outcome measures: The odds ratios (ORs) of a previous history of asthma in dementia patients were analyzed using conditional logistic regression analysis stratified for age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia. Subgroup analysis was performed according to age and sex.

Results: There were 22.6% (2,587/ 11,442) and 22.3% (10,229/ 45,768) of the participants in the dementia and control groups that had a previous history of asthma. The odds ratio for asthma in the dementia group was not higher than in the control group (adjusted OR = 0.97, 95% confidence interval [95% CI] = 0.92 – 1.02, P = 0.207). All age and sex subgroups demonstrated consistent results.

Conclusions: Asthma was not related to an increased risk of dementia.

Strengths and limitations of this study

- Dementia patients did not demonstrate a higher rate of previous histories of asthma than the control group in the present study.
- This result was consistent in all age and sex subgroups. This study was based on the older adult population considering the high prevalence of dementia in these age groups.
- Moreover, the potential biases between dementia and control groups were minimized by matching past medical histories as well as demographic factors.
- Although ICD-10 codes are based on the diagnosis of physician, they lack information on the severity of disease and treatment history.

Funding: This research was supported by funding from the National Research Foundation (NRF) of Korea (NRF-2018-R1D1A1A02085328 and 2018R1D1A1B07048092).

Competing interest: None declared.

Introduction

Dementia is an age-related neurodegenerative disease with a spectrum from mild cognitive impairment to a full-blown dementia state. Because of an aging society and improved life expectancy by virtue of advanced medical care, an increasing number of people suffer from dementia. The incidence of dementia was estimated to be approximately 14.3 per 1000 person-years in men and 17.0 per 1000 person-years in women aged ≥ 50 years old in Western countries [1]. In Korea, the prevalence of dementia was estimated to be approximately 6% – 10% [2]. Because older adults have a higher number of comorbidities, such as cardiovascular and metabolic diseases, the impact of these systemic disorders on neurodegenerative changes is anticipated to grow. Consistent with these findings, numerous studies have reported associations of various chronic diseases, including hypertension, diabetes, dyslipidemia, coronary heart disease, and depression, with dementia [3-6].

Asthma is a chronic airway disease defined by typical pulmonary dysfunction and airway symptoms. The prevalence of asthma has been reported to be approximately 2% – 20% with both increasing and decreasing tendencies, depending on the ethnic group studied [7]. The incidence of asthma in Korea was reported to be stable at approximately 6.07 per 1,000 person-years [8]. In addition to the well-known type 2 helper T-cell-related asthma, various endotypes of asthma associated with multiple pathophysiologic mechanisms have been described [9]. Due to these multiple contributors, asthma was reported to be associated with many chronic diseases, such as hypertension, diabetes, dyslipidemia, coronary heart disease, and depression [10-13]. Dementia has also been proposed to be related to asthma. A national population study reported a 2.17 times higher risk of dementia in asthma patients > 45 years old (95% confidence intervals [95% CI] = 1.87 – 2.52) [14]. Another national population study showed a 1.27 times higher risk of dementia in asthma patients ≥ 20 years old (95% CI = 1.15

– 1.41) [15]. The authors of that study hypothesized that the common pathophysiology of inflammation, immune dysfunction, and cardiovascular compromise might link asthma to dementia. However, both studies used young and middle-aged adult populations. In addition, control groups were matched with asthma patients for age and sex only; thus, comorbidities, such as hypertension, diabetes, and dyslipidemia, were higher in asthma groups. Adjusting for these comorbidities might influence the differences in the risk of dementia between the asthma and control groups.

Therefore, it was questioned whether asthma increases the risk of dementia in the old population, irrespective of other comorbid conditions. We hypothesized that the risk of dementia in asthma patients may have been overestimated in previous studies. To test this hypothesis, dementia patients were investigated for the previous histories of asthma compared with the control group matched for age, sex, income, region of residence, and past medical histories of hypertension, diabetes, and dyslipidemia.

Materials and Methods

Study Population and Data Collection

The ethics committee of Hallym University (2017-I102) approved the use of these data. The Institutional Review Board waived the requirement for written informed consent.

This national cohort study used data from the Korean National Health Insurance Service-National Sample Cohort (NHIS-NSC). The detailed description of this data was described in our previous studies[16,17].

Participant Selection

Out of 1,125,691 cases with 114,369,638 medical claim codes, we included participants who were diagnosed with dementia from 2002 through 2013 (n = 13,102). Dementia was categorized if the participants were diagnosed with Alzheimer's disease (ICD-10 code: G30) or Dementia in Alzheimer's disease (F00). For accurate diagnosis, we only selected participants who were treated ≥ 2 times. We described the reliability of the diagnosis of dementia in the supplementary material (S1). The control participants were extracted from this cohort of 1,112,589 participants who were never diagnosed with dementia from 2002 through 2013.

We included participants who were diagnosed with asthma (ICD-10: J45) or status asthmaticus (J46). Among them, we selected the participants who were treated ≥ 2 times and who were treated with a corticosteroid, steroid inhaler, LMMA, LTRA, or Xantine (n = 230,764). This method has been modified from a previous study [18].

The dementia participants were matched at a 1:4 ratio with patients (control group) in this cohort who had never been treated for dementia from 2002 through 2013. The control group was selected from the original population (n = 1,112,589). These subjects were matched for age, sex, income, region of residence, and past medical history (hypertension, diabetes, and dyslipidemia). To prevent a selection bias when selecting the matched participants, the control group participants were sorted using a random number order, and they were then selected from top to bottom. The matched control participants were assumed to be involved at the same time as each matched dementia participant (index date). Therefore, the control group subjects who died before the index date were excluded. Dementia participants for whom we could not identify enough matched participants were excluded (n = 1,148). We also excluded participants aged less than 60 years (n = 512). Finally, 1:4 matching resulted in the inclusion of 11,442 dementia participants and 45,768 control participants (Figure 1).

However, they were not matched for ischemic heart disease, cerebral stroke, and depression because strict matching would have increased the number of excluded study participants due to a lack of control participants. After matching, we analyzed the participants' previous histories of asthma in both the dementia and control groups.

Variables

The age groups were classified using 5-year intervals as follows: 60-64, 65-69, 70-74…, and 85+ years old. Age was defined as the age at the onset of dementia. Six age groups were designated. The income groups were initially divided into 41 classes (one health aid class, 20 self-employed health insurance classes, and 20 employed health insurance classes). These groups were recategorized into 5 classes (class 1 [lowest income] - class 5 [highest income]). Region of residence was divided into 16 areas according to administrative district. These regions were regrouped into urban (Seoul, Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan) and rural (Gyeonggi, Gangwon, Chungcheongbuk, Chungcheongnam, Jeollabuk, Jeollanam, Gyeongsangbuk, Gyeongsangnam, and Jeju) areas.

The past medical histories of the participants were evaluated using ICD-10 codes. For the accuracy of diagnosis, hypertension (I10 and I15), diabetes (E10-E14), and dyslipidemia (E78) were assessed if the participants were treated ≥ 2 times. Ischemic heart disease (I24 and I25) and cerebral stroke (I60-I66) were assessed if the participants were treated ≥ 1 time. Depression was defined using ICD-10 codes F31 (bipolar affective disorder) through F39 (unspecified mood disorder) recorded by a psychiatrist ≥ 2 times. Chronic obstructive pulmonary disease (COPD) was determined by J43 (emphysema) through J44 (other chronic obstructive pulmonary disease) who were treated with SABA, LABA, LAMA, or corticosteroids [19].

Statistical Analyses

A chi-square test was used to compare the rate of general characteristics between the dementia and control groups.

To analyze the odds ratio (OR) of asthma (dependent variable) with dementia (independent variable), conditional logistic regression analysis was used. In these analyses, crude (simple) and adjusted (ischemic heart disease, cerebral stroke, depression, and COPD) models were used, and 95% CIs were calculated. In these analyses, groups were stratified by age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia.

For the subgroup analyses, we divided the participants by age and sex (men < 80 years old, women < 80 years old, men ≥ 80 years old, and women ≥ 80 years old). The dividing point of age group was determined by median values.

Two-tailed analyses were conducted, and P values < 0.05 were considered to indicate significance. The results were analyzed using SPSS v. 22.0 (IBM, Armonk, NY, USA).

Results

The rate of asthma was not higher in dementia participants (22.6% [2,587/11,442]) than in controls (22.3% [10,229/45,768], Table 1). The general characteristics (age, sex, income, region of residence, and histories of hypertension, diabetes, and dyslipidemia) of participants were identical due to matching. Higher rates of histories of ischemic heart disease, cerebral stroke, depression, and COPD were observed in the dementia group. The adjusted OR for asthma in the dementia group was 0.97 (95% CI = 0.93-1.01, P values > 0.05, Table 2).

In the subgroup analyses, adjusted ORs for asthma were not higher in dementia participants (Table 3). Adjusted ORs were 0.88 (95% CI = 0.78 – 1.00, P = 0.050) in < 80-

year-old men, 1.01 (95% CI = 0.93-1.09, P = 0.882) in < 80-year-old women, 0.95 (95% CI = 0.81-1.12, P = 0.523) in ≥ 80-year-old men, and 0.98 (95% CI = 0.89-1.09, P = 0.735) in ≥ 80-year-old women.

Discussion

Dementia patients did not demonstrate a higher rate of previous histories of asthma than the control group in the present study. This result was consistent in all age and sex subgroups. This study was based on the older adult population considering the high prevalence of dementia in these age groups. Moreover, the potential biases between dementia and control groups were minimized by matching past medical histories as well as demographic factors.

Similar to the present results, a population-based study reported a nonsignificant association between asthma and dementia in older adults [20]. They demonstrated that asthma was related to depression (OR = 2.45, 95% CI = 1.06 – 5.69) but not dementia [20]. Their results might have resulted from the exclusion criteria; adjustment for the confounding effects of chronic illnesses, psychological and social factors; and medication histories predisposing depression. Another population-based study using a twin cohort showed that the risk of dementia was not high in asthma patients [21]. The authors postulated that atopic disease could impact the occurrence of dementia [21]. Thus, the unexpected result of no significant association between asthma and dementia was speculated due to the poor survival rates of asthma patients in their cohort [21]. On the other hand, several previous studies reported a high risk of dementia in asthma patients [14,15]. Although asthma could have an impact on the risk of dementia, this influence could not be significant when possible confounding effects were attenuated by matching the control group for comorbidities, as in the present study.

The effects of other pulmonary diseases, such as COPD, on the risk of dementia have been mixed for the relation between asthma and dementia in previous studies. A number of studies reported an elevated risk of dementia in COPD patients [22,23]. The hypoxemia due to deteriorated pulmonary function was suggested to accentuate cognitive dysfunction [23]. Therefore, no asthma-specific factors but general pulmonary problems could considerably contribute to the risk of dementia. Indeed, the overall pulmonary diseases, but not asthma alone, were related to the elevated risk of dementia in a previous study [24]. A population cohort study demonstrated that COPD or combined COPD and asthma groups had a higher risk of dementia, but not in the asthma-only group (hazard ratio [HR] = 1.85, 95% CI = 1.05 – 3.28 for COPD and HR = 1.94, 95% CI = 1.16 – 3.27 for combined asthma and COPD groups) [24]. On the other hand, the current study adjusted for COPD, thus minimizing the confounding effects of COPD in assessing the association between asthma and dementia.

In addition to the confounding effects of other respiratory diseases, the influence of cardiovascular diseases and other unadjusted inflammatory or immune disorders could have mediated the association between asthma and dementia in prior studies. A number of researchers have reported that asthma is associated with inflammatory conditions besides those in the airway [25,26]. Asthma was related to the elevated risk of the proinflammatory conditions coronary heart disease and diabetes (HR = 1.47, 95% CI = 1.05 – 2.06, P = 0.02 for coronary heart disease and HR = 2.11, 95% CI = 1.43 – 3.13, P < 0.001 for diabetes) [25]. Likewise, multiple inflammatory processes were reported to accelerate neurodegenerative changes and dementia [27]. To exclude the impact of these confounding factors of cardiovascular comorbidities, the matching of the control group, in addition to the adjustments with multivariable analysis, might be effective [28].

Heterogeneous biologic and phenotypic features of adult asthma could mitigate the impact of asthma on dementia in this study. Although early-onset asthma is mainly related to atopic responses, late-onset asthma includes a considerable portion of nonatopic asthma and has various pathophysiologies associated with the different endotypes of asthma [29]. Thus, the impact of asthma on dementia via atopy could have been attenuated in older adults. Atopy has been presumed to increase the risk of dementia probably by elevating the inflammatory burden [21]. Atopic patients with asthma, eczema, and rhinitis showed a 1.16 times higher risk of dementia (95% CI = 1.01 – 1.33) [21]. However, asthma alone, relative to the control group, did not result in a higher risk of dementia [21].

The large, representative nature of the population examined here potentiated the fidelity of the analyzed results of the present study. The age of the study population was restricted to the relevant age groups of ≥ 60 years old to minimize the early-onset dementia population. Early-onset dementia, which occurs in the < 65 year-old population, is different from late-onset dementia in aspects of genetics, underlying pathology, and relation with cardiovascular or metabolic disorders [30]. Therefore, the exclusion of this younger population was important to prevent the interference of specific early-onset dementia cases for the true association between asthma and dementia. In addition, socioeconomic factors were matched between the dementia and control groups in this study. Because this study used a health insurance database, the conditions for the use of medical care, which is largely determined by socioeconomic factors, should be comparable between the dementia and control groups. In addition to socioeconomic factors, other demographic and past medical histories were matched between the dementia and control groups in the present study. The methods of classification of both asthma and dementia in our study were verified in prior studies [18] (supplementary material S1). However, a few limitations exist, mainly due to the lack of

detailed medical information in the NHIS database. The subtypes, severity, and treatment of each disease could not be assessed. The subclinical or untreated dementia or asthma was not considered in this study. Although several confounders were matched or adjusted for in this study, there are still a number of possible confounding factors, including smoking, alcohol consumption, and obesity.

Conclusion

Asthma was not related to the elevated risk of neurodegenerative dementia in the older adult population.

Authors' contributions: HGC designed the study; CM, and DJO analyzed the data; SYK, HGC drafted and revised the paper; all authors approved the final version of the manuscript.

Data sharing statement

Releasing of the data by the researcher is not allowed legally. All of data are available from the database of National health Insurance Sharing Service (NHISS) (https://nhiss.nhis.or.kr/). NHISS allows all of this data for the any researcher who promises to follow the research ethics with some cost. If you want to access the data of this article, you could download it from the website after promising to follow the research ethics.

References

1. Ahmadi-Abhari S, Guzman-Castillo M, Bandosz Pet al. Temporal trend in dementia incidence since 2002 and projections for prevalence in England and Wales to 2040: modelling study. *BMJ* 2017; 358:j2856.
2. Cho MJ, Lee JY, Kim BS, Lee HW, Sohn JH. Prevalence of the major mental disorders among the Korean elderly. *J Korean Med Sci* 2011; 26:1-10.
3. Liang X, Shan Y, Ding Det al. Hypertension and High Blood Pressure Are Associated With Dementia Among Chinese Dwelling Elderly: The Shanghai Aging Study. *Front Neurol* 2018; 9:664.
4. Kim YK, Nam KI, Song J. The Glymphatic System in Diabetes-Induced Dementia. *Front Neurol* 2018; 9:867.
5. Bennett S, Thomas AJ. Depression and dementia: cause, consequence or coincidence? *Maturitas* 2014; 79:184-90.
6. Deckers K, Schievink SHJ, Rodriquez MMFet al. Coronary heart disease and risk for cognitive impairment or dementia: Systematic review and meta-analysis. *PloS One* 2017; 12:e0184244.
7. Sears MR. Trends in the prevalence of asthma. *Chest* 2014; 145:219-25.
8. Shin JY, Sohn KH, Shin JEet al. Changing patterns of adult asthma incidence: results from the National Health Insurance Service-National Sample Cohort (NHIS-NSC) database in Korea. *Sci Rep* 2018; 8:15052.
9. Svenningsen S, Nair P. Asthma Endotypes and an Overview of Targeted Therapy for Asthma. *Front Med (Lausanne)* 2017; 4:158.
10. Christiansen SC, Schatz M, Yang SJ, Ngor E, Chen W, Zuraw BL. Hypertension and Asthma: A Comorbid Relationship. *J Allergy Clin Immunol Pract*. 2016; 4:76-81.

11. Perez MK, Piedimonte G. Metabolic asthma: is there a link between obesity, diabetes, and asthma? *Immunol Allergy Clin North Am* 2014; 34:777-84.

12. Wang L, Gao S, Yu M, Sheng Z, Tan W. Association of asthma with coronary heart disease: A meta analysis of 11 trials. *PloS One* 2017; 12:e0179335.

13. Gao YH, Zhao HS, Zhang FRet al. The Relationship between Depression and Asthma: A Meta-Analysis of Prospective Studies. *PloS One* 2015; 10:e0132424.

14. Chen MH, Li CT, Tsai CFet al. Risk of dementia among patients with asthma: a nationwide longitudinal study. *J Am Med Dir Assoc* 2014; 15:763-767.

15. Peng YH, Wu BR, Su CHet al. Adult asthma increases dementia risk: a nationwide cohort study. *J Epidemiol Community Health* 2015; 69:123-8.

16. Kim SY, Kim HJ, Lim H, Kong IG, Kim M, Choi HG. Bidirectional association between gastroesophageal reflux disease and depression: Two different nested case-control studies using a national sample cohort. *Sci Rep* 2018; 8:11748.

17. Kim SY, Lim JS, Kong IG, Choi HG. Hearing impairment and the risk of neurodegenerative dementia: A longitudinal follow-up study using a national sample cohort. *Sci Rep* 2018; 8:15266.

18. Kim S, Kim J, Kim Ket al. Healthcare use and prescription patterns associated with adult asthma in Korea: analysis of the NHI claims database. *Allergy* 2013; 68:1435-42.

19. Psillas G, Arnaoutoglou M, Gatsios T, Rizos D, Koutsouraki E, Vital V. Autoimmune recurrent facial palsy and bilateral sudden sensorineural hearing loss following Ramsay Hunt-like syndrome. *Auris Nasus Larynx* 2012; 39:229-32.

20. Ng TP, Chiam PC, Kua EH. Mental disorders and asthma in the elderly: a population-based study. Int J Geriatr Psychiatry 2007; 22:668-74.

21. Eriksson UK, Gatz M, Dickman PW, Fratiglioni L, Pedersen NL. Asthma, eczema, rhinitis and the risk for dementia. *Dement Geriatr Cogn Disord* 2008; 25:148-56.

22. Tondo G, De Marchi F, Terazzi Eet al. Chronic obstructive pulmonary disease may complicate Alzheimer's disease: a comorbidity problem. *Neurol Sci* 2018.

23. Kakkera K, Padala KP, Kodali M, Padala PR. Association of chronic obstructive pulmonary disease with mild cognitive impairment and dementia. *Curr Opin Pulm Med* 2018; 24:173-8.

24. Rusanen M, Ngandu T, Laatikainen T, Tuomilehto J, Soininen H, Kivipelto M. Chronic obstructive pulmonary disease and asthma and the risk of mild cognitive impairment and dementia: a population based CAIDE study. *Curr Alzheimer Res* 2013; 10:549-55.

25. Yun HD, Knoebel E, Fenta Yet al. Asthma and proinflammatory conditions: a population-based retrospective matched cohort study. *Mayo Clin Proc* 2012; 87:953-60.

26. Fenta YA, Tello N, Jung JAet al. Inflammatory bowel disease and asthma: a population-based, case-control study. *Inflamm Bowel Dis* 2010; 16:1957-62.

27. Newcombe EA, Camats-Perna J, Silva ML, Valmas N, Huat TJ, Medeiros R. Inflammation: the link between comorbidities, genetics, and Alzheimer's disease. *J Neuroinflammation* 2018; 15:276.

28. Kim SY, Sim S, Kim HJ, Choi HG. Sudden sensory neural hearing loss is not predictive of myocardial infarction: A longitudinal follow-up study using a national sample cohort. *Sci Rep* 2018; 8:946.

29. Hirano T, Matsunaga K. Late-onset asthma: current perspectives. *J Asthma Allergy* 2018; 11:19-27.

30. Mendez MF. Early-Onset Alzheimer Disease. *Neurol Clin* 2017; 35:263-81.

Figure legend

Figure 1 Schematic illustration of the participant selection process that was used in the present study. Of a total of 1,125,691 participants, 11,442 dementia participants were matched with 45,768 control participants with respect to age, sex, income, region of residence, and past medical history.

Table 1 General Characteristics of Participants

Characteristics	Total participants		
	Dementia (n, %)	Control group (n, %)	P-value
Age (years old)			1.000
60-64	580 (5.1)	2,320 (5.1)	
65-69	1,289 (11.3)	5,156 (11.3)	
70-74	2,325 (20.3)	9,300 (20.3)	
75-79	2,979 (26.0)	11,916 (26.0)	
80-84	2,703 (23.6)	10,812 (23.6)	
85+	1,566 (13.7)	6,264 (13.7)	
Sex			1.000
Male	3,663 (32.0)	14,652 (32.0)	
Female	7,779 (68.0)	31,116 (68.0)	
Income			1.000
1 (lowest)	2,866 (25.0)	11,464 (25.0)	
2	1,034 (9.0)	4,136 (9.0)	
3	1,374 (12.0)	5,496 (12.0)	
4	1,884 (16.5)	7,536 (16.5)	
5 (highest)	4,284 (37.4)	17,136 (37.4)	
Region of residence			1.000
Urban	4,623 (40.4)	18,492 (40.4)	
Rural	6,819 (59.6)	27,276 (59.6)	
Hypertension	8,316 (72.7)	33,264 (72.7)	1.000
Diabetes	4,065 (35.5)	16,260 (35.5)	1.000

Dyslipidemia	3,554 (31.1)	14,216 (31.1)	1.000
Ischemic heart disease	1,707 (14.9)	6,118 (13.4)	<0.001*
Cerebral stroke	5,518 (48.2)	11,390 (24.9)	<0.001*
Depression	3,231 (28.2)	4,782 (10.4)	<0.001*
COPD	1,273 (11.1)	4,419 (9.7)	<0.001*
Asthma	2,587 (22.6)	10,229 (22.3)	0.551

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease

*Chi-square test. Significance at $P < 0.05$

Table 2 Crude and adjusted odd ratios (95% confidence interval) of asthma in dementia participants

Characteristics	Asthma			
	Crude†	P-value	Adjusted†‡	P-value
Dementia	1.02 (0.97-1.07)	0.547	0.97 (0.92-1.02)	0.207
Control	1.00		1.00	

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease

* Conditional logistic regression analyses, Significance at $P < 0.05$

† Stratified model for age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia histories.

‡ Adjusted model for ischemic heart disease, cerebral stroke, depression, and COPD histories.

Table 3 Subgroup analyses of crude and adjusted odd ratios (95% confidence interval) of asthma in dementia participants according to age and sex

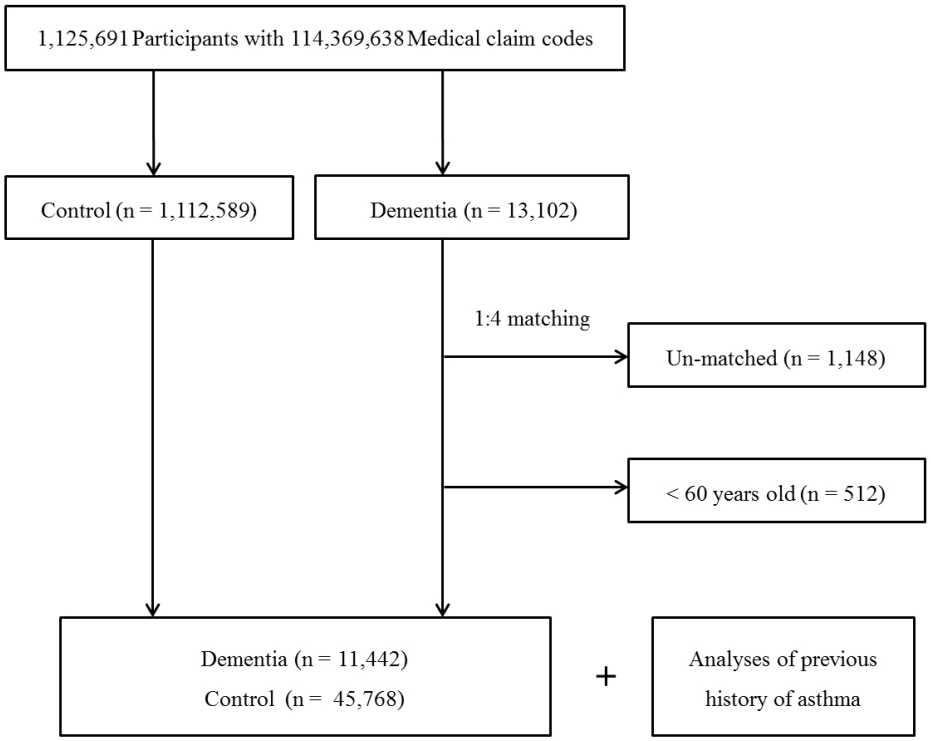
Characteristics	Asthma			
	Crude†	P-value	Adjusted†‡	P-value
Age < 80 years old men (n = 12,455)				
Dementia	0.95 (0.85-1.06)	0.361	0.88 (0.78-1.00)	0.050
Control	1.00		1.00	
Age < 80 years old women (n = 23,410)				
Dementia	1.05 (0.97-1.13)	0.197	1.01 (0.93-1.09)	0.882
Control	1.00		1.00	
Age ≥ 80 years old men (n = 5,860)				
Dementia	0.98 (0.85-1.14)	0.818	0.95 (0.81-1.12)	0.523
Control	1.00		1.00	
Age ≥ 80 years old women (n = 15,485)				
Dementia	1.02 (0.93-1.13)	0.641	0.98 (0.89-1.09)	0.735
Control	1.00		1.00	

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease

* Conditional logistic regression analyses, Significance at $P < 0.05$

† Stratified model for age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia histories.

‡ Adjusted model for ischemic heart disease, cerebral stroke, depression, and COPD histories.



S1 Description of diagnosis of dementia

Dementia was categorized if the participants were diagnosed Alzheimer's disease (G30) or Dementia in Alzheimer's disease (F00). We selected if the participants were treated ≥ 2 times.

In this national sample cohort, 123,025 participants were ≥ 65 years old in 2012 year. Among them, 9,740 (7.9%) of participants were categorized as dementia according to our methods (5.4% [n =2,758] in male; 9.7% [n= 6,982] in female).

We could compare these results of central dementia center of Korea (www.nid.or.kr) which is controlled by Ministry of Health and Welfare of Korea. The earliest data was 2012 year, and it was available in ≥ 65 years old. According to their data, the prevalence of dementia (Alzheimer's disease, and others) except vascular dementia were 7.63% (4.47% in male; 9.85% in female).

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (p1-2)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found (p2)
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported (p4-5)
Objectives	3	State specific objectives, including any prespecified hypotheses (p5)
Methods		
Study design	4	Present key elements of study design early in the paper (p5-6)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection (p5-6)
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (p5-7) *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed (p7) *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable (p7-8)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group (p5-7)
Bias	9	Describe any efforts to address potential sources of bias (p5-8)
Study size	10	Explain how the study size was arrived at (p7)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why (p7-9)
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (p8)
		(*b*) Describe any methods used to examine subgroups and interactions (p8-9)
		(*c*) Explain how missing data were addressed (p6)
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed (p6) *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (p8)
		(b) Give reasons for non-participation at each stage (p6)
		(c) Consider use of a flow diagram (p6)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (p8)
		(b) Indicate number of participants with missing data for each variable of interest (p6)
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time (p8-9)
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (p8-9)
		(*b*) Report category boundaries when continuous variables were categorized (p8-9)
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses (p8-9)
Discussion		
Key results	18	Summarise key results with reference to study objectives (p9)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias (p11-12)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence (p9-11)
Generalisability	21	Discuss the generalisability (external validity) of the study results (p9-11)
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based (p3)

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

The risk of neurodegenerative dementia in asthma patients: A nested case-control study using a national sample cohort

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-030227.R1
Article Type:	Original research
Date Submitted by the Author:	02-Jul-2019
Complete List of Authors:	Kim, So Young; CHA University, Department of Otorhinolaryngology-Head & Neck Surgery Min, Chanyang; Hallym University College of Medicine, Hallym Data Science Laboratory Oh, Dong Jun; Asan Medical Center, University of Ulsan College of Medicine Choi, Hyo Geun; Hallym University,
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Respiratory medicine
Keywords:	Asthma < THORACIC MEDICINE, Dementia < NEUROLOGY, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

The risk of neurodegenerative dementia in asthma patients: A nested case-control study using a national sample cohort

So Young Kim, MD[1], Chanyang Min, PhD[2,3], Dong Jun Oh, MD[4], Hyo Geun Choi, MD[2,5]

[1]Department of Otorhinolaryngology-Head & Neck Surgery, CHA Bundang Medical Center, CHA University, Seongnam, Korea

[2]Hallym Data Science Laboratory, Hallym University College of Medicine, Anyang, Korea

[3]Graduate School of Public Health, Seoul National University, Seoul, Korea

[4]Department of Internal medicine, Soonchunhyang University College of Medicine, Seoul

[5]Department of Otorhinolaryngology-Head & Neck Surgery, Hallym University College of Medicine, Anyang, Korea

Running title: Asthma and dementia

***Correspondence:** Hyo Geun Choi

Department of Otorhinolaryngology-Head & Neck Surgery, Hallym University Sacred Heart Hospital, 22, Gwanpyeong-ro 170beon-gil, Dongan-gu, Anyang-si, Gyeonggi-do, 14068 Republic of Korea

Tel: 82-31-380-3849

Fax: 82-31-386-3860

Email: pupen@naver.com

Key words: Asthma; dementia; Risk factors; Cohort studies; Epidemiology

Abstract

Objectives: This study investigated the risk of neurodegenerative dementia following asthma.

Design: A nested case-control study

Setting: The ≥ 60-year-old population was selected from the Korean Health Insurance Review and Assessment Service - National Sample Cohort from 2002 through 2013.

Participants and Interventions: The 11,442 dementia cases were matched with 45,768 control cases for age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia. Asthma was classified using ICD-10 codes (J45 and J46) and medication history. Dementia was identified based on ICD-10 codes (G30 and F00).

Primary and secondary outcome measures: The odds ratios (ORs) of a previous history of asthma in dementia patients were analyzed using conditional logistic regression analysis stratified for age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia. Subgroup analysis was performed according to age and sex.

Results: There were 22.6% (2,587/ 11,442) and 22.3% (10,229/ 45,768) of the cases in the dementia and control groups that had a previous history of asthma. The odds ratio for asthma in the dementia group was not higher than in the control group (adjusted OR = 0.97, 95% confidence interval [95% CI] = 0.92 – 1.02, P = 0.207). All age and sex subgroups demonstrated consistent results.

Conclusions: Asthma was not related to an increased risk of dementia.

Strengths and limitations of this study

- This study was based on the large number of older adult population considering the high prevalence of dementia in these age groups.
- Moreover, the potential biases between dementia and control groups were minimized by matching past medical histories as well as demographic factors.
- Although ICD-10 codes are based on the diagnosis of physician, they lack information on the severity of disease and treatment history.

Funding: This research was supported by funding from the National Research Foundation (NRF) of Korea (NRF-2018-R1D1A1A02085328 and NRF-2017R1C1B1007696).

Competing interest: None declared.

Introduction

Dementia is an age-related neurodegenerative disease with a spectrum from mild cognitive impairment to a full-blown dementia state. Because of an aging society and improved life expectancy by virtue of advanced medical care, an increasing number of people suffer from dementia. The incidence of dementia was estimated to be approximately 14.3 per 1000 person-years in men and 17.0 per 1000 person-years in women aged ≥ 50 years old in Western countries [1]. In Korea, the prevalence of dementia was estimated to be approximately 6% – 10% [2]. Because older adults have a higher number of comorbidities, such as cardiovascular and metabolic diseases, the impact of these systemic disorders on neurodegenerative changes is anticipated to grow. Consistent with these findings, numerous studies have reported associations of various chronic diseases, including hypertension, diabetes, dyslipidemia, coronary heart disease, and depression, with dementia [3-6].

Asthma is a chronic airway disease defined by typical pulmonary dysfunction and airway symptoms. The prevalence of asthma has been reported to be approximately 2% – 20% with both increasing and decreasing tendencies, depending on the ethnic group studied [7]. The incidence of asthma in Korea was reported to be stable at approximately 6.07 per 1,000 person-years [8]. In addition to the well-known type 2 helper T-cell-related asthma, various endotypes of asthma associated with multiple pathophysiologic mechanisms have been described [9]. Due to these multiple contributors, asthma was reported to be associated with many chronic diseases, such as hypertension, diabetes, dyslipidemia, coronary heart disease, and depression [10-13]. Dementia has also been proposed to be related to asthma. A national population study reported a 2.17 times higher risk of dementia in asthma patients > 45 years old (95% confidence intervals [95% CI] = 1.87 – 2.52) [14]. Another national population study showed a 1.27 times higher risk of dementia in asthma patients ≥ 20 years old (95% CI = 1.15

– 1.41) [15]. The authors of that study hypothesized that the common pathophysiology of inflammation, immune dysfunction, and cardiovascular compromise might link asthma to dementia. However, both studies used young and middle-aged adult populations. In addition, control groups were matched with asthma patients for age and sex only; thus, comorbidities, such as hypertension, diabetes, and dyslipidemia, were higher in asthma groups. Adjusting for these comorbidities might influence the differences in the risk of dementia between the asthma and control groups.

Therefore, it was questioned whether asthma increases the risk of dementia in the old population, irrespective of other comorbid conditions. We hypothesized that the risk of dementia in asthma patients may have been overestimated in previous studies. To test this hypothesis, dementia patients were investigated for the previous histories of asthma compared with the control group matched for age, sex, income, region of residence, and past medical histories of hypertension, diabetes, and dyslipidemia.

Materials and Methods

Patients and Public Involvement statement

The ethics committee of Hallym University (2017-I102) approved the use of these data. The Institutional Review Board waived the requirement for written informed consent.

This national cohort study used data from the Korean National Health Insurance Service-National Sample Cohort (NHIS-NSC). The detailed description of this data was described in our previous studies[16,17]. We have no plan to disseminate the results to the cases. Because the NHIS-NSC data based on the national health claim codes, releasing of the data by the researcher is not allowed legally. All of data are available from the database of National health Insurance Sharing Service (NHISS) (https://nhiss.nhis.or.kr/).

NHISS allows all of this data for the any researcher who promises to follow the research ethics with some cost. If you want to access the data of this article, you could download it from the website after promising to follow the research ethics.

Participant Selection

Out of 1,125,691 cases with 114,369,638 medical claim codes, we included cases who were diagnosed with dementia from 2002 through 2013 (n = 13,102). Dementia was categorized if the cases were diagnosed with Alzheimer's disease (ICD-10 code: G30) or Dementia in Alzheimer's disease (F00). For accurate diagnosis, we only selected cases who were treated ≥ 2 times. We described the reliability of the diagnosis of dementia in the supplementary material (S1). The control cases were extracted from this cohort of 1,112,589 participants who were never diagnosed with dementia from 2002 through 2013.

We included cases who were diagnosed with asthma (ICD-10: J45) or status asthmaticus (J46). Among them, we selected the participants who were treated ≥ 2 times and who were treated with a corticosteroid, steroid inhaler, LMMA, LTRA, or Xantine (n = 230,764). This method has been modified from a previous study [18].

The dementia cases were matched at a 1:4 ratio with patients (control group) in this cohort who had never been treated for dementia from 2002 through 2013. The control group was selected from the original population (n = 1,112,589). These subjects were matched for age, sex, income, region of residence, and past medical history (hypertension, diabetes, and dyslipidemia). To prevent a selection bias when selecting the matched cases, the control group cases were sorted using a random number order, and they were then selected from top to bottom. The matched control cases were assumed to be involved at the same time as each matched dementia cases (index date). Therefore, the control group subjects who died before

the index date were excluded. Dementia cases for whom we could not identify enough matched cases were excluded (n = 1,148). We also excluded cases aged less than 60 years (n = 512). Finally, 1:4 matching resulted in the inclusion of 11,442 dementia cases and 45,768 control cases (Figure 1). However, they were not matched for ischemic heart disease, cerebral stroke, and depression because strict matching would have increased the number of excluded study cases due to a lack of control cases. After matching, we analyzed the cases' previous histories of asthma in both the dementia and control groups.

Variables

The age groups were classified using 5-year intervals as follows: 60-64, 65-69, 70-74…, and 85+ years old. Age was defined as the age at the onset of dementia. Six age groups were designated. The income groups were initially divided into 41 classes (one health aid class, 20 self-employed health insurance classes, and 20 employed health insurance classes). These groups were recategorized into 5 classes (class 1 [lowest income] - class 5 [highest income]). Region of residence was divided into 16 areas according to administrative district. These regions were regrouped into urban (Seoul, Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan) and rural (Gyeonggi, Gangwon, Chungcheongbuk, Chungcheongnam, Jeollabuk, Jeollanam, Gyeongsangbuk, Gyeongsangnam, and Jeju) areas.

The past medical histories of the cases were evaluated using ICD-10 codes. For the accuracy of diagnosis, hypertension (I10 and I15), diabetes (E10-E14), and dyslipidemia (E78) were assessed if the cases were treated ≥ 2 times. Ischemic heart disease (I24 and I25) and cerebral stroke (I60-I66) were assessed if the cases were treated ≥ 1 time. Depression was defined using ICD-10 codes F31 (bipolar affective disorder) through F39 (unspecified mood disorder) recorded by a psychiatrist ≥ 2 times. Chronic obstructive pulmonary disease (COPD)

was determined by J43 (emphysema) through J44 (other chronic obstructive pulmonary disease) who were treated with SABA, LABA, LAMA, or corticosteroids [19].

Statistical Analyses

A chi-square test was used to compare the rate of general characteristics between the dementia and control groups.

To analyze the odds ratio (OR) of asthma (dependent variable) with dementia (independent variable), conditional logistic regression analysis was used. In these analyses, crude (simple) and adjusted (ischemic heart disease, cerebral stroke, depression, and COPD) models were used, and 95% CIs were calculated. In these analyses, groups were stratified by age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia.

For the subgroup analyses, we divided the cases by age and sex (men < 80 years old, women < 80 years old, men ≥ 80 years old, and women ≥ 80 years old). The dividing point of age group was determined by median values.

Two-tailed analyses were conducted, and P values < 0.05 were considered to indicate significance. The results were analyzed using SPSS v. 22.0 (IBM, Armonk, NY, USA).

Results

The rate of asthma was not higher in dementia cases (22.6% [2,587/11,442]) than in controls (22.3% [10,229/45,768], Table 1). The general characteristics (age, sex, income, region of residence, and histories of hypertension, diabetes, and dyslipidemia) of cases were identical due to matching. Higher rates of histories of ischemic heart disease, cerebral stroke, depression, and COPD were observed in the dementia group. The adjusted OR for asthma in the dementia group was 0.97 (95% CI = 0.93-1.01, P values > 0.05, Table 2).

In the subgroup analyses, adjusted ORs for asthma were not higher in dementia cases (Table 3). Adjusted ORs were 0.88 (95% CI = 0.78 – 1.00, P = 0.050) in < 80-year-old men, 1.01 (95% CI = 0.93-1.09, P = 0.882) in < 80-year-old women, 0.95 (95% CI = 0.81-1.12, P = 0.523) in ≥ 80-year-old men, and 0.98 (95% CI = 0.89-1.09, P = 0.735) in ≥ 80-year-old women.

Discussion

Dementia patients did not demonstrate a higher rate of previous histories of asthma than the control group in the present study. This result was consistent in all age and sex subgroups. This study was based on the older adult population considering the high prevalence of dementia in these age groups. Moreover, the potential biases between dementia and control groups were minimized by matching past medical histories as well as demographic factors.

Similar to the present results, a population-based study reported a nonsignificant association between asthma and dementia in older adults [20]. They demonstrated that asthma was related to depression (OR = 2.45, 95% CI = 1.06 – 5.69) but not dementia [20]. Their results might have resulted from the exclusion criteria; adjustment for the confounding effects of chronic illnesses, psychological and social factors; and medication histories predisposing depression. Another population-based study using a twin cohort showed that the risk of dementia was not high in asthma patients [21]. The authors postulated that atopic disease could impact the occurrence of dementia [21]. Thus, the unexpected result of no significant association between asthma and dementia was speculated due to the poor survival rates of asthma patients in their cohort [21]. On the other hand, several previous studies reported a high risk of dementia in asthma patients [14,15]. Although asthma could have an impact on the risk of

dementia, this influence could not be significant when possible confounding effects were attenuated by matching the control group for comorbidities, as in the present study.

The effects of other pulmonary diseases, such as COPD, on the risk of dementia have been mixed for the relation between asthma and dementia in previous studies. A number of studies reported an elevated risk of dementia in COPD patients [22,23]. The hypoxemia due to deteriorated pulmonary function was suggested to accentuate cognitive dysfunction [23]. Therefore, no asthma-specific factors but general pulmonary problems could considerably contribute to the risk of dementia. Indeed, the overall pulmonary diseases, but not asthma alone, were related to the elevated risk of dementia in a previous study [24]. A population cohort study demonstrated that COPD or combined COPD and asthma groups had a higher risk of dementia, but not in the asthma-only group (hazard ratio [HR] = 1.85, 95% CI = 1.05 – 3.28 for COPD and HR = 1.94, 95% CI = 1.16 – 3.27 for combined asthma and COPD groups) [24]. On the other hand, the current study adjusted for COPD, thus minimizing the confounding effects of COPD in assessing the association between asthma and dementia.

In addition to the confounding effects of other respiratory diseases, the influence of cardiovascular diseases and other unadjusted inflammatory or immune disorders could have mediated the association between asthma and dementia in prior studies. A number of researchers have reported that asthma is associated with inflammatory conditions besides those in the airway [25,26]. Asthma was related to the elevated risk of the proinflammatory conditions coronary heart disease and diabetes (HR = 1.47, 95% CI = 1.05 – 2.06, P = 0.02 for coronary heart disease and HR = 2.11, 95% CI = 1.43 – 3.13, P < 0.001 for diabetes) [25]. Likewise, multiple inflammatory processes were reported to accelerate neurodegenerative changes and dementia [27]. To exclude the impact of these confounding factors of

cardiovascular comorbidities, the matching of the control group, in addition to the adjustments with multivariable analysis, might be effective [28].

Heterogeneous biologic and phenotypic features of adult asthma could mitigate the impact of asthma on dementia in this study. Although early-onset asthma is mainly related to atopic responses, late-onset asthma includes a considerable portion of nonatopic asthma and has various pathophysiologies associated with the different endotypes of asthma [29]. Thus, the impact of asthma on dementia via atopy could have been attenuated in older adults. Atopy has been presumed to increase the risk of dementia probably by elevating the inflammatory burden [21]. Atopic patients with asthma, eczema, and rhinitis showed a 1.16 times higher risk of dementia (95% CI = 1.01 – 1.33) [21]. However, asthma alone, relative to the control group, did not result in a higher risk of dementia [21].

The large, representative nature of the population examined here potentiated the fidelity of the analyzed results of the present study. The age of the study population was restricted to the relevant age groups of ≥ 60 years old to minimize the early-onset dementia population. Early-onset dementia, which occurs in the < 65 year-old population, is different from late-onset dementia in aspects of genetics, underlying pathology, and relation with cardiovascular or metabolic disorders [30]. Therefore, the exclusion of this younger population was important to prevent the interference of specific early-onset dementia cases for the true association between asthma and dementia. We additionally analyzed for the association between asthma and dementia in in ≥ 40 years old population. The odds ratio of asthma in dementia patients was not high in this age group (Table S1). In addition, socioeconomic factors were matched between the dementia and control groups in this study. Because this study used a health insurance database, the conditions for the use of medical care, which is largely determined by socioeconomic factors, should be comparable between the dementia

and control groups. In addition to socioeconomic factors, other demographic and past medical histories were matched between the dementia and control groups in the present study. To evaluate the impact of matching variables for the relation between asthma and dementia, we additionally analyzed the OR of asthma in dementia cases using control group matched for age and sex (Table S2). The result also indicated the no high OR of asthma in dementia patients. The methods of classification of both asthma and dementia in our study were verified in prior studies [18] (supplementary material S3). However, a few limitations exist, mainly due to the lack of detailed medical information in the NHIS database. The subtypes, severity, and treatment of each disease could not be assessed. The subclinical or untreated dementia or asthma was not considered in this study. Although several confounders were matched or adjusted for in this study, there are still a number of possible unmeasured confounding factors, including smoking, alcohol consumption, and obesity. For the matched comorbidities, the matching of comorbidities could be a negative bias on the association of asthma with dementia in this study, because the timing of comorbidities was distributed throughout the follow-up period. In addition, the healthy survival effect was possible, because the asthma patients who died before the occurrence of dementia were excluded in this study.

Conclusion

Asthma was not related to the elevated risk of neurodegenerative dementia in the older adult population.

Authors' contributions: HGC designed the study; CM, and DJO analyzed the data; SYK, HGC drafted and revised the paper; all authors approved the final version of the manuscript.

Data sharing statement

Releasing of the data by the researcher is not allowed legally. All of data are available from the database of National health Insurance Sharing Service (NHISS) (https://nhiss.nhis.or.kr/). NHISS allows all of this data for the any researcher who promises to follow the research ethics with some cost. If you want to access the data of this article, you could download it from the website after promising to follow the research ethics.

References

1. Ahmadi-Abhari S, Guzman-Castillo M, Bandosz Pet al. Temporal trend in dementia incidence since 2002 and projections for prevalence in England and Wales to 2040: modelling study. *BMJ* 2017; 358:j2856.
2. Cho MJ, Lee JY, Kim BS, Lee HW, Sohn JH. Prevalence of the major mental disorders among the Korean elderly. *J Korean Med Sci* 2011; 26:1-10.
3. Liang X, Shan Y, Ding Det al. Hypertension and High Blood Pressure Are Associated With Dementia Among Chinese Dwelling Elderly: The Shanghai Aging Study. *Front Neurol* 2018; 9:664.
4. Kim YK, Nam KI, Song J. The Glymphatic System in Diabetes-Induced Dementia. *Front Neurol* 2018; 9:867.
5. Bennett S, Thomas AJ. Depression and dementia: cause, consequence or coincidence? *Maturitas* 2014; 79:184-90.
6. Deckers K, Schievink SHJ, Rodriquez MMFet al. Coronary heart disease and risk for cognitive impairment or dementia: Systematic review and meta-analysis. *PloS One* 2017; 12:e0184244.
7. Sears MR. Trends in the prevalence of asthma. *Chest* 2014; 145:219-25.
8. Shin JY, Sohn KH, Shin JEet al. Changing patterns of adult asthma incidence: results from the National Health Insurance Service-National Sample Cohort (NHIS-NSC) database in Korea. *Sci Rep* 2018; 8:15052.
9. Svenningsen S, Nair P. Asthma Endotypes and an Overview of Targeted Therapy for Asthma. *Front Med (Lausanne)* 2017; 4:158.
10. Christiansen SC, Schatz M, Yang SJ, Ngor E, Chen W, Zuraw BL. Hypertension and Asthma: A Comorbid Relationship. *J Allergy Clin Immunol Pract*. 2016; 4:76-81.

11. Perez MK, Piedimonte G. Metabolic asthma: is there a link between obesity, diabetes, and asthma? *Immunol Allergy Clin North Am* 2014; 34:777-84.

12. Wang L, Gao S, Yu M, Sheng Z, Tan W. Association of asthma with coronary heart disease: A meta analysis of 11 trials. *PloS One* 2017; 12:e0179335.

13. Gao YH, Zhao HS, Zhang FRet al. The Relationship between Depression and Asthma: A Meta-Analysis of Prospective Studies. *PloS One* 2015; 10:e0132424.

14. Chen MH, Li CT, Tsai CFet al. Risk of dementia among patients with asthma: a nationwide longitudinal study. *J Am Med Dir Assoc* 2014; 15:763-767.

15. Peng YH, Wu BR, Su CHet al. Adult asthma increases dementia risk: a nationwide cohort study. *J Epidemiol Community Health* 2015; 69:123-8.

16. Kim SY, Kim HJ, Lim H, Kong IG, Kim M, Choi HG. Bidirectional association between gastroesophageal reflux disease and depression: Two different nested case-control studies using a national sample cohort. *Sci Rep* 2018; 8:11748.

17. Kim SY, Lim JS, Kong IG, Choi HG. Hearing impairment and the risk of neurodegenerative dementia: A longitudinal follow-up study using a national sample cohort. *Sci Rep* 2018; 8:15266.

18. Kim S, Kim J, Kim Ket al. Healthcare use and prescription patterns associated with adult asthma in Korea: analysis of the NHI claims database. *Allergy* 2013; 68:1435-42.

19. Psillas G, Arnaoutoglou M, Gatsios T, Rizos D, Koutsouraki E, Vital V. Autoimmune recurrent facial palsy and bilateral sudden sensorineural hearing loss following Ramsay Hunt-like syndrome. *Auris Nasus Larynx* 2012; 39:229-32.

20. Ng TP, Chiam PC, Kua EH. Mental disorders and asthma in the elderly: a population-based study. Int J Geriatr Psychiatry 2007; 22:668-74.

21. Eriksson UK, Gatz M, Dickman PW, Fratiglioni L, Pedersen NL. Asthma, eczema, rhinitis and the risk for dementia. *Dement Geriatr Cogn Disord* 2008; 25:148-56.

22. Tondo G, De Marchi F, Terazzi Eet al. Chronic obstructive pulmonary disease may complicate Alzheimer's disease: a comorbidity problem. *Neurol Sci* 2018.

23. Kakkera K, Padala KP, Kodali M, Padala PR. Association of chronic obstructive pulmonary disease with mild cognitive impairment and dementia. *Curr Opin Pulm Med* 2018; 24:173-8.

24. Rusanen M, Ngandu T, Laatikainen T, Tuomilehto J, Soininen H, Kivipelto M. Chronic obstructive pulmonary disease and asthma and the risk of mild cognitive impairment and dementia: a population based CAIDE study. *Curr Alzheimer Res* 2013; 10:549-55.

25. Yun HD, Knoebel E, Fenta Yet al. Asthma and proinflammatory conditions: a population-based retrospective matched cohort study. *Mayo Clin Proc* 2012; 87:953-60.

26. Fenta YA, Tello N, Jung JAet al. Inflammatory bowel disease and asthma: a population-based, case-control study. *Inflamm Bowel Dis* 2010; 16:1957-62.

27. Newcombe EA, Camats-Perna J, Silva ML, Valmas N, Huat TJ, Medeiros R. Inflammation: the link between comorbidities, genetics, and Alzheimer's disease. *J Neuroinflammation* 2018; 15:276.

28. Kim SY, Sim S, Kim HJ, Choi HG. Sudden sensory neural hearing loss is not predictive of myocardial infarction: A longitudinal follow-up study using a national sample cohort. *Sci Rep* 2018; 8:946.

29. Hirano T, Matsunaga K. Late-onset asthma: current perspectives. *J Asthma Allergy* 2018; 11:19-27.

30. Mendez MF. Early-Onset Alzheimer Disease. *Neurol Clin* 2017; 35:263-81.

Figure legend

Figure 1 Schematic illustration of the participant selection process that was used in the present study. Of a total of 1,125,691 cases, 11,442 dementia cases were matched with 45,768 control cases with respect to age, sex, income, region of residence, and past medical history.

Table 1 General Characteristics of Participants

Characteristics	Total participants		
	Dementia (n, %)	Control group (n, %)	P-value
Age (years old)			1.000
60-64	580 (5.1)	2,320 (5.1)	
65-69	1,289 (11.3)	5,156 (11.3)	
70-74	2,325 (20.3)	9,300 (20.3)	
75-79	2,979 (26.0)	11,916 (26.0)	
80-84	2,703 (23.6)	10,812 (23.6)	
85+	1,566 (13.7)	6,264 (13.7)	
Sex			1.000
Male	3,663 (32.0)	14,652 (32.0)	
Female	7,779 (68.0)	31,116 (68.0)	
Income			1.000
1 (lowest)	2,866 (25.0)	11,464 (25.0)	
2	1,034 (9.0)	4,136 (9.0)	
3	1,374 (12.0)	5,496 (12.0)	
4	1,884 (16.5)	7,536 (16.5)	
5 (highest)	4,284 (37.4)	17,136 (37.4)	
Region of residence			1.000
Urban	4,623 (40.4)	18,492 (40.4)	
Rural	6,819 (59.6)	27,276 (59.6)	
Hypertension	8,316 (72.7)	33,264 (72.7)	1.000
Diabetes	4,065 (35.5)	16,260 (35.5)	1.000

Dyslipidemia	3,554 (31.1)	14,216 (31.1)	1.000
Ischemic heart disease	1,707 (14.9)	6,118 (13.4)	<0.001*
Cerebral stroke	5,518 (48.2)	11,390 (24.9)	<0.001*
Depression	3,231 (28.2)	4,782 (10.4)	<0.001*
COPD	1,273 (11.1)	4,419 (9.7)	<0.001*
Asthma	2,587 (22.6)	10,229 (22.3)	0.551

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease

*Chi-square test. Significance at $P < 0.05$

Table 2 Crude and adjusted odd ratios (95% confidence interval) of asthma in dementia participants

Characteristics	Asthma			
	Crude†	P-value	Adjusted†‡	P-value
Dementia	1.02 (0.97-1.07)	0.547	0.97 (0.92-1.02)	0.207
Control	1.00		1.00	

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease

* Conditional logistic regression analyses, Significance at $P < 0.05$

† Stratified model for age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia histories.

‡ Adjusted model for ischemic heart disease, cerebral stroke, depression, and COPD histories.

Table 3 Subgroup analyses of crude and adjusted odd ratios (95% confidence interval) of asthma in dementia participants according to age and sex

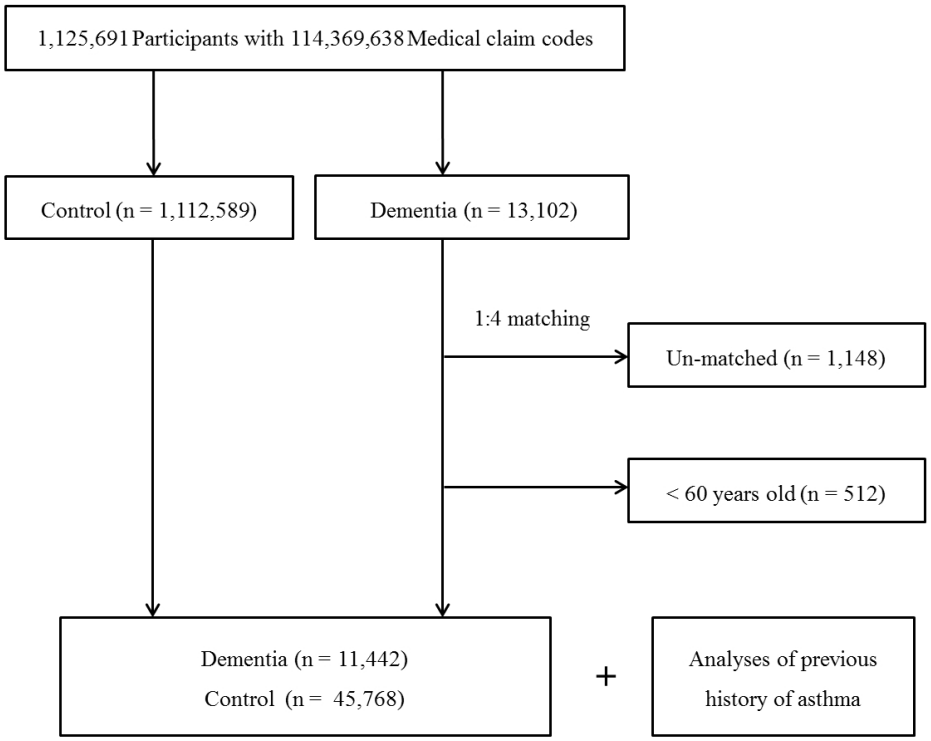
Characteristics	Asthma			
	Crude†	P-value	Adjusted†‡	P-value
Age < 80 years old men (n = 12,455)				
Dementia	0.95 (0.85-1.06)	0.361	0.88 (0.78-1.00)	0.050
Control	1.00		1.00	
Age < 80 years old women (n = 23,410)				
Dementia	1.05 (0.97-1.13)	0.197	1.01 (0.93-1.09)	0.882
Control	1.00		1.00	
Age ≥ 80 years old men (n = 5,860)				
Dementia	0.98 (0.85-1.14)	0.818	0.95 (0.81-1.12)	0.523
Control	1.00		1.00	
Age ≥ 80 years old women (n = 15,485)				
Dementia	1.02 (0.93-1.13)	0.641	0.98 (0.89-1.09)	0.735
Control	1.00		1.00	

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease

* Conditional logistic regression analyses, Significance at $P < 0.05$

† Stratified model for age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia histories.

‡ Adjusted model for ischemic heart disease, cerebral stroke, depression, and COPD histories.



S1 Table Crude and adjusted odd ratios (95% confidence interval) of asthma in dementia cases (≥40 years old)

Characteristics	Asthma			
	Crude†	P-value	Adjusted†‡	P-value
Dementia	1.02 (0.97-1.07)	0.519	0.93 (0.89-0.99)	0.013*
Control	1.00		1.00	

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease

* Conditional logistic regression analyses, Significance at $P < 0.05$

† Stratified model for age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia histories.

‡ Adjusted model for ischemic heart disease, cerebral stroke, depression, and COPD histories.

S2 Table Crude and adjusted odd ratios (95% confidence interval) of asthma in dementia cases

Characteristics	Asthma			
	Crude†	P-value	Adjusted†‡	P-value
Dementia	0.92 (0.88-0.96)	<0.001*	0.80 (0.76-0.84)	<0.001*
Control	1.00		1.00	

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease

* Conditional logistic regression analyses, Significance at $P < 0.05$

† Stratified model for age and sex.

‡ Adjusted model for income, region of residence, hypertension, diabetes, dyslipidemia, ischemic heart disease, cerebral stroke, depression, and COPD histories.

S3 Description of diagnosis of dementia

Dementia was categorized if the participants were diagnosed Alzheimer's disease (G30) or Dementia in Alzheimer's disease (F00). We selected if the participants were treated ≥ 2 times.

In this national sample cohort, 123,025 participants were ≥ 65 years old in 2012 year. Among them, 9,740 (7.9%) of participants were categorized as dementia according to our methods (5.4% [n =2,758] in male; 9.7% [n= 6,982] in female).

We could compare these results of central dementia center of Korea (www.nid.or.kr) which is controlled by Ministry of Health and Welfare of Korea. The earliest data was 2012 year, and it was available in ≥ 65 years old. According to their data, the prevalence of dementia (Alzheimer's disease, and others) except vascular dementia were 7.63% (4.47% in male; 9.85% in female).

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (p1-2)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found (p2)
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported (p4-5)
Objectives	3	State specific objectives, including any prespecified hypotheses (p5)
Methods		
Study design	4	Present key elements of study design early in the paper (p5-6)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection (p5-6)
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (p5-7) *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed (p7) *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable (p7-8)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group (p5-7)
Bias	9	Describe any efforts to address potential sources of bias (p5-8)
Study size	10	Explain how the study size was arrived at (p7)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why (p7-9)
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (p8)
		(*b*) Describe any methods used to examine subgroups and interactions (p8-9)
		(*c*) Explain how missing data were addressed (p6)
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed (p6) *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (p8)
		(b) Give reasons for non-participation at each stage (p6)
		(c) Consider use of a flow diagram (p6)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (p8)
		(b) Indicate number of participants with missing data for each variable of interest (p6)
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time (p8-9)
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (p8-9)
		(*b*) Report category boundaries when continuous variables were categorized (p8-9)
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses (p8-9)
Discussion		
Key results	18	Summarise key results with reference to study objectives (p9)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias (p11-12)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence (p9-11)
Generalisability	21	Discuss the generalisability (external validity) of the study results (p9-11)
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based (p3)

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

The risk of neurodegenerative dementia in asthma patients: A nested case-control study using a national sample cohort

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-030227.R2
Article Type:	Original research
Date Submitted by the Author:	29-Aug-2019
Complete List of Authors:	Kim, So Young; CHA University, Department of Otorhinolaryngology-Head & Neck Surgery Min, Chanyang; Hallym University College of Medicine, Hallym Data Science Laboratory Oh, Dong Jun; Asan Medical Center, University of Ulsan College of Medicine Choi, Hyo Geun; Hallym University,
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Respiratory medicine
Keywords:	Asthma < THORACIC MEDICINE, Dementia < NEUROLOGY, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

The risk of neurodegenerative dementia in asthma patients: A nested case-control study using a national sample cohort

So Young Kim, MD[1], Chanyang Min, PhD[2,3], Dong Jun Oh, MD[4], Hyo Geun Choi, MD[2,5]

[1]Department of Otorhinolaryngology-Head & Neck Surgery, CHA Bundang Medical Center, CHA University, Seongnam, Korea

[2]Hallym Data Science Laboratory, Hallym University College of Medicine, Anyang, Korea

[3]Graduate School of Public Health, Seoul National University, Seoul, Korea

[4]Department of Internal medicine, Soonchunhyang University College of Medicine, Seoul

[5]Department of Otorhinolaryngology-Head & Neck Surgery, Hallym University College of Medicine, Anyang, Korea

Running title: Asthma and dementia

***Correspondence:** Hyo Geun Choi

Department of Otorhinolaryngology-Head & Neck Surgery, Hallym University Sacred Heart Hospital, 22, Gwanpyeong-ro 170beon-gil, Dongan-gu, Anyang-si, Gyeonggi-do, 14068 Republic of Korea

Tel: 82-31-380-3849

Fax: 82-31-386-3860

Email: pupen@naver.com

Key words: Asthma; Dementia; Risk factors; Cohort studies; Epidemiology

Abstract

Objectives: This study investigated the risk of neurodegenerative dementia following asthma.

Design: A nested case-control study

Setting: The ≥ 60-year-old population was selected from the Korean Health Insurance Review and Assessment Service - National Sample Cohort from 2002 through 2013.

Participants and Interventions: The 11,442 dementia cases were matched with 45,768 control cases for age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia. Asthma was classified using ICD-10 codes (J45 and J46) and medication history. Dementia was identified based on ICD-10 codes (G30 and F00).

Primary and secondary outcome measures: The odds ratios (ORs) of a previous history of asthma in dementia patients were analyzed using conditional logistic regression analysis stratified for age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia. Subgroup analysis was performed according to age and sex.

Results: Overall, 22.6% (2,587/11,442) and 22.3% (10,229/45,768) of the cases in the dementia and control groups, respectively, had a previous history of asthma. The odds ratio for asthma in the dementia group was not higher than that in the control group (adjusted OR = 0.97, 95% confidence interval [95% CI] = 0.92 – 1.02, P = 0.207). All age and sex subgroups demonstrated consistent results.

Conclusions: Asthma was not related to an increased risk of dementia.

Strengths and limitations of this study

- This study was based on a large population of older adults considering the high prevalence of dementia in this age group.
- Moreover, the potential biases between the dementia and control groups were minimized by matching past medical histories as well as demographic factors.
- Although ICD-10 codes are based on the diagnosis of physicians, they lack information on the severity of disease and treatment history.

Funding: This research was supported by funding from the National Research Foundation (NRF) of Korea (NRF-2018-R1D1A1A02085328 and NRF-2017R1C1B1007696).

Competing interest: None declared.

Introduction

Dementia is an age-related neurodegenerative disease on a spectrum from mild cognitive impairment to a full-blown dementia state. Because of an aging society and improved life expectancy by virtue of advanced medical care, an increasing number of people suffer from dementia. The incidence of dementia is estimated to be approximately 14.3 per 1000 person-years in men and 17.0 per 1000 person-years in women aged ≥ 50 years old in Western countries [1]. In Korea, the prevalence of dementia was estimated to be approximately 6% – 10% [2]. Because older adults have a higher number of comorbidities such as cardiovascular and metabolic diseases, the impact of these systemic disorders on neurodegenerative changes is anticipated to grow. Consistent with these findings, numerous studies have reported associations of various chronic diseases, including hypertension, diabetes, dyslipidemia, coronary heart disease, and depression, with dementia [3-6].

Asthma is a chronic airway disease defined by typical pulmonary dysfunction and airway symptoms. The prevalence of asthma has been reported to be approximately 2% – 20% with both increasing and decreasing tendencies, depending on the ethnic group studied [7]. The incidence of asthma in Korea was reported to be stable at approximately 6.07 per 1,000 person-years [8]. In addition to the well-known type 2 helper T-cell-related asthma, various endotypes of asthma associated with multiple pathophysiologic mechanisms have been described [9]. Due to the many contributors, asthma was reported to be associated with many chronic diseases, such as hypertension, diabetes, dyslipidemia, coronary heart disease, and depression [10-13]. Dementia has also been proposed to be related to asthma. A national population study reported a 2.17-fold higher risk of dementia in asthma patients > 45 years old (95% confidence intervals [95% CI] = 1.87 – 2.52) [14]. Another national population study showed a 1.27-fold higher risk of dementia in asthma patients ≥ 20 years old (95% CI = 1.15

– 1.41) [15]. The authors of that study hypothesized that the common pathophysiology of inflammation, immune dysfunction, and cardiovascular compromise might link asthma to dementia. However, both studies used young and middle-aged adult populations. In addition, control groups were matched with asthma patients for age and sex only; thus, comorbidities such as hypertension, diabetes, and dyslipidemia were higher in the asthmatic groups. Adjusting for these comorbidities might influence the differences in the risk of dementia between the asthma and control groups.

Therefore, it was questioned whether asthma increases the risk of dementia in the older population, irrespective of other comorbid conditions. We hypothesized that the risk of dementia in asthma patients may have been overestimated in previous studies. To test this hypothesis, dementia patients were investigated for a previous history of asthma compared with the control group matched for age, sex, income, region of residence, and past medical histories of hypertension, diabetes, and dyslipidemia.

Materials and Methods

Participant Selection

Out of 1,125,691 cases with 114,369,638 medical claim codes, we included cases with a diagnosis of dementia from 2002 through 2013 (n = 13,102). Cases were also classified as dementia if a diagnosis of Alzheimer's disease (ICD-10 code: G30) or Dementia in Alzheimer's disease (F00) had been made. For accurate diagnosis, we selected only cases who were treated ≥ 2 times. We described the reliability of the diagnosis of dementia in the supplementary material (S1). The control cases who were never diagnosed with dementia were extracted from this cohort of 1,112,589 participants from 2002 through 2013.

We included cases who were diagnosed with asthma (ICD-10: J45) or status asthmaticus (J46). Among them, we selected participants who were treated ≥ 2 times and who were treated with a corticosteroid, steroid inhaler, LMMA, LTRA, or Xantine (n = 230,764). This method has been modified from a previous study [16].

The dementia cases were matched at a 1:4 ratio with patients (control group) in this cohort who had never been treated for dementia from 2002 through 2013. The control group was selected from the original population (n = 1,112,589). These subjects were matched for age, sex, income, region of residence, and past medical history (hypertension, diabetes, and dyslipidemia). To prevent a selection bias when selecting the matched cases, the control group cases were sorted using a random number order, and they were then selected from top to bottom. The matched control cases were assumed to be involved at the same time as each matched dementia case (index date). Therefore, control group subjects who died before the index date were excluded. Dementia cases for whom we could not identify enough matched cases were excluded (n = 1,148). We also excluded cases under 60 years old (n = 512). Finally, 1:4 matching resulted in the inclusion of 11,442 dementia cases and 45,768 control cases (Figure 1). However, the cases were not matched for ischemic heart disease, cerebral stroke, and depression because strict matching would have increased the number of excluded study cases due to a lack of control cases. After matching, we analyzed the cases' previous histories of asthma in both the dementia and control groups.

Variables

The cases were grouped by age using 5-year intervals as follows: 60-64, 65-69, 70-74…, and 85+ years old. Age was defined as age at the onset of dementia, and six age groups were designated. The income groups were initially divided into 41 classes (one health aid class, 20

self-employed health insurance classes, and 20 employed health insurance classes). These groups were recategorized into 5 classes (class 1 [lowest income] - class 5 [highest income]). Region of residence was divided into 16 areas according to administrative district. These regions were regrouped into urban (Seoul, Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan) and rural (Gyeonggi, Gangwon, Chungcheongbuk, Chungcheongnam, Jeollabuk, Jeollanam, Gyeongsangbuk, Gyeongsangnam, and Jeju) areas.

The past medical histories of the cases were evaluated using ICD-10 codes. For the accuracy of diagnosis, hypertension (I10 and I15), diabetes (E10-E14), and dyslipidemia (E78) were assessed if the cases were treated ≥ 2 times. Ischemic heart disease (I24 and I25) and cerebral stroke (I60-I66) were assessed if the cases were treated ≥ 1 time. Depression was defined using ICD-10 codes F31 (bipolar affective disorder) through F39 (unspecified mood disorder) recorded by a psychiatrist ≥ 2 times. Chronic obstructive pulmonary disease (COPD) was determined by J43 (emphysema) through J44 (other chronic obstructive pulmonary disease) and treatment with SABA, LABA, LAMA, or corticosteroids [17].

Statistical Analyses

A chi-square test was used to compare the rate of general characteristics between the dementia and control groups.

To analyze the odds ratio (OR) of asthma (dependent variable) with dementia (independent variable), conditional logistic regression analysis was used. In these analyses, crude (simple) and adjusted (ischemic heart disease, cerebral stroke, depression, and COPD) models were used, and 95% CIs were calculated. In these analyses, groups were stratified by age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia.

For the subgroup analyses, we divided the cases by age and sex (men < 80 years old, women < 80 years old, men ≥ 80 years old, and women ≥ 80 years old). The dividing point of the age groups was determined by median values.

Two-tailed analyses were conducted, and P values < 0.05 were considered to indicate significance. The results were analyzed using SPSS v. 22.0 (IBM, Armonk, NY, USA).

Patients and Public Involvement Statement

This national cohort study used data from the Korean National Health Insurance Service-National Sample Cohort (NHIS-NSC). The detailed description of these data was described in our previous studies[18,19]. No patients were involved in the development of the research question or the design of the study. We have no plan to disseminate the results to the cases. Because the NHIS-NSC data are based on national health claim codes, releasing the data by the researcher is not allowed legally. All data are available from the database of National Health Insurance Sharing Service (NHISS) (https://nhiss.nhis.or.kr/).

NHISS allows all of these data for any researcher who promises to follow the research ethics with some cost. If one wants to access the data described in this article, one could download it from the website after promising to follow the research ethics requirements.

Results

The rate of asthma was not higher in dementia cases (22.6% [2,587/11,442]) than in controls (22.3% [10,229/45,768], Table 1). The general characteristics (age, sex, income, region of residence, and histories of hypertension, diabetes, and dyslipidemia) of cases were identical due to matching. Higher rates of histories of ischemic heart disease, cerebral stroke,

depression, and COPD were observed in the dementia group. The adjusted OR for asthma in the dementia group was 0.97 (95% CI = 0.93-1.01, P values > 0.05, Table 2).

In the subgroup analyses, adjusted ORs for asthma were not higher in dementia cases (Table 3). Adjusted ORs were 0.88 (95% CI = 0.78 – 1.00, P = 0.050) in < 80-year-old men, 1.01 (95% CI = 0.93-1.09, P = 0.882) in < 80-year-old women, 0.95 (95% CI = 0.81-1.12, P = 0.523) in ≥ 80-year-old men, and 0.98 (95% CI = 0.89-1.09, P = 0.735) in ≥ 80-year-old women.

Discussion

Dementia patients did not demonstrate a higher rate of previous histories of asthma than the control group in the present study. This result was consistent across all age and sex subgroups. This study was based on the older adult population considering the high prevalence of dementia in these age groups. Moreover, the potential biases between dementia and control groups were minimized by matching past medical histories as well as demographic factors.

Similar to the present results, a population-based study reported a nonsignificant association between asthma and dementia in older adults [20]. They demonstrated that asthma was related to depression (OR = 2.45, 95% CI = 1.06 – 5.69) but not dementia [20]. Their results might have resulted from the exclusion criteria, adjustment for the confounding effects of chronic illnesses, psychological and social factors, and medication histories predisposing depression. Another population-based study using a twin cohort showed that the risk of dementia was not high in asthma patients [21]. The authors postulated that atopic disease could impact the occurrence of dementia [21]. Thus, the unexpected result of no significant association between asthma and dementia was speculated due to the poor survival rates of asthma patients in their cohort [21]. On the other hand, several previous studies reported a high

risk of dementia in asthma patients [14,15]. Although asthma could have an impact on the risk of dementia, this influence could not be significant when possible confounding effects were attenuated by matching the control group for comorbidities, as in the present study.

The effects of other pulmonary diseases such as COPD, on the risk of dementia have been mixed in the relation between asthma and dementia in previous studies. A number of studies reported an elevated risk of dementia in COPD patients [22,23]. The hypoxemia due to deteriorated pulmonary function was suggested to accentuate cognitive dysfunction [23]. Therefore, general pulmonary problems, rather than asthma-specific factors, could considerably contribute to the risk of dementia. Indeed, overall pulmonary disease, but not asthma alone, were related to the elevated risk of dementia in a previous study [24]. A population cohort study demonstrated that COPD or combined COPD and asthma groups had a higher risk of dementia, but not the asthma-only group (hazard ratio [HR] = 1.85, 95% CI = 1.05 – 3.28 for COPD and HR = 1.94, 95% CI = 1.16 – 3.27 for combined asthma and COPD groups) [24]. On the other hand, the current study adjusted for COPD, thus minimizing the confounding effects of COPD in assessing the association between asthma and dementia.

In addition to the confounding effects of other respiratory diseases, the influence of cardiovascular diseases and other unadjusted inflammatory or immune disorders could have mediated the association between asthma and dementia in prior studies. A number of researchers have reported that asthma is associated with inflammatory conditions in addition to those in the airway [25,26]. Asthma was related to the elevated risk of the proinflammatory conditions coronary heart disease and diabetes (HR = 1.47, 95% CI = 1.05 – 2.06, P = 0.02 for coronary heart disease and HR = 2.11, 95% CI = 1.43 – 3.13, P < 0.001 for diabetes) [25]. Likewise, multiple inflammatory processes were reported to accelerate neurodegenerative changes and dementia [27]. To exclude the impact of these confounding factors of

cardiovascular comorbidities, the matching of the control group, in addition to the adjustments with multivariable analysis, might be effective [28].

Heterogeneous biologic and phenotypic features of adult asthma could mitigate the impact of asthma on dementia in this study. Although early-onset asthma is mainly related to atopic responses, late-onset asthma includes a considerable portion of nonatopic asthma and has various pathophysiologies associated with the different endotypes of asthma [29]. Thus, the impact of asthma on dementia via atopy could have been attenuated in older adults. Atopy has been presumed to increase the risk of dementia probably by elevating the inflammatory burden [21]. Atopic patients with asthma, eczema, and rhinitis showed a 1.16-fold higher risk of dementia (95% CI = 1.01 – 1.33) [21]. However, asthma alone, relative to the control group, did not result in a higher risk of dementia [21].

The large, representative nature of the population examined here potentiated the fidelity of the analyzed results of the present study. The age of the study population was restricted to the relevant age groups of ≥ 60 years old to minimize the early-onset dementia population. Early-onset dementia, which occurs in the < 65-year-old population, is different from late-onset dementia with regard to genetics, underlying pathology, and relation to cardiovascular or metabolic disorders [30]. Therefore, the exclusion of this younger population was important to prevent the interference of specific early-onset dementia cases with the true association between asthma and dementia. We additionally analyzed the association between asthma and dementia in a ≥ 40-year-old population. The ORs of asthma in dementia patients were not high in this age group (Table S1). In addition, socioeconomic factors were matched between the dementia and control groups in this study. Because this study used a health insurance database, the conditions for the use of medical care, which is largely determined by socioeconomic factors, should be comparable between the dementia and control groups. In

addition to socioeconomic factors, other demographic and past medical histories were matched between the dementia and control groups in the present study. To evaluate the impact of matching variables on the relation between asthma and dementia, we additionally analyzed the OR of asthma in dementia cases using a control group matched for age and sex (Table S2). The results also indicated no high OR of asthma in dementia patients. The methods of classification of both asthma and dementia in our study were verified in prior studies [16] (S3 Description). However, a few limitations exist, mainly due to the lack of detailed medical information in the NHIS database. The subtypes, severity, and treatment of each disease could not be assessed. Subclinical or untreated dementia or asthma was not considered in this study. Although several confounders were matched or adjusted for in this study, there are still a number of possible unmeasured confounding factors, including smoking, alcohol consumption, and obesity. For the matched comorbidities, the matching of comorbidities could be a negative bias on the association of asthma with dementia in this study because the timing of comorbidities was distributed throughout the follow-up period. In addition, a healthy survival effect was possible because the asthma patients who died before the occurrence of dementia were excluded from this study.

Conclusion

Asthma was not related to the elevated risk of neurodegenerative dementia in this older adult population.

Authors' contributions: HGC designed the study; CM and DJO analyzed the data; SYK and HGC drafted and revised the paper; all authors approved the final version of the manuscript.

Data sharing statement

Release of the data by the researcher is not allowed legally. All data are available from the database of National Health Insurance Sharing Service (NHISS) (https://nhiss.nhis.or.kr/). NHISS allows all of these data for any researcher who promises to follow the research ethics with some cost. If one wants to access the data of this article, one can download it from the website after promising to follow the research ethics requirements.

References

1. Ahmadi-Abhari S, Guzman-Castillo M, Bandosz Pet al. Temporal trend in dementia incidence since 2002 and projections for prevalence in England and Wales to 2040: modelling study. BMJ 2017; 358:j2856.
2. Cho MJ, Lee JY, Kim BS, Lee HW, Sohn JH. Prevalence of the major mental disorders among the Korean elderly. Journal of Korean medical science 2011; 26:1-10.
3. Liang X, Shan Y, Ding Det al. Hypertension and High Blood Pressure Are Associated With Dementia Among Chinese Dwelling Elderly: The Shanghai Aging Study. Front Neurol 2018; 9:664.
4. Kim YK, Nam KI, Song J. The Glymphatic System in Diabetes-Induced Dementia. Front Neurol 2018; 9:867.
5. Bennett S, Thomas AJ. Depression and dementia: cause, consequence or coincidence? Maturitas 2014; 79:184-190.
6. Deckers K, Schievink SHJ, Rodriquez MMFet al. Coronary heart disease and risk for cognitive impairment or dementia: Systematic review and meta-analysis. PloS one 2017; 12:e0184244.
7. Sears MR. Trends in the prevalence of asthma. Chest 2014; 145:219-225.
8. Shin JY, Sohn KH, Shin JEet al. Changing patterns of adult asthma incidence: results from the National Health Insurance Service-National Sample Cohort (NHIS-NSC) database in Korea. Sci Rep 2018; 8:15052.
9. Svenningsen S, Nair P. Asthma Endotypes and an Overview of Targeted Therapy for Asthma. Front Med (Lausanne) 2017; 4:158.

10. Christiansen SC, Schatz M, Yang SJ, Ngor E, Chen W, Zuraw BL. Hypertension and Asthma: A Comorbid Relationship. The journal of allergy and clinical immunology In practice 2016; 4:76-81.

11. Perez MK, Piedimonte G. Metabolic asthma: is there a link between obesity, diabetes, and asthma? Immunology and allergy clinics of North America 2014; 34:777-784.

12. Wang L, Gao S, Yu M, Sheng Z, Tan W. Association of asthma with coronary heart disease: A meta analysis of 11 trials. PloS one 2017; 12:e0179335.

13. Gao YH, Zhao HS, Zhang FRet al. The Relationship between Depression and Asthma: A Meta-Analysis of Prospective Studies. PloS one 2015; 10:e0132424.

14. Chen MH, Li CT, Tsai CFet al. Risk of dementia among patients with asthma: a nationwide longitudinal study. J Am Med Dir Assoc 2014; 15:763-767.

15. Peng YH, Wu BR, Su CHet al. Adult asthma increases dementia risk: a nationwide cohort study. J Epidemiol Community Health 2015; 69:123-128.

16. Kim S, Kim J, Kim Ket al. Healthcare use and prescription patterns associated with adult asthma in Korea: analysis of the NHI claims database. Allergy 2013; 68:1435-1442.

17. The Korea Academy of Tuberculosis and Respiratory diseases. Clinical Practice Guideline. 2018. Available at: https://www.lungkorea.org/bbs/?code=guide.

18. Kim SY, Kim HJ, Lim H, Kong IG, Kim M, Choi HG. Bidirectional association between gastroesophageal reflux disease and depression: Two different nested case-control studies using a national sample cohort. Scientific reports 2018; 8:11748.

19. Kim SY, Lim JS, Kong IG, Choi HG. Hearing impairment and the risk of neurodegenerative dementia: A longitudinal follow-up study using a national sample cohort. Scientific reports 2018; 8:15266.

20. Ng TP, Chiam PC, Kua EH. Mental disorders and asthma in the elderly: a population-based study. International journal of geriatric psychiatry 2007; 22:668-674.

21. Eriksson UK, Gatz M, Dickman PW, Fratiglioni L, Pedersen NL. Asthma, eczema, rhinitis and the risk for dementia. Dementia and geriatric cognitive disorders 2008; 25:148-156.

22. Tondo G, De Marchi F, Terazzi Eet al. Chronic obstructive pulmonary disease may complicate Alzheimer's disease: a comorbidity problem. Neurol Sci 2018.

23. Kakkera K, Padala KP, Kodali M, Padala PR. Association of chronic obstructive pulmonary disease with mild cognitive impairment and dementia. Current opinion in pulmonary medicine 2018; 24:173-178.

24. Rusanen M, Ngandu T, Laatikainen T, Tuomilehto J, Soininen H, Kivipelto M. Chronic obstructive pulmonary disease and asthma and the risk of mild cognitive impairment and dementia: a population based CAIDE study. Current Alzheimer research 2013; 10:549-555.

25. Yun HD, Knoebel E, Fenta Yet al. Asthma and proinflammatory conditions: a population-based retrospective matched cohort study. Mayo Clin Proc 2012; 87:953-960.

26. Fenta YA, Tello N, Jung JAet al. Inflammatory bowel disease and asthma: a population-based, case-control study. Inflamm Bowel Dis 2010; 16:1957-1962.

27. Newcombe EA, Camats-Perna J, Silva ML, Valmas N, Huat TJ, Medeiros R. Inflammation: the link between comorbidities, genetics, and Alzheimer's disease. J Neuroinflammation 2018; 15:276.

28. Kim SY, Sim S, Kim HJ, Choi HG. Sudden sensory neural hearing loss is not predictive of myocardial infarction: A longitudinal follow-up study using a national sample cohort. Sci Rep 2018; 8:946.

29. Hirano T, Matsunaga K. Late-onset asthma: current perspectives. J Asthma Allergy 2018; 11:19-27.

30. Mendez MF. Early-Onset Alzheimer Disease. Neurol Clin 2017; 35:263-281.

Figure legend

Figure 1 Schematic illustration of the participant selection process that was used in the present study. Of a total of 1,125,691 cases, 11,442 dementia cases were matched with 45,768 control cases with respect to age, sex, income, region of residence, and past medical history.

Table 1 General Characteristics of Participants

Characteristics	Total participants		
	Dementia (n, %)	Control group (n, %)	P-value
Age (years old)			1.000
60-64	580 (5.1)	2,320 (5.1)	
65-69	1,289 (11.3)	5,156 (11.3)	
70-74	2,325 (20.3)	9,300 (20.3)	
75-79	2,979 (26.0)	11,916 (26.0)	
80-84	2,703 (23.6)	10,812 (23.6)	
85+	1,566 (13.7)	6,264 (13.7)	
Sex			1.000
Male	3,663 (32.0)	14,652 (32.0)	
Female	7,779 (68.0)	31,116 (68.0)	
Income			1.000
1 (lowest)	2,866 (25.0)	11,464 (25.0)	
2	1,034 (9.0)	4,136 (9.0)	
3	1,374 (12.0)	5,496 (12.0)	
4	1,884 (16.5)	7,536 (16.5)	
5 (highest)	4,284 (37.4)	17,136 (37.4)	
Region of residence			1.000
Urban	4,623 (40.4)	18,492 (40.4)	
Rural	6,819 (59.6)	27,276 (59.6)	
Hypertension	8,316 (72.7)	33,264 (72.7)	1.000
Diabetes	4,065 (35.5)	16,260 (35.5)	1.000

Dyslipidemia	3,554 (31.1)	14,216 (31.1)	1.000
Ischemic heart disease	1,707 (14.9)	6,118 (13.4)	<0.001*
Cerebral stroke	5,518 (48.2)	11,390 (24.9)	<0.001*
Depression	3,231 (28.2)	4,782 (10.4)	<0.001*
COPD	1,273 (11.1)	4,419 (9.7)	<0.001*
Asthma	2,587 (22.6)	10,229 (22.3)	0.551

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease

*Chi-square test. Significance at $P < 0.05$

Table 2 Crude and adjusted odds ratios (95% confidence interval) of asthma in dementia participants

Characteristics	Asthma			
	Crude†	P-value	Adjusted†‡	P-value
Dementia	1.02 (0.97-1.07)	0.547	0.97 (0.92-1.02)	0.207
Control	1.00		1.00	

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease

* Conditional logistic regression analyses, Significance at $P < 0.05$

† Model stratified for age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia histories.

‡ Model adjusted for ischemic heart disease, cerebral stroke, depression, and COPD histories.

Table 3 Subgroup analyses of crude and adjusted odds ratios (95% confidence interval) of asthma in dementia participants according to age and sex

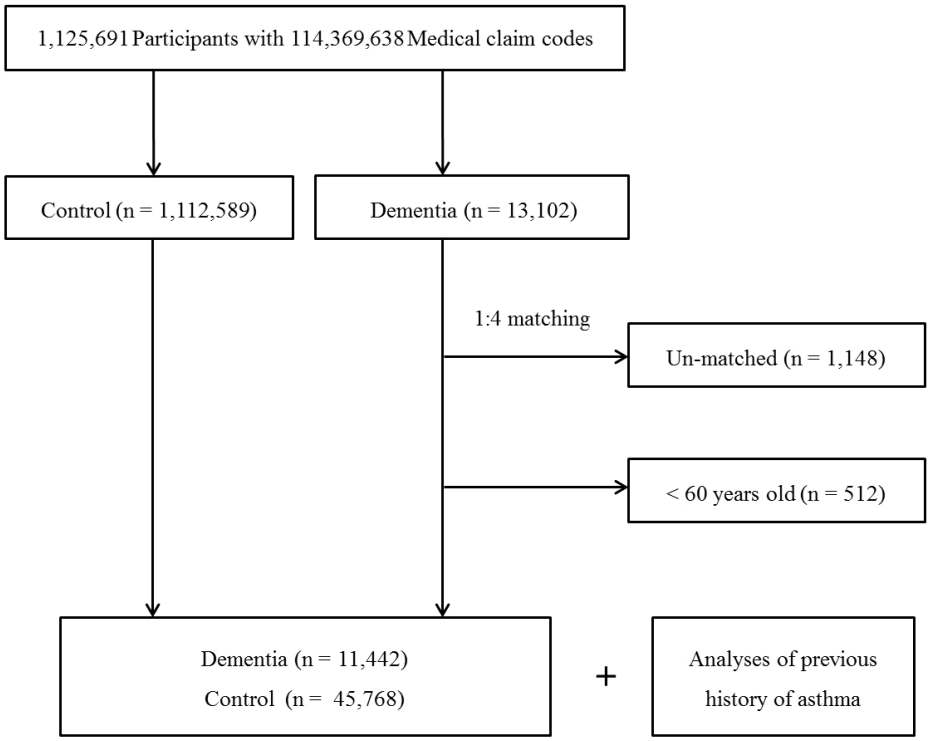
Characteristics	Asthma			
	Crude†	P-value	Adjusted†‡	P-value
Age < 80-year-old men (n = 12,455)				
Dementia	0.95 (0.85-1.06)	0.361	0.88 (0.78-1.00)	0.050
Control	1.00		1.00	
Age < 80-year-old women (n = 23,410)				
Dementia	1.05 (0.97-1.13)	0.197	1.01 (0.93-1.09)	0.882
Control	1.00		1.00	
Age ≥ 80-year-old men (n = 5,860)				
Dementia	0.98 (0.85-1.14)	0.818	0.95 (0.81-1.12)	0.523
Control	1.00		1.00	
Age ≥ 80-year-old women (n = 15,485)				
Dementia	1.02 (0.93-1.13)	0.641	0.98 (0.89-1.09)	0.735
Control	1.00		1.00	

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease

* Conditional logistic regression analyses, Significance at $P < 0.05$

† Model stratified for age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia histories.

‡ Model adjusted for ischemic heart disease, cerebral stroke, depression, and COPD histories.



S1 Table Crude and adjusted odd ratios (95% confidence interval) of asthma in dementia cases (≥40 years old)

Characteristics	Asthma			
	Crude†	P-value	Adjusted†‡	P-value
Dementia	1.02 (0.97-1.07)	0.519	0.93 (0.89-0.99)	0.013*
Control	1.00		1.00	

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease

* Conditional logistic regression analyses, Significance at $P < 0.05$

† Stratified model for age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia histories.

‡ Adjusted model for ischemic heart disease, cerebral stroke, depression, and COPD histories.

S2 Table Crude and adjusted odd ratios (95% confidence interval) of asthma in dementia cases

Characteristics	Asthma			
	Crude†	P-value	Adjusted†‡	P-value
Dementia	0.92 (0.88-0.96)	<0.001*	0.80 (0.76-0.84)	<0.001*
Control	1.00		1.00	

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease

* Conditional logistic regression analyses, Significance at $P < 0.05$

† Stratified model for age and sex.

‡ Adjusted model for income, region of residence, hypertension, diabetes, dyslipidemia, ischemic heart disease, cerebral stroke, depression, and COPD histories.

S3 Description of diagnosis of dementia

Dementia was categorized if the participants were diagnosed Alzheimer's disease (G30) or Dementia in Alzheimer's disease (F00). We selected if the participants were treated ≥ 2 times.

In this national sample cohort, 123,025 participants were ≥ 65 years old in 2012 year. Among them, 9,740 (7.9%) of participants were categorized as dementia according to our methods (5.4% [n =2,758] in male; 9.7% [n= 6,982] in female).

We could compare these results of central dementia center of Korea (www.nid.or.kr) which is controlled by Ministry of Health and Welfare of Korea. The earliest data was 2012 year, and it was available in ≥ 65 years old. According to their data, the prevalence of dementia (Alzheimer's disease, and others) except vascular dementia were 7.63% (4.47% in male; 9.85% in female).

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (p1-2)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found (p2)
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported (p4-5)
Objectives	3	State specific objectives, including any prespecified hypotheses (p5)
Methods		
Study design	4	Present key elements of study design early in the paper (p5-6)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection (p5-6)
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (p5-7) *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed (p7) *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable (p7-8)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group (p5-7)
Bias	9	Describe any efforts to address potential sources of bias (p5-8)
Study size	10	Explain how the study size was arrived at (p7)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why (p7-9)
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (p8)
		(*b*) Describe any methods used to examine subgroups and interactions (p8-9)
		(*c*) Explain how missing data were addressed (p6)
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed (p6) *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (p8)
		(b) Give reasons for non-participation at each stage (p6)
		(c) Consider use of a flow diagram (p6)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (p8)
		(b) Indicate number of participants with missing data for each variable of interest (p6)
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time (p8-9)
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (p8-9)
		(*b*) Report category boundaries when continuous variables were categorized (p8-9)
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses (p8-9)
Discussion		
Key results	18	Summarise key results with reference to study objectives (p9)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias (p11-12)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence (p9-11)
Generalisability	21	Discuss the generalisability (external validity) of the study results (p9-11)
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based (p3)

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.