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Original Article

Chronic Obstructive Pulmonary Disease as a Risk Factor of Alzheimer's Disease among Elderly Population in Taiwan: A Population-Based Retrospective Cohort Study

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SUMMARY

Purpose: To evaluate the association between chronic obstructive pulmonary disease (COPD) and Alzheimer's disease (AD) among the elderly and to use those findings to guide the formulation of suggestions aimed at improving clinical and health policies.
Methods: This nationwide population-based cohort study used data from the National Health Insurance Research Database for the period 2000–2013 to identify patients aged 65 years or older who were diagnosed with COPD (i.e., the case group). The control group was formed by performing 1:1 matching for age, sex, insurance premiums (as a proxy for salary), and the Charlson Comorbidity Index. Kaplan Meier's Survival Curves and the time-dependent Cox proportional-hazards regression model were used to assessing the association between COPD and AD.
Results: After matching related covariates, 13,438 subjects were respectively assigned to the case and control groups. The cumulative incidence of AD was higher in the COPD group than in the non-COPD group (p-value for log-rank test < 0.001). The hazard ratio of AD in the case group was 1.04 times (95% confidence interval: 1.02–1.06, p = 0.002) that in the control group, based on the competing risk model.
Conclusions: This study observed a positive correlation between COPD and AD; therefore, health policy related to the prevention of AD should treat COPD as a risk factor rather than a co-morbidity of AD.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of death among the elderly.[1] Statistics from the World Health Organization (WHO) indicate that in 2014, there were an estimated 64 million patients with COPD worldwide. Three million of those patients died as a direct result of COPD within the same year, accounting for 5% of the global mortality rate.[2] The WHO has also predicted that by 2030, COPD will be the third most prevalent cause of death in the world.[2] Clearly, the prevention and treatment of COPD deserve serious consideration.

Alzheimer's disease (AD) is a contributing factor in 60% of dementia cases, making it one of the most prevalent diseases among geriatric populations.[3,4] The WHO has reported that worldwide, an estimated 35.6 million patients had AD in 2010 and that number has been growing by 7.7 million per year (equating to a new patient every 4 seconds). In efforts to counter this threat, global expenditures on AD-related treatment have reached 60.4 million USD per year.[5–7] It was estimated by the end of 2017, the number of people living with dementia would exceed 270,000.[8] Population statistics from the National Development Council and known dementia prevalence rates in the community (inclusive of AD) indicate that the number of dementia patients in Taiwan will exceed 620,000 by 2046.[8] In response to the staggering growth rate of the AD population and the substantial resources required to treat them, the WHO has suggested that every country should consider AD a national health priority.[5,9]

From a clinical viewpoint, COPD and AD are closely related; however, few studies have examined the risk factors of these diseases in geriatric populations, and findings obtained up to this point have presented considerable variability.[10–13] A number of studies have noted a degree of correlation between COPD and AD; though, they have thus far been unable to present a clear picture of how COPD could lead to mild cognitive impairment (MCI). One plausible explanation is that hypoxemia or hypercarbia resulting from COPD leads to nerve cell damage, thereby reducing cognitive function and/or leading to MCI, which in turn predisposes the individual to AD.[11,13,14]

The lack of a definitive connection between COPD and AD based on demographic evidence (essential for external validity) renders existing findings inapplicable to the formulation of public health policy or the advancement of clinical practice.[15–17] Our objective in the current study was to determine whether a relationship exists between COPD and AD using data from the National Health Insurance Research Database (NHIRD) in Taiwan.

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2. Methods

2.1. Research design and data source

This retrospective cohort study was conducted using a random sample of 1 million enrollees in the 2010 Registry for Beneficiaries, which is maintained by the Bureau of National Health Insurance. NHIRD data collected from insurance claims include a patient's sex, age, payroll bracket, insurance provider, and medical records. The medical records include five diagnoses; five procedural codes from the ICD-9-CM (International Classification of Disease, 9th Version, Clinical Modification); and the monetary charges for all examinations, tests, treatments, and therapies. ICD-9-CM codes are scrutinized by automated software systems as well as IT professionals to ensure high reliability and validity. The quality of this database has led to its adoption in a wide range of studies.[18] NHIRD data are anonymized before being transferred to the National Health Research Institute for public access.[19] The fact that the data source is anonymized and exists in the public domain exempted the present study from reviews by the Institutional Review Board of Taipei Veterans General Hospital (IRB-TPEVGH No: 2015-11-001BC).

2.2. Samples

The patient selection process is illustrated in Figure 1. Briefly, samples were drawn from patients newly diagnosed with COPD between 2003 and 2006. Note that inclusion required two confirmed diagnoses in accordance with ICD-9-CM codes 490-492, 494, or 496.[13] Patients who had been diagnosed with AD (ICD-9-CM codes 290.40-290.43, Table 1) at least 3 years prior to the sampling period (2000–2002) were excluded. The date of COPD diagnosis was considered the index date for the COPD group. The non-COPD group was composed of persons who had never been diagnosed with COPD. Controls from the LHID 2005 were carefully matched with COPD patients at a ratio of 1:1 in terms of age, sex, insurance premiums, and the Charlson Comorbidity Index (CCI). The index date for the non-COPD control group was the same as the COPD patients to whom they were matched. All subjects with a history of AD prior to the index date were excluded. There was an even 1:1 distribution of patients in the two groups (13,438 patients in each). We then compared the two groups in terms of AD incidence throughout a follow-up period of seven years.

2.3. Study variables

Patient variables included the following: gender, age, the Charlson Comorbidity Index (CCI), a history of COPD (initial confirmation of COPD and > 3 outpatients visits), insurance premiums, and occupation. The dependent variable in this study was the presence/absence of AD, defined as AD diagnosis within seven years after the index date of COPD.

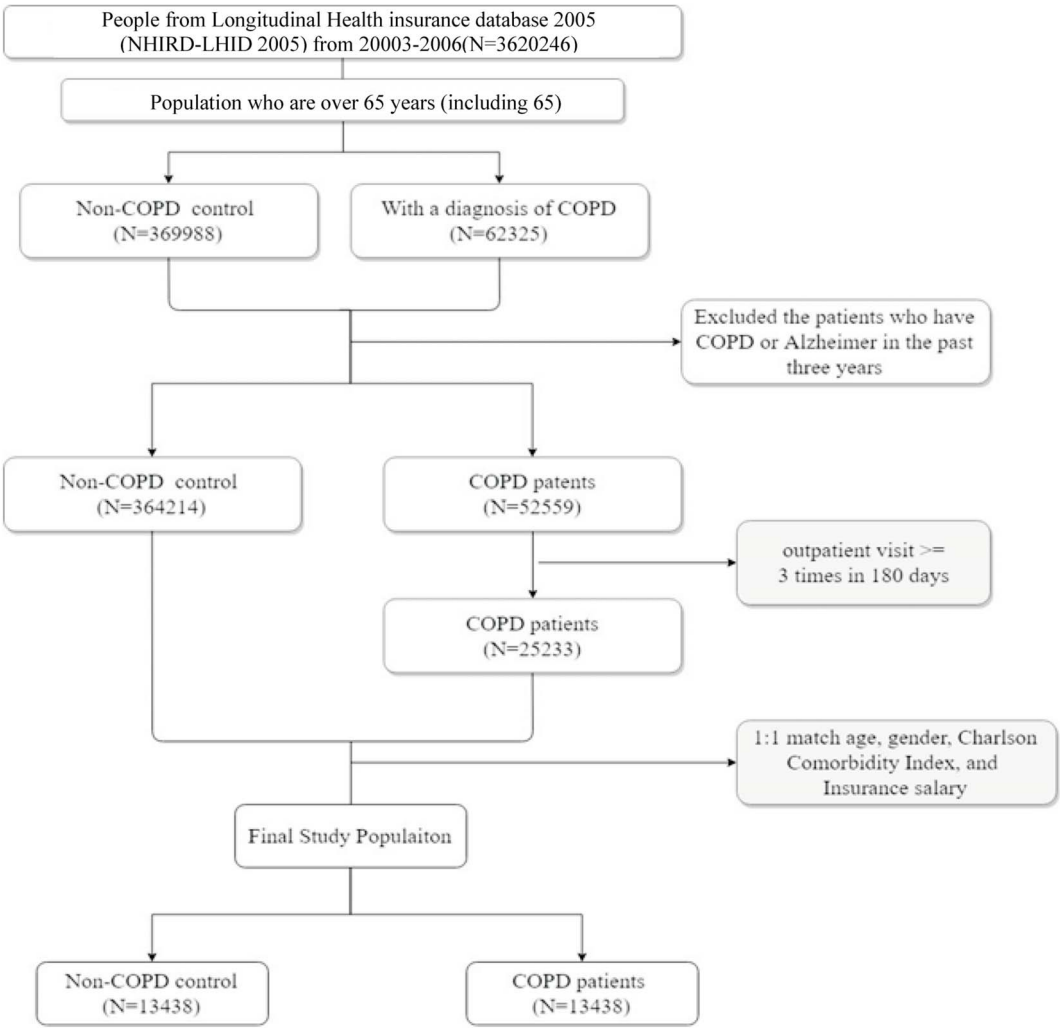


Figure 1. Flow chart of selection of the study population.

Table 1
National Health Insurance's prescription standards for Alzheimer's disease.

Prior Review	Division	Diagnostic Evidence	Proof
1st Application	Neurology Psychiatry	NINDS-ADRDA, DSM-IV ICD-9-CM o(ICD-10)	1. One of CT, MRI, or Hachinski ischemic scale results 2.CBC, VDRL, BUN, Creatinine, GOT, GPT, T4, and TSH tests 3. Case abstract 4. Diagnosis standards for AD 5. MMSE or CDR results
2nd Application	To be reviewed every 6 months for MMSE or CDR results. Prescription to stop if MMSE results are 2 score points lower than when treatment started, or CDR drops 1 level.		1. Mild to moderate dementia (MMSE score 10–26 or CDR level 1 or 2) 2. Moderate to severe dementia (MMSE score 10–14 or CDR level 2) Prescription to stop if MMSE results are more than 2 score points lower than when treatment started, or CDR drops 1 level.

NINDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; DSM-IV, diagnostic and statistical manual of mental disorders; CT, computed tomography; MRI, magnetic resonance imaging; CBC, complete blood count; VDRL, Venereal Disease Research Laboratory; BUN, blood urea nitrogen; GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; T4, Thyroxine Test; TSH, thyroid-stimulating hormone; MMSE, Mini-Mental State Examination; CDR, clinical dementia rating.

2.4. Statistical analysis

All statistical analysis was performed using the suite SAS version 9.4 (SAS Institute, Cary, NC, USA). Classification variables were presented as numbers and percentages, whereas continuous variables were presented using the mean and standard deviation. Chi-square tests were used to determine whether any differences existed in the distributions of COPD occurrence values. Fisher's exact test was used in cases where the number of expected values was less than 5. Independent t-tests were used to determine differences between the means of continuous variables. Specifically, these tests were used to determine the time interval between confirmation of COPD and the onset of AD and whether any continuous variables differed significantly in terms of mean values or standard deviation. Kaplan-Meier survival analysis was used to derive survival curves and characterize the influence of COPD on the probability distribution of AD.

Note that co-morbidities may have been present at baseline or may have developed during the follow-up period. Thus, after adjusting for potentially confounding factors (sex, age, insurance status, and payroll bracket), the Cox time-dependent proportional hazard model was used to determine the likelihood (hazard ratio) that patients with COPD would contract AD. To avoid the impact of death competing with the risk of AD, we also performed the Fine and Gray's competing risk analysis considering all competing causes of death.[20,21] In the current study, patients who were withdrawn from the NHI system were defined as deaths.22 A two-sided p value of < 0.05 was considered statistically significant.

3. Results

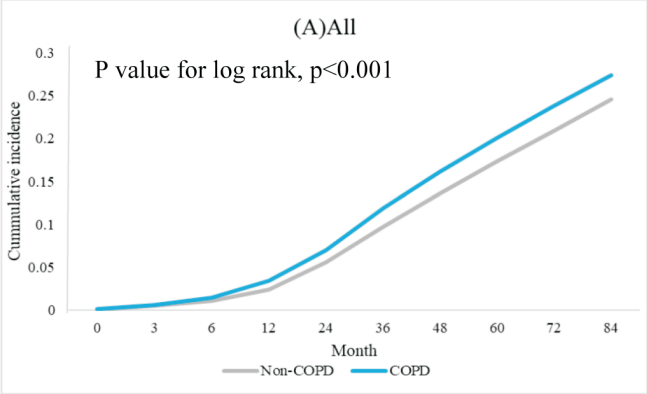
Table 2 lists the distribution of demographic variables in the COPD and control groups. The final study population comprised a total of 26,876 patients, including 13,438 in the COPD group and 13,438 in the control group. The two groups were carefully matched in terms of age, sex, CCI, and insurance salary distribution.

Figure 2(A) presents the cumulative incidence curves of COPD patients in developing AD. In both groups, the p-value for log-rank tests attained the level of significance ($p < 0.001$), wherein the cumulative incidence of AD was higher in the COPD group than in the non-COPD group. As shown in Figures 2(B) and 2(C), the two groups differed significantly in the number of male patients but not in the number of female patients.

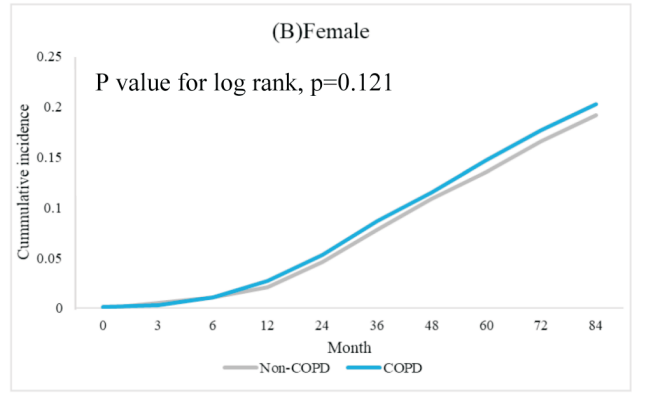
Overall, the number of patients who developed AD was significantly higher in the control group than in the COPD group. In the absence of a competing risk in the model, CCI and COPD were identified as risk factors for AD. The risk of AD was 0.76 times lower in the COPD group than in the non-COPD group (95% CI: 0.66–0.87). Table 3 lists the degree of correlation between specific variables and the risk of AD in the COPD group. Work type (labor or non-labor) was not significantly correlated with the risk of AD. Specifically, patients identified as laborers were 1.04 times (95% CI: 0.86–1.26) more likely to develop AD than were their non-laborer counterparts; however, this difference was not significant. Similarly, no significant correlation was observed between the risk of AD and insurance premiums. The risk of AD was found to increase significantly with age (hazard ratio (HR): 1.05; 95% CI: 1.04–1.06) and CCI (HR: 1.30; 95%

Table 2
Baseline characteristics between chronic obstructive pulmonary disease (COPD) and control group (n = 26,876).

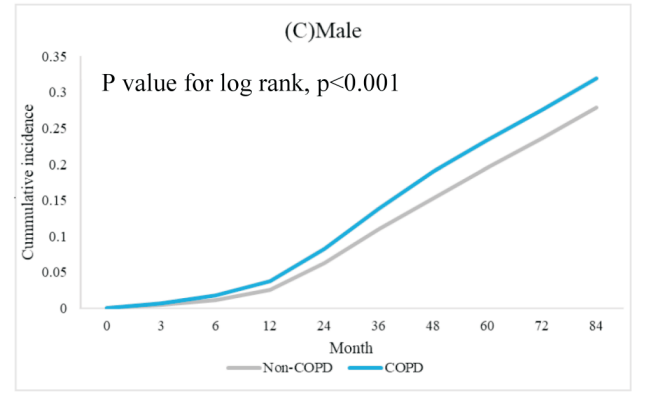
Variables	COPD group (n = 13438)	Non-COPD group (n = 13438)	p-value
	N (%) or Mean ± SD	N (%) or Mean ± SD	
Age (yrs)	74.88 ± 6.72	74.88 ± 6.72	0.989
Charlson Comorbidity Index	5.55 ± 1.84	5.57 ± 1.87	0.384
Insurance salary (NT dollars)	7625.05 ± 9917.14	7629.70 ± 9936.13	0.954
Sex			1.000
Male	8271 (61.5%)	8271 (61.5%)	
Female	5167 (38.5%)	5167 (38.5%)	
Labor			0.089
Yes	5857 (43.6%)	5719 (42.6%)	
No	7581 (56.4%)	7719 (57.4%)	



Time (month)	0	3	6	12	24	36	48	60	72	84
Incidence										
Non-COPD	0.000	0.005	0.011	0.024	0.056	0.097	0.136	0.173	0.209	0.246
COPD	0.001	0.006	0.015	0.034	0.07	0.119	0.161	0.201	0.238	0.274



Time (month)	0	3	6	12	24	36	48	60	72	84
Incidence										
Non-COPD	0.000	0.005	0.011	0.021	0.046	0.078	0.109	0.135	0.166	0.192
COPD	0.001	0.003	0.011	0.027	0.053	0.087	0.115	0.147	0.177	0.203



Time (month)	0	3	6	12	24	36	48	60	72	84
Incidence										
Non-COPD	0.000	0.005	0.011	0.026	0.063	0.11	0.153	0.196	0.236	0.279
COPD	0.000	0.007	0.018	0.038	0.082	0.139	0.19	0.234	0.276	0.319

Figure 2. The overall (A) and sex specific (B, C) Kaplan-Meier curves for contracting Alzheimer's disease between case (COPD) and control (non COPD) groups.

CI: 1.23–1.39). Females were 1.03 times more likely to suffer from AD as males (95% CI: 0.90–1.19); however, this difference was not significant. Based on the competing risk in the model, all of the variables were significantly correlated with the risk of AD, including insurance premiums: CCI (HR: 1.38, 95% CI: 1.35–1.40), sex (HR: 1.12, 95% CI: 1.10–1.15), COPD (HR: 1.04, 95% CI: 1.02–1.06), age (HR: 1.021, 95% CI: 1.019–1.023), and type of labor (HR: 0.97, 95% CI: 0.94–1.00).

4. Discussion

4.1. Correlation between chronic obstructive pulmonary disease and Alzheimer's disease: clinical implications

After adjustment for confounding factors based on the competing risk model in this study, our results indicate that a history of COPD significantly increases the risk of developing AD. Empirical studies on the influence of COPD on the onset of AD have been performed by Derkacz et al. (2007),[11] Kozora et al. (1999),[23] and Negewo et al. (2014).[16] The results from all of these studies indicated a significant positive correlation between a history of COPD and the incidence of AD. There remains some debate as to the means by which COPD affects AD; however, there appears little doubt that preventing COPD would have a corresponding effect on lowering the incidence of AD.

Considering the findings in previous studies, it was not surprising that age was identified as a significant risk factor for AD. One study in Finland in which participants were followed for more than 25 years reported that the risk of developing MCI was nearly twice as high among patients who suffered COPD during middle age than among those who developed COPD later in life. However, those results could be interpreted to mean that the elderly patients did not survive long enough to develop cognitive impairments.[24]

Eriksson et al. (2008) focused on the relationship between the risk of AD and dementia, asthma, eczema, and rhinitis.[25] That study though did not include COPD. They found that patients who suffered from asthma, eczema, rhinitis, or any type of atopy faced an elevated risk of AD. There was the possibility which was hard to follow up population who had COPD and AD at the same time, one reason that the study didn't include COPD was because it may have been difficult to do follow-ups with COPD patients.[21] Scarlata et al. reported elevated mortality rates among patients with restrictive respiratory diseases. That study also identified cognitive dysfunction as a risk factor for mortality over the long term.[26] Those two studies provided evidence that COPD and AD increase the risk of mortality. It should be noted, however, that many COPD patients die before developing AD, and many AD patients die before developing COPD.[26,27]

Liao et al. used NHIRD data to examine the influence of COPD on the risk of developing dementia. They found that the likelihood of developing dementia (including AD and Parkinson's disease) was 1.74 times higher among patients with a history of COPD than in the

Table 3
Factors of Alzheimer disease at the end of follow-up stratified by variables listed in the table by using time-dependent Cox regression and Fine and Gray's competing risk model (n = 26,876).

Alzheimer disease	No competing risk in the model				Competing risk in the model			
Variables	HR	95% CI		p-value	HR	95% CI		p-value
		Lower	Upper			Lower	Upper	
Age (yrs)	1.05	1.04	1.06	< 0.001	1.021	1.019	1.023	< 0.001
Charlson Comorbidity Index	1.30	1.23	1.39	< 0.001	1.38	1.35	1.40	< 0.001
Insurance salary	1.00	1.00	1.00	----	1.00	1.00	1.00	----
Sex (female vs. male)	1.03	0.90	1.19	0.66	1.12	1.10	1.15	< 0.001
Labor (yes vs. no)	1.04	0.86	1.26	0.69	0.97	0.94	1.00	0.03
COPD (yes vs. no)	0.76	0.66	0.87	< 0.001	1.04	1.02	1.06	0.002

general population (HR: 1.74, 95% CI: 1.55–1.96).[13] Note that the data used in that study were collected between 2002 and 2012, which is close to the period from which we obtained the longitudinal data in this study. Note, however, that our cohort study used 1:1 matching and rigorous standards in the selection of AD samples, thereby enhancing the reliability of our results.

Schou et al. (2012) examined the correlation between COPD and cognitive dysfunction in 665 COPD patients with 394 control patients.[28] They found that only extremely acute cases of COPD were correlated with cognitive function;[28] however, the reason(s) for this has yet to be elucidated. It should be noted that the focus of that study was cognitive dysfunction rather than AD, and they investigated correlations rather than causal relationships. Thus, their results should not be considered as reliable as the findings in the current study.

Among 8,089 residents of residential care facilities in the US, Wheaton et al. (2010) estimated the prevalence of COPD at 12.4%.[29] Marcon et al. (2016) investigated the underlying causes of death among local residents of Verona, Italy, and found that 7.9% of the coroner reports mentioned COPD as a cause.[31] In an examination of death registries in Lazio, Italy, Faustini et al. (2007) discovered that COPD was implicated in the deaths of 2.39 males and 1.91 females for every 10,000 people.[31] All of the aforementioned studies indicate that COPD is a serious disease.

According to Akushevich et al. (2013), who investigated the prevalence trends of 19 chronic diseases in the US between 1992 and 2005, the occurrence of COPD has been declining (average annual percentage change: -5.14%; 95% CI: -6.78% to -3.47%), whereas the occurrence of AD has been increasing (average annual percentage change: 3.96%; 95% CI: 2.62% to 5.26%).[1] Considering that both COPD and AD are related to age, this apparent negative correlation is worthy of further investigation. Note that Akushevich et al. (2013) were unable to offer a satisfactory explanation for their findings.[1]

In an investigation into the mortality rates of various diseases, Singh and Siahpauh (2014) observed gradual increases in the gap between COPD mortality rates in urban and rural areas during two periods (1990–1992 and 2005–2009).[32] Sommer et al. (2015) reported that lower socioeconomic status, residing in a rural area, and being from a low-income country were all correlated with the prevalence of COPD.[9] Muka et al. (2015) reported that the prevalence of COPD is increasing among people of lower socioeconomic status and those living in rural areas.[33] Those results are in agreement with our findings in the present study, in which insurance status and payroll bracket (indicators of socioeconomic status) were significantly correlated with AD. This is an indication that measures aimed at preventing COPD among laborers and/or people from a low socioeconomic background should be pursued.

4.2. Methodological considerations

A number of limitations should be considered in interpreting the results of the current study. First, the data source of this study was the NHIRD, which lacks data pertaining to relevant clinical variables, such as laboratory data and pathology findings, thereby opening the door to misclassification bias. Second, the secondary data used in this study should be interpreted conservatively. The NHIRD is a reliable source that has been used in a large number of studies; however, the insurance information contained in this database may have compromised the reliability of our research findings. Third, excluding subjects with a history of AD from the COPD cohort led to an underestimation of the overall disease burden of AD. Fourth, despite our efforts to mitigate the effects of confounding factors (i.e., matching and adjusting for known confounders), there is no way to eliminate these effects. Fifth, COPD and AD may be linked by inflammation-related conditions. Further analysis should be conducted to clarify the exacerbation of the frequency of COPD with exacerbation and the risk of AD. Finally, due to a lack of data pertaining to the medications used in the treatment of COPD (e.g., steroids), we were unable to examine the potential impact of medications on the association between COPD and AD.

5. Conclusions

This study observed a positive correlation between COPD and AD; therefore, health policy related to the prevention of AD should treat COPD as a risk factor rather than a co-morbidity of AD. A multidisciplinary approach should be adopted to identify the most effective clinical treatment for AD.

Competing interests

The authors have no proprietary interest in any aspect of this study.

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Data sharing statement

All data underlying the findings are within the paper.

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