

The association between adherence and dementia in chronic obstructive pulmonary disease

Kuang-Ming Liao, MD, PhD^a, Chung-Yu Chen, PhD^{b,c,d,*}

Abstract

Our previous studies have shown that patients with chronic obstructive pulmonary disease (COPD) have an increased risk of dementia and that COPD combined with dementia confers an increased risk of acute respiratory dysfunction, severe sepsis, and hospital mortality. The aim of this study was to investigate whether medication adherence can decrease the risk of dementia in COPD.

This retrospective study enrolled COPD patients from 1 million beneficiaries randomly sampled from all beneficiaries in Taiwan. We excluded COPD patients not prescribed a bronchodilator or those using theophylline or short-acting β_2 -agonists for <1 year. To ensure a sufficient observation period, we excluded patients diagnosed with dementia within 1 year after the diagnosis of COPD or those prescribed bronchodilators after the diagnosis of dementia. Patients with COPD and a history of severe mental disorders were also excluded.

There was a total of 13,015 first diagnoses of COPD from 1998 to 2012, of whom 9,489 had a proportion of days covered (PDC) <80% and 1,206 had a PDC \geq 80% before matching. In the high PDC group, 226 (18.74%) patients had acute exacerbations of COPD and were hospitalized within 1 year after diagnosis. Compared with the PDC <80% group, the PDC \geq 80% group had a risk of dementia with an adjusted hazard ratio of 0.88, but there were no statistically significant differences (95% confidence interval, 0.57–1.35).

Medication adherence to bronchodilators may not modify the risk of dementia in patients with COPD.

Abbreviations: AD = Alzheimer's disease, CI = confidence interval, COPD = chronic obstructive pulmonary disease, HR = hazard ratio, LABA+ICS = long-acting β_2 -agonists and inhaled corticosteroids, LABAs = long-acting β_2 -agonists, LAMAs = long-acting muscarinic antagonists, NTD = New Taiwan Dollar, PD = Parkinson's disease, PDC = proportion of days covered, SABA = short-acting β_2 -agonists.

Keywords: adherence, chronic obstructive pulmonary disease, dementia

1. Introduction

The number of people living with dementia worldwide is currently estimated at 47 million and is projected to increase to 75 million by 2030; despite these figures, a small number of studies show modifiable risk factors associated with dementia.

Patients with chronic obstructive pulmonary disease (COPD) have a systemic inflammatory status, and inflammatory cytokines can cause neuronal damage and result in neurodegenerative disorders. COPD is one of the comorbidities showing increasing evidence of an association with cognitive dysfunction and

dementia.^[1] Moreover, COPD patients with dementia have increased rates of severe sepsis, acute respiratory failure, and mortality.^[2] Therefore, it is currently of great interest to clarify which features predict progression to dementia and identify modifiable risk factors. The aim of our study was to investigate whether medication adherence in patients with COPD can decrease the risk of dementia.

2. Materials and methods

2.1. Study population

We retrieved our retrospective study sample from 1 million beneficiaries randomly sampled from all beneficiaries registered in 2005. All medical records from January 1, 1998 to December 31, 2013, for these 1 million beneficiaries were available, including inpatient claims, outpatient claims, and prescription drugs.

In this cohort study, the eligible subjects were patients who received an outpatient diagnosis or discharge diagnosis of COPD (ICD-9-CM codes: 490–492, 496) and were >40 years of age between January 1, 1998 and December 31, 2012. Only the first COPD diagnosis was enrolled. The first date of a diagnosis of COPD was defined as the index date. We used the presence of Alzheimer's disease (AD) or Parkinson's disease (PD) to represent dementia.^[3] We excluded patients with a previous diagnosis of asthma (ICD-9-CM code: 493), AD (ICD-9-CM code: 331), or PD (ICD-9-CM code: 332). We further excluded COPD patients not prescribed long-acting bronchodilators, including long-acting β_2 -agonists (LABAs), long-acting muscarinic antagonists (LAMAs), or long-acting β_2 -agonists and inhaled corticosteroids

Editor: Chaur-Jong Hu.

The authors have no funding and conflicts of interest to disclose.

^a Department of Internal Medicine, Chi Mei Medical Center, Chiali, ^b Master Program in Clinical Pharmacy, School of Pharmacy, Kaohsiung Medical University, Kaohsiung, ^c Department of Pharmacy, Kaohsiung Medical University Hospital, Kaohsiung, ^d Department of Medical Research, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan.

* Correspondence: Chung-Yu Chen, No. 100, Shiquan 1st Rd., Sanmin Dist., Kaohsiung 807, Taiwan (ROC) (e-mail: jk2975525@kmu.edu.tw).

Copyright © 2019 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Medicine (2019) 98:20(e15646)

Received: 22 January 2019 / Received in final form: 26 March 2019 / Accepted: 16 April 2019

<http://dx.doi.org/10.1097/MD.00000000000015646>

(LABA+ICS). We also excluded COPD patients who had been using theophylline or short-acting β 2-agonists (SABA) for <1 year.

To ensure that we had a sufficiently long observation period to study the effect of adherence, we excluded patients diagnosed with dementia within 1 year after the diagnosis of COPD or those prescribed bronchodilators (LABA, LAMA, LAMA+ICS, theophylline, or SABA) after the diagnosis of dementia. Patients with COPD and a history of severe mental disorders (ICD-9-CM codes 291–298) were also excluded. These conditions included alcohol-induced mental disorders, drug-induced mental disorders, transient mental disorders due to conditions classified elsewhere, persistent mental disorders due to conditions classified elsewhere, schizophrenic disorders, episodic mood disorders, delusional disorders, and other nonorganic psychoses.

The severity of COPD was classified into 2 groups. The severe group included patients admitted to the hospital for COPD exacerbation within 1 year after the index date with discharge diagnoses of COPD (ICD-9-CM codes: 490–492, 496). The other patients were classified into the nonsevere group.

We used the proportion of days covered (PDC) to evaluate medication adherence in the COPD patients, which was defined as the proportion of days in the measurement period “covered” by prescription claims for the same medication or another (LABA, LAMA, LAMA+ICS, theophylline, or SABA) in its therapeutic category. The measurement period for adherence lasted from the index date to when an outcome occurred, death, or December 31, 2013. Adherence was divided into high PDC ($\geq 80\%$) and low PDC ($< 80\%$) groups. We also measured the PDC in different groups as follows: $\geq 70\%$ and $< 70\%$, $\geq 60\%$ and $< 60\%$, $\geq 50\%$ and $< 50\%$. The high PDC ($\geq 80\%$) was chosen to allow the medication to have a reasonable likelihood of achieving most of the potential clinical benefit. Monthly income was categorized as follows: <New Taiwan Dollar (NTD) \$20,000, NTD \$20,000 to 40,000, and >NTD \$40,000. This study has received the approval by the Institutional Review Board (IRB) of the Chi Mei Medical Center, Taiwan (IRB no. 10705-E03). Informed consent from the participants was waived because the NHIRD contains de-identified information.

2.2. Statistical analysis

We first described the demographic characteristics and comorbidities of COPD patients with a high or low PDC. Student *t* test was used to estimate mean differences in continuous variables, and the χ^2 test was used for categorical variables. The level of urbanization was categorized into 4 levels based on the population density of the patient’s area of residence, where “1” was most urbanized and “4” was the least urbanized. A Cox proportional hazard regression model with adjustment for potential confounders was used to assess the risk of dementia. The potential confounders included medication adherence (PDC), COPD severity, sex, age, urbanization, and comorbidities, including coronary artery disease, stroke, hyperlipidemia, hypertension, and diabetes.

We also performed Kaplan–Meier analysis to compare the incidence of dementia in COPD patients with a high and low PDC. A *P* value of <.05 was considered to indicate statistical significance. All statistical analyses were performed using Statistical Analysis Software (SAS), version 9.3 (SAS Institute Inc., Cary, NC).

3. Results

Table 1 lists the demographic characteristics and comorbidities of the COPD patients with a PDC <80% and a PDC $\geq 80\%$ before matching. There was a total of 13,015 first diagnoses of COPD from 1998 to 2012 (Fig. 1), of whom 9,489 had a PDC <80% and 1,206 had a PDC $\geq 80\%$ before matching. In the high PDC group, 226 (18.74%) patients had acute exacerbations of COPD and were hospitalized within 1 year after the diagnosis of COPD, which was higher than the percentage in the low PDC group, of whom only 3.43% had acute exacerbations. The percentage of male patients was higher than that of females in both groups. Approximately 36% of the patients were 64 years of age or younger, and 23% of the patients were 75 years of age or older in the PDC $\geq 80\%$ group. Comorbidities including hyperlipidemia and diabetes were significantly higher in the PDC $\geq 80\%$ group than in the PDC <80% group before matching. There were no significant differences in the prevalence of cancer.

Table 2 lists the demographic characteristics and comorbidities of the COPD patients with a PDC <80% and a PDC $\geq 80\%$ after matching for age, sex, and COPD severity.

Table 3 shows the adjusted hazard ratio (HR) for the risk of dementia in COPD patients among a PDC <80% and a PDC $\geq 80\%$ and different factors before matching. Compared with COPD patients with a PDC <80%, those with a PDC $\geq 80\%$ had a risk of dementia with an adjusted HR of 1.07, but the difference was not statistically significant (95% confidence interval [CI],

Table 1
Demographic characteristics and comorbidities in COPD patients with a PDC <80% and those with a PDC $\geq 80\%$ before matching.

Variable	PDC <80%	PDC $\geq 80\%$	P
	N = 9489 n (%)	N = 1206 n (%)	
Severity			
Nonsevere	9164 (96.57)	980 (81.26)	<.01
Severe	325 (3.43)	226 (18.74)	
Sex			
Female	3479 (36.66)	153 (12.69)	<.01
Male	6010 (63.34)	1053 (87.31)	
Age stratification			
≤ 64	4986 (52.55)	437 (36.24)	<.01
65–74	3044 (32.08)	490 (40.63)	
≥ 75	1459 (15.38)	279 (23.13)	
Urbanization ^c			
1 (highest)	2070 (21.81)	281 (23.30)	.63
2	4254 (44.74)	539 (44.69)	
3	1679 (17.69)	204 (16.92)	
4 (lowest)	1495 (15.76)	182 (15.09)	
Comorbidity			
CAD	2448 (25.8)	318 (26.37)	.67
Stroke	1409 (14.85)	174 (14.43)	.70
Hyperlipidemia	1445 (15.23)	130 (10.78)	<.01
Hypertension	4704 (49.57)	565 (46.85)	.07
Diabetes	1778 (18.74)	177 (14.68)	<.01
Head injury	295 (3.11)	37 (3.07)	.94
Cancer	946 (9.97)	111 (9.2)	.40
Income (NTD)			
<20,000	5933 (62.53)	823 (68.24)	<.01
20,000–40,000	3145 (33.14)	357 (29.60)	
>40,000	411 (4.33)	26 (2.16)	

CAD = coronary artery disease, COPD = chronic obstructive pulmonary disease, NTD = New Taiwan Dollar, PDC = proportion of days covered.

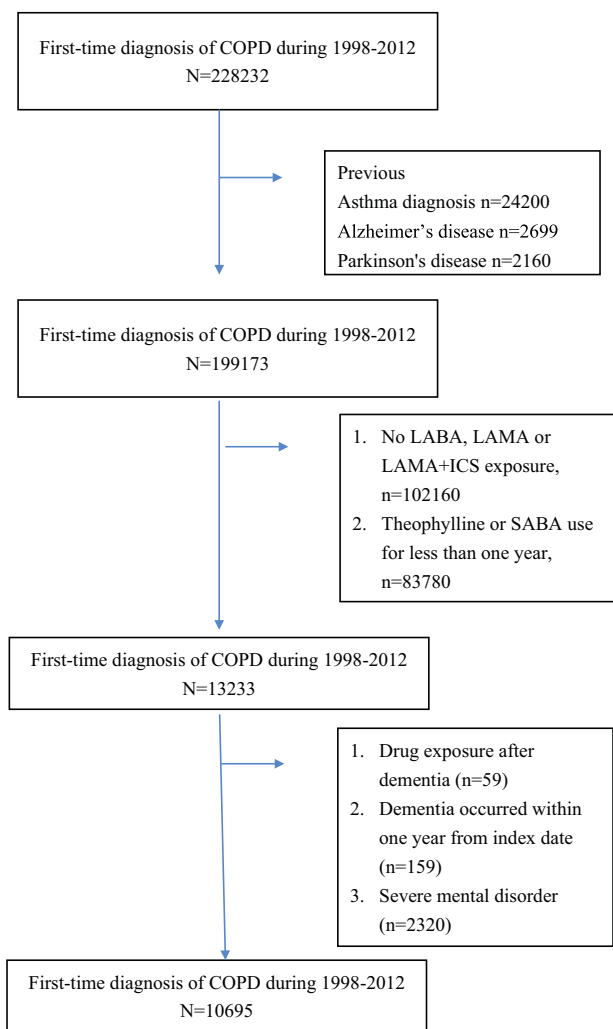


Figure 1. Flow diagram of patient selection.

0.75–1.53). The COPD patients with acute exacerbations requiring admission (more severe) had a risk of dementia with an adjusted HR of 1.31 (95% CI, 0.81–2.12) compared with those who were not hospitalized. Gender and comorbidities including coronary artery disease, hyperlipidemia, diabetes, and cancer also had no statistically significant impact on dementia. However, age was an important risk factor for dementia, and the risk of dementia was much higher among the patients >74 years (adjusted HR 2.58, 95% CI, 1.33–5.02). The risk of dementia was higher in COPD patients with comorbidities of stroke, hypertension, and head injury. The risk of dementia was lower in COPD patients with income between NTD 20,000 and 40,000 than in those with income <NTD 20,000 per month. There was no significant difference in the risk of dementia between COPD patients with monthly income >40,000 and those with monthly income <NTD 20,000.

Table 4 demonstrates the adjusted HRs of dementia risk in COPD patients with a PDC ≥80% after matching. Compared with COPD patients with a PDC <80%, those with a PDC ≥80% had a risk of dementia with an adjusted HR of 0.88, but the difference was not statistically significant (95% CI, 0.57–1.35).

Table 2
Demographic characteristics and comorbidities in COPD patients with a PDC <80% and those with a PDC ≥80% after matching.

Variable	PDC <80% N = 1206n (%)	PDC ≥80% N = 1206n (%)	P
Severity			1
Nonsevere	980 (81.26)	980 (81.26)	
Severe	226 (18.74)	226 (18.74)	
Sex			1
Female	153 (12.69)	153 (12.69)	
Male	1053 (87.31)	1053 (87.31)	
Age stratification			1
≤64	437 (36.24)	437 (36.24)	
65–74	490 (40.63)	490 (40.63)	
≥75	279 (23.13)	279 (23.13)	
Urbanization ^c			.17
1 (highest)	237 (19.65)	281 (23.30)	
2	557 (46.19)	539 (44.69)	
3	212 (17.58)	204 (16.92)	
4 (lowest)	200 (16.58)	182 (15.09)	
Comorbidity			
CAD	320 (26.53)	318 (26.37)	.93
Stroke	191 (15.84)	174 (14.43)	.33
Hyperlipidemia	186 (15.42)	130 (10.78)	<.01
Hypertension	623 (51.66)	565 (46.85)	.02
Diabetes	226 (18.74)	177 (14.68)	<.01
Head injury	42 (3.48)	37 (3.07)	.57
Cancer	120 (9.95)	111 (9.2)	.53
Income (NTD)			.03
<20,000	772 (64.01)	823 (68.24)	
20,000–40,000	392 (32.50)	357 (29.60)	
>40,000	42 (3.48)	26 (2.16)	

CAD=coronary artery disease, COPD=chronic obstructive pulmonary disease, NTD=New Taiwan Dollar, PDC=proportion of days covered.

Figure 2 illustrates the Kaplan–Meier curve showing the effect of a PDC ≥80% and a PDC <80% on the risk of dementia in COPD patients.

4. Discussion

To the best of our knowledge, this is the first study to evaluate the association between the PDC of COPD medication and the risk of dementia. The major finding is that a high PDC of COPD medication may not decrease the risk of dementia.

4.1. Adherence in COPD

We found that only 11.28% of the COPD patients had a PDC ≥80%. A previous study conducted in 7 Latin American countries, the Latin American Study of 24-hour Symptoms in Chronic Obstructive Pulmonary Disease (LASSYC), used self-reported medication adherence and questionnaires and found that 54.1% of the patients had good adherence,^[4] and their results were much higher than ours. We used a nationwide database and comprehensively enrolled COPD patients in Taiwan. Self-reports of medication adherence may not be a reliable method for estimating adherence in COPD.

Another study used retrospective administrative claims data from the Humana Research Database in the United States from January 1, 2008 to December 31, 2012^[5]. There were some similarities between our study and their study in that they used

Table 3
Adjusted hazard ratios of dementia risk for COPD patients with a PDC $\geq 80\%$ before matching.

Variable	Dementia risk aHR (95% CI)	P
PDC group		
High ($\geq 80\%$)	1.066 (0.75–1.53)	.73
Low	1	
Severity		
Severe	1.31 (0.81–2.12)	.27
Nonsevere	1	
Sex		
Female	1	
Male	0.93 (0.74–1.18)	.55
Age stratification		
≤ 64	1	
65–74	1.77 (1.13–2.78)	.01
≥ 75	2.58 (1.33–5.02)	<.01
Urbanization		
1 (highest)	1	
2	1.21 (0.892–1.642)	.22
3	1.594 (1.103–2.302)	.01
4 (lowest)	1.211 (0.795–1.845)	.37
Comorbidity		
CAD	1.22 (0.962–1.548)	.10
Stroke	1.384 (1.062–1.804)	.02
Hyperlipidemia	1.212 (0.895–1.641)	.21
Hypertension	1.336 (1.042–1.713)	.02
Diabetes	1.045 (0.792–1.378)	.76
Head injury	2.092 (1.326–3.302)	<.01
Cancer	0.937 (0.646–1.359)	.73
Income (NTD)		
<20,000	1	
20,000–40,000	0.708 (0.535–0.938)	.02
>40,000	0.187 (0.026–1.355)	.10

aHR = adjusted hazard ratio, CAD = coronary artery disease, CI = confidence interval, COPD = chronic obstructive pulmonary disease, NTD = New Taiwan Dollar, PDC = proportion of days covered.

Table 4
Adjusted hazard ratio of dementia risk for COPD patients with a PDC $\geq 80\%$ after matching.

Variable	Dementia risk aHR (95% CI)	P
PDC group		
High ($\geq 80\%$)	0.88 (0.57–1.35)	.55
Low	1	
Severity		
Severe	1.44 (0.85–2.44)	.17
Nonsevere	1	
Sex		
Female	1	
Male	1.42 (0.72–2.79)	.31
Age stratification		
≤ 64	1	
65–74	2.17 (0.80–5.86)	.13
≥ 75	2.75 (0.65–11.57)	.17
Urbanization		
1 (highest)	1	
2	1.75 (0.90–3.41)	.10
3	2.60 (1.22–5.57)	.01
4 (lowest)	1.79 (0.75–4.30)	.19
Comorbidity		
CAD	1.26 (0.80–2.0)	.32
Stroke	0.91 (0.51–1.63)	.76
Hyperlipidemia	0.67 (0.32–1.41)	.29
Hypertension	1.36 (0.85–2.18)	.21
Diabetes	1.26 (0.72–2.23)	.42
Head injury	1.78 (0.65–4.87)	.27
Cancer	0.63 (0.25–1.55)	.31
Income		
<20,000	1	
20,000–40,000	0.66 (0.38–1.13)	.13
>40,000	0 (0)	1.00

aHR = adjusted hazard ratio, CAD = coronary artery disease, CI = confidence interval, COPD = chronic obstructive pulmonary disease, NTD = New Taiwan Dollar, PDC = proportion of days covered.

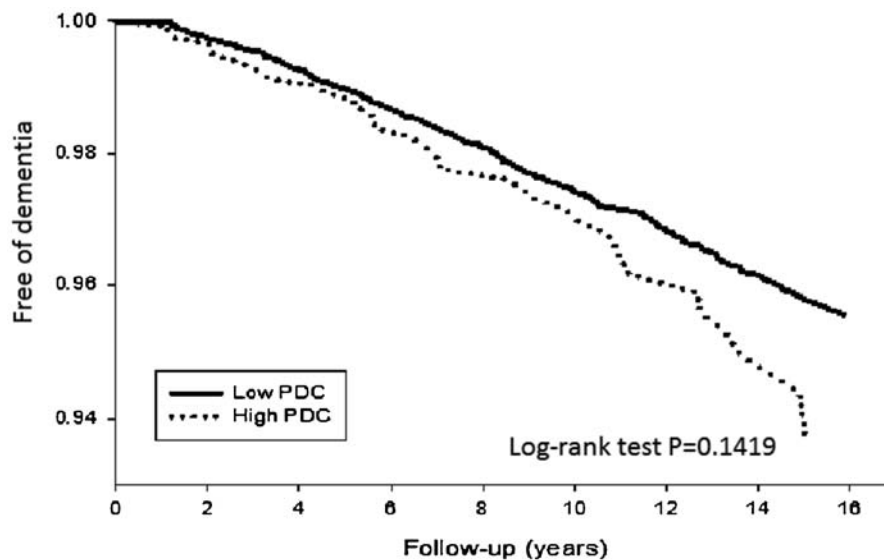


Figure 2. Kaplan–Meier curve showing the effect of a PDC $\geq 80\%$ and a PDC $< 80\%$ on the risk of dementia in COPD patients.

ICD-9-CM codes to diagnose COPD, required 2 medical claims with a COPD diagnosis code on separate days but no >90 days apart, included patients aged from 40 to 89 years, required at least one prescription claim for COPD bronchodilators, and assessed COPD medication adherence for 1 year after the index date (diagnosis of COPD). They found that the mean adherence to COPD bronchodilators was 0.47 and that less than one-quarter (20.8%) of the COPD patients adhered to treatment based on the threshold of a PDC $\geq 80\%$.^[5] Our data also showed that adherence in COPD was low, although there were some differences in our study. Only LAMAs and LABAs/ICSs were included in their study. In our study, we included LAMAs, LABAs/ICSs, LABAs, SABAs, and theophylline. We evaluated more types of bronchodilators, including oral theophylline. Theophylline has been used as a bronchodilator to treat COPD for >70 years; however, a higher number of side effects including tachycardia, arrhythmia, and gastrointestinal upset have reduced its popularity. After the introduction of more effective inhaled bronchodilators with fewer side effects, theophylline has become a third-line bronchodilator after inhaled anticholinergics and β_2 agonists. Moreover, it seems to be used less frequently for COPD patients in Western countries than in Taiwan (75.7%).^[6]

4.2. Adherence and sex

In the study by Dhamane et al,^[5] 59% of their COPD patients were female, which is different from the present study in which only 35% of the patients were female. Our previous studies also showed male predominance in Taiwan patients with COPD. The low percentage of female COPD patients in Taiwan may be related to a lower prevalence of female smoking or to underdiagnosis in Taiwan compared with those in the United States.^[7] There were no significant differences in adherence to COPD medications with respect to sex and age in Dhamane et al's study.^[5] In our study, we found that adherence was 74.62% higher among men than among women (87.31% vs 12.69%; $P < .05$). In Manteuffel et al's study, men were more likely than women to adhere to chronic medications.^[8] Another study conducted in Taiwan also found that female patients adhered less effectively to medications than male patients.^[9]

4.3. Adherence and the risk of dementia

Several possible mechanisms may explain why high adherence cannot reduce the risk of dementia in COPD patients. First, high adherence may not reduce the inflammatory status in COPD patients, and the mechanism of dementia (neurological damage from inflammatory cytokines) in the brain also cannot be alleviated. Second, there was no assessment of lung function or hypoxemia status in the COPD patients in our study. The decline in lung function and the hypoxemia status may play an important role in the occurrence of dementia in COPD. Third, a previous study showed that astrocytic β_2 -adrenergic receptors could regulate brain inflammatory responses.^[10] However, we doubt that bronchodilators have an anti-inflammatory effect on brain cells. The bronchodilators may not mitigate the risk of dementia via regulation of brain cells.

Factors associated with improved adherence include communication between the physician and patient, mutual agreement of what is helpful, shared responsibility, and patient self-management.^[11] The adherence to bronchodilator use was low in COPD

patients in our study. Further studies are needed to evaluate another benefit of adherence and how to overcome obstacles to adherence in COPD. Effective management of COPD depends on finding ways to improve adherence and encourage patients to participate in their own treatment.

4.4. Limitations

The results of this study should be interpreted in the context of several limitations. This is a retrospective and observational study, and therefore the possibility of confounding and various biases exists. The patients may have overestimated adherence and been unaware of their actual medication-taking behaviors when using pharmacy claims to assess adherence. In addition, information about the reasons for nonadherence was lacking. Another limitation was the inability to assess medication use outside of the National Health Insurance Research Database (NHIRD). However, the likelihood of this possibility is low, as the National Health Insurance (NHI) program provides comprehensive healthcare coverage and ease of accessibility to healthcare facilities. Alternatively, we may need a prospective study to delineate the relationship between adherence and dementia in COPD patients.

The mechanisms of brain pathology and dementia are likely to be complex and multifactorial in COPD. Further studies are required to delineate cerebrovascular mechanisms of brain pathology and dementia in COPD. Otherwise, patients who initiated treatment with once-daily dosing had significantly higher adherence than other daily dosing frequencies. In recent years, more once-daily and higher potency bronchodilators have been developed for COPD maintenance treatment. A future study can investigate whether these medications can help COPD patients increase medication adherence and reduce comorbidities, and further prospective studies are needed to evaluate the effect of COPD adherence on reducing the risk of dementia.

5. Conclusions

We found that an improvement in medication adherence to bronchodilators may not reduce the risk of dementia in COPD. For better treatment, new drug development, evolving physician and patient education, and the introduction and promotion of continuing medical education may also have influenced prescribing practices. Poor adherence is common in clinical practice and frequently ignored by physicians, resulting in increased rates of morbidity, healthcare expenditures, hospitalizations, and mortality. Although increasing patient adherence to treatment is important work, our study found that adherence to bronchodilator use does not modify the disease course of dementia in COPD, and more important risk factors that can ameliorate the risk of dementia need to be further studied.

Author contributions

Conceptualization: Kuang-Ming Liao.

Data curation: Chung-Yu Chen.

Formal analysis: Chung-Yu Chen.

Funding acquisition: Chung-Yu Chen.

Investigation: Chung-Yu Chen.

Methodology: Chung-Yu Chen.

Project administration: Chung-Yu Chen.

Resources: Chung-Yu Chen.

Software: Chung-Yu Chen.

Supervision: Chung-Yu Chen.

Validation: Kuang-Ming Liao.

Writing – original draft: Kuang-Ming Liao.

Writing – review and editing: Kuang-Ming Liao.

References

- [1] Liao KM, Ho CH, Ko SC, et al. Increased risk of dementia in patients with chronic obstructive pulmonary disease. *Medicine (Baltimore)* 2015;94:e930.
- [2] Liao KM, Lin TC, Li CY, et al. Dementia increases severe sepsis and mortality in hospitalized patients with chronic obstructive pulmonary disease. *Medicine (Baltimore)* 2015;94:e967.
- [3] Nussbaum RL, Ellis CE. Alzheimer's disease and Parkinson's disease. *N Engl J Med* 2003;348:1356–64.
- [4] Montes de Oca M, Menezes A, Wehrmeister FC, et al. Adherence to inhaled therapies of COPD patients from seven Latin American countries: the LASSYC study. *PLoS One* 2017;12:e0186777.
- [5] Dhamane AD, Schwab P, Hopson S, et al. Association between adherence to medications for COPD and medications for other chronic conditions in COPD patients. *Int J Chron Obstruct Pulmon Dis* 2016;12:115–22.
- [6] Wang MT, Lo YW, Tsai CL, et al. Statin use and risk of COPD exacerbation requiring hospitalization. *Am J Med* 2013;126:598–606.
- [7] Koong SL, Serdula MK, Williamson DF, et al. Smoking prevalence in the United States and Taipei City, Taiwan. *Am J Prev Med* 1991;7:161–5.
- [8] Manteuffel M, Williams S, Chen W, et al. Influence of patient sex and gender on medication use, adherence, and prescribing alignment with guidelines. *J Womens Health (Larchmt)* 2014;23:112–9.
- [9] Chen SL, Lee WL, Liang T, et al. Factors associated with gender differences in medication adherence: a longitudinal study. *J Adv Nurs* 2014;70:2031–40.
- [10] Laureys G, Gerlo S, Spooren A, et al. β_2 -adrenergic agonists modulate TNF- α induced astrocytic inflammatory gene expression and brain inflammatory cell populations. *J Neuroinflammation* 2014;11:21.
- [11] Mellins RB, Evans D, Zimmerman B, et al. Patient compliance: are we wasting our time and don't know it? *Am Rev Respir Dis* 1992;146:1376–7.