Associations of Pulmonary Function with Dementia and Depression in an Older Korean Population

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Objective   Previous studies reported an association between pulmonary function and cognitive function. However, not much has been investigated in this regard concerning dementia in a community population, taking depression into account. We aimed to examine the associations of pulmonary function with dementia and depression in a community-dwelling elderly population.

Methods   A total of 1,038 participants were evaluated for dementia and depression using the Korean version of the Geriatric Mental State Schedule B3 (GMS B3-K), the Community Screening Interview for Dementia-Korean version (CSID-K) and a modified 10-item Word List Learning from the Consortium to Establish a Registry of Alzheimer's Disease (CERAD). Pulmonary function was measured as forced expiratory volume in 1 s (FEV_1) from a forced expiratory maneuver.

Results   Prevalence rates of dementia and depression were 11.0% and 10.4%, respectively. Individuals who were diagnosed with dementia manifested a lower mean FEV_1, as compared to those without dementia after adjusting for potential confounders, including disability and depression [OR=1.34 (1.05−1.72)]. Following gender-stratified analysis, the association was only statistically significant in women [OR=1.40 (1.04−1.89)]. The association between depression and mean FEV_1 was less significant compared to dementia [OR=1.32 (1.10−1.58)]. However, the association was no longer significant after adjusting for age and years of education. No association was significant in the gender-stratified analysis.

Conclusion   Decreased pulmonary function was associated with dementia status only in an older female Korean population. Pulmonary function and depression were not significantly associated in either gender.   **Psychiatry Investig 2015;12(4):443-450**

Key Words   Pulmonary function, Forced expiratory volume, Dementia, Depression, Disability.

INTRODUCTION

In the course of aging, pulmonary function declines with associated physiological changes.[1] Poorer pulmonary function predicts all-cause mortality.[2] Pulmonary disorder is not only related to physical conditions but is also associated with higher psychiatric morbidity, which decreases quality of life in the elderly.[3] The psychiatric field has examined pulmonary disorder in relation to several psychiatric disorders, such as cognitive impairment, dementia, and depression.

Cross-sectional studies showed that various pulmonary measures are associated with cognitive function.[4-10] Pulmonary function is also correlated with structural brain changes. Sachdev et al.[7] reported that forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) could be significant predictors of ventricle-to-brain ratio, an indicator of brain atrophy. In an effort to examine the causative relationship of the association between pulmonary measures and cognitive function, longitudinal studies were also conducted. In those studies, baseline pulmonary function predicted cognitive function later in life.[11-13] Results from observational studies focused on specific cognitive disorders suggest that pulmonary function predicts mild cognitive impairment or dementia in late life.[14-16]

With respect to depression, the bidirectional relationship between depression and physical health is well known. Poor physical health is a risk factor for depression[17-19] and depression influences the outcomes of underlying medical illness and mortality.[20-22] Of various medical illnesses, depressive symptoms are often recognized in patients with pulmonary

disorders. Not only is depression prevalent in chronic obstructive pulmonary disease (COPD) but it is also related to disease outcome, hospital stay, and physical and social functioning.[23] In an effort to understand this association, both psychological and physiological models were suggested in COPD patients,[24] inferring that the relationship between pulmonary function and depression is complex.

Previous studies on the associations of pulmonary function with dementia and depression have typically been carried out in patients with specific pulmonary disorders, particularly COPD.[3,25-27] There have been few studies conducted in a community population,[4,12,15,16] which would be more generalizable in elderly populations as a whole. Furthermore, the direct association between depression and pulmonary function has rarely been tested.[25,28]

In our study, we examined the associations of pulmonary function, as measured by FEV_1, with dementia and depression in a Korean community-dwelling elderly population.

METHODS

Sampling and data collection

Study data were drawn from a larger prospective community survey (from 2001 to 2006) of late life psychiatric morbidity in collaboration with the 10/66 International Dementia Research Program in Developing Countries.[29] All community residents aged 65 or older within a defined geographic area of Gwangju, South Korea, were systematically identified from national registration lists and were approached to participate. The data for this study were collected in 2006. A letter explaining the study was sent to all potential participants identified before the survey. Home-based interviews were administered to all participants by research nurses who were trained and supervised by the project psychiatrist. The study was approved by the Chonnam National University Hospital Institutional Review Board, and all participants or their family members provided formal written informed consent.

Ascertainment of dementia and depression

The participants completed the Korean version of the Geriatric Mental State Schedule B3 (GMS B3-K),[30] the Community Screening Interview for Dementia-Korean version (CSID-K),[31] and a modified 10-item Word List Learning from the Consortium to Establish a Registry of Alzheimer's Disease (CERAD). The GMS B3 is a fully structured diagnostic interview in wide international use with an accompanying Automated Geriatric Examination for Computer Assisted Taxonomy (AGECAT) algorithm that provides likelihoods of individual diagnoses for mental disorders, including organicity and depression. The GMS B3 was translated into Korean

according to a formal standardization process.[32] A dementia diagnosis was made using a 10/66 dementia diagnostic algorithm using the results derived from the three above measures.[29] Depression was diagnosed using the GMS B3, in which a 'stage one' (non-hierarchical) confidence level of three or above in the AGECAT algorithm was used. The instrument and algorithm were designed to define current depression present at a level of severity warranting clinical intervention, and focuses on the one-month time period preceding the interview. Here, 'case-level depression' encompasses both moderate and severe symptomatology, and therefore represents a broader syndrome than major depression as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV).

Pulmonary function

Pulmonary function was measured as forced expiratory volume in 1 s (FEV_1) from a forced expiratory maneuver. For the assessment, participants were instructed to perform a spirometry test using a peak flow meter. The test was performed on two occasions, resulting in a mean FEV_1. In the area of internal medicine, the spirometry test is a basic and standardized method for evaluating pulmonary function and detecting various lung diseases.[33] Of the various measures of the spirometry test, the FEV_1 is by far the most frequently used and the sensitive index, which was applied for not only those with lung diseases but also for psychiatric patients such as dementia or depression.[4,7,8,13,17]

Covariates

Covariates potentially associated with the relationships between dementia/depression and pulmonary function were evaluated.[34] Data on socio-demographic variables, such as age, gender, marital status, education, religion, past and current occupation and accommodation status were collected from participants and family members. For the lung disease covariates, information on asthma and persistent coughing diagnoses and treatment histories, and a smoking history were obtained by self-report and corroborated with a family member when possible. Disability was assessed using the Korean version of the World Health Organization Disability Assessment Schedule (WHO-DAS II).[35]

Statistical analyses

Data analysis was performed using Statistical Package for the Social Sciences (SPSS 21; SPSS Inc., Chicago, IL, USA). Chi-squared and t-tests were used for the descriptive analysis of dementia and depression status. The prevalence rates of dementia and depression with 95% confidence intervals (95% CIs) are presented by mean FEV_1 quartile. In univariate

Table 1. Characteristics of study participants by dementia and depression status

	Dementia analysis			Depression analysis		
	No dementia N=924	Dementia N=114	p-value	No depression N=927	Depression N=108	p-value
Age, years (SD)	72.8 (6.5)	78.1 (7.6)	<0.001	73.1 (6.7)	75.6 (7.2)	<0.001
Gender (female), N (%)	579 (62.7)	97 (85.1)	<0.001	588 (63.4)	86 (79.6)	<0.01
Education years (SD)	5.0 (4.4)	1.4 (3.0)	<0.001	4.8 (4.5)	2.2 (3.2)	<0.001
Married, N (%)	520 (56.3)	24 (21.1)	<0.001	512 (55.2)	31 (28.7)	<0.001
Religion (have), N (%)	598 (35.3)	81 (28.9)	0.210	601 (64.8)	108 (10.4)	0.200
Accommodation (rented), N (%)	223 (24.1)	53 (46.5)	<0.001	233 (25.1)	41 (38.0)	<0.01
Past occupation (manual), N (%)	765 (82.8)	108 (94.7)	<0.001	770 (83.1)	101 (93.5)	<0.01
Current occupation (No), N (%)	846 (91.6)	112 (98.2)	<0.01	853 (92.0)	102 (94.4)	0.450
Asthma, N (%)	126 (13.7)	22 (19.3)	0.118	124 (13.4)	24 (22.2)	<0.05
Persistent cough, N (%)	93 (10.1)	22 (19.3)	<0.01	93 (9.8)	23 (21.3)	<0.01
Current smoking, N (%)	189 (20.5)	19 (16.7)	0.387	194 (20.9)	12 (11.1)	<0.05
WHODAS score (SD)	35.8 (21.8)	49.0 (19.9)	<0.001	35.6 (21.6)	51.7 (19.8)	<0.001

SD: standard deviation, WHODAS: The World Health Organization Disability Assessment Schedule

analysis, associations among mean FEV_1 and participant characteristics were assessed using logistic regression analysis. For multivariate analysis, logistic regression models were introduced by entering mean FEV_1 quartile as a numerical variable to reach statistical significance. In multivariate logistic regression models, associations between mean FEV_1 and dementia/depression status were evaluated after stratifying for sex, considering anatomical differences in lung volume. For each analysis of dementia and depression status, variables that were significantly different in the univariate analysis were subsequently entered. Additionally, variables such as religion, current occupation, asthma, and current smoking status were entered after controlling for possible confounding effects.

RESULTS

Recruitment

Of the 2,201 community residents aged 65 or older identified, 1,038 (47%) completed the assessment and participated in the study. There was no significant difference between participants and non-participants regarding age or gender (all p<0.05). Among the 1,038 participants who completed the assessment, 676 (65.1%) were female. The mean age was 73.4 (standard deviation, SD=6.84); 114 (11.0%) were diagnosed with dementia and 108 (10.4%) had case-level depression.

Association of participant characteristics with dementia and depression

Participant characteristics by dementia and depression status are presented in Table 1. For dementia, characteristics such as older age, being female, lower education, unmarried

status, rented accommodations, past manual occupation and greater disability were associated with disorder status (all p<0.001). Current occupation (p=0.008) and persistent coughing (p=0.006) were also associated, but with lesser statistical significance. There were no differences in region, asthma or current smoking status between the dementia and non-dementia groups.

Depression status was associated with older age (p<0.001), being female (p<0.01), less education (p<0.001), unmarried status (p<0.001), rented accommodations (p<0.01), past manual occupation (p<0.01), asthma (p<0.05), persistent coughing (p<0.01), not currently smoking (p<0.05), and greater disability (p<0.001). No significant differences were found regarding religion or current occupation status between the depressed and non-depressed groups.

Prevalence of dementia and depression by mean FEV_1

Figure 1 shows prevalence rates of dementia and depression by mean FEV_1 quartile. For dementia, prevalence rates were 4.8%, 4.7%, 10.7%, 22.9% (χ^2=59.4, p<0.001) for each mean FEV_1 quartile from lowest to highest. Participants with lower pulmonary function were more likely to be diagnosed with dementia. Prevalence rates of depression for mean FEV_1 quartile were 6.8%, 9.1%, 11.1%, 14.4%, respectively (χ^2=8.9, p=0.031). The trend of increased prevalence in lower pulmonary function was similar to that of dementia, but the significance was less.

Associations between FEV_1 and participant characteristics

Associations among participant characteristics and mean
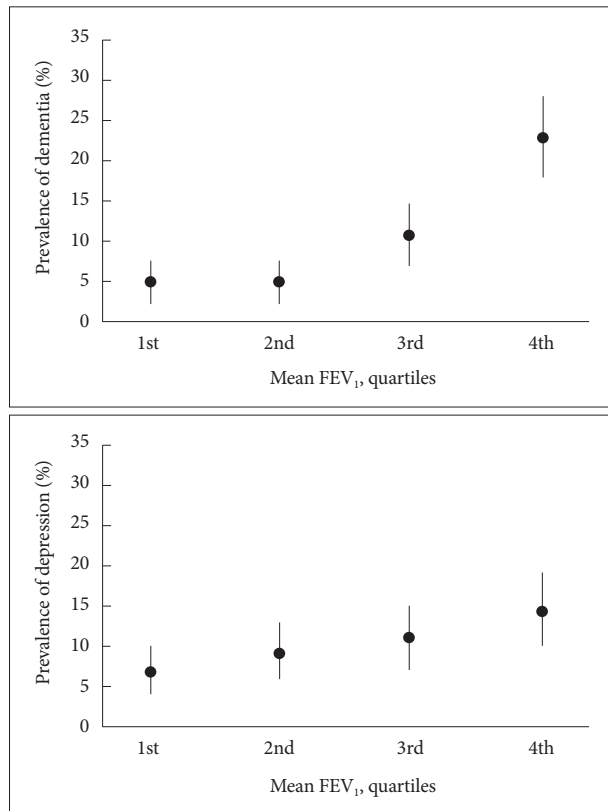
Figure 1. Prevalence rates of dementia and depression by forced expiratory volume in one second (FEV₁) quartiles.

FEV_1 are shown in Table 2. Those aged 75 or older had a lower mean FEV_1 compared to those aged 65 to 74 (p<0.001). Subjects who were female, uneducated, unmarried, practiced religion, and living in a rented accommodation had lower mean FEV_1. With regard to occupational status, those who engaged in a past manual occupation and were currently without an occupation had a lower mean FEV_1. Participants with asthma, persistent coughing, and non-smokers were more likely to have a lower mean FEV_1. Greater disability, as defined as a WHODAS score >1, was associated with a lower mean FEV_1.

Multivariate associations of dementia and depression with FEV_1

Total and gender stratified multivariate analyses are summarized in Table 3. For dementia, the unadjusted odds ratio (OR) for mean FEV_1 was 2.02 (OR=2.02; 95% CI=1.64−2.48). The association remained significant but weakened after subsequently entering variables (OR=1.34; 95% CI=1.05−1.72). In a separate analysis, the association was not detected in males after adjusting for age and years of education. On the contrary, we detected a significant association between dementia status and mean FEV_1 in the female group, even after adjusting for depression status (OR=1.40; 95% CI=1.04−1.89).

Table 2. Associations with forced expiratory volume in one second (FEV₁) and characteristics

Characteristic	Number (%)	FEV₁ (SD), mL	p-value
Age, years*			<0.001
65−74	626 (60.3)	242.4 (91.0)	
75+	411 (39.6)	194.2 (88.1)	
Gender			<0.001
Male	362 (34.9)	277.2 (108.4)	
Female	676 (65.1)	194.3 (67.6)	
Education, years*			<0.001
0	372 (35.8)	179.8 (72.2)	
1+	665 (64.1)	247.5 (94.4)	
Marital status			<0.001
Married	544 (52.4)	249.0 (97.5)	
Unmarried	494 (47.6)	194.9 (78.3)	
Religion			<0.01
Have	679 (65.4)	216.8 (90.8)	
No	359 (34.6)	235.4 (95.6)	
Accommodation			<0.001
Owned	762 (73.4)	235.1 (94.1)	
Rented	276 (26.6)	190.4 (80.8)	
Past occupation			<0.001
Non-manual	165 (15.9)	292.5 (105.7)	
Manual	873 (84.1)	210.1 (84.1)	
Current occupation			<0.05
No	958 (92.3)	221.1 (92.3)	
Have	80 (7.7)	248.6 (96.7)	
Asthma*			<0.001
No	889 (85.7)	231.5 (94.2)	
Have	148 (14.3)	174.2 (65.7)	
Persistent cough*			<0.001
No	922 (88.8)	226.8 (93.4)	
Have	115 (11.1)	194.2 (84.0)	
Current smoking			<0.001
No	830 (80.0)	213.1 (86.1)	
Yes	208 (20.0)	263.5 (107.1)	
WHODAS score			<0.001
0	145 (14.0)	283.1 (96.5)	
1+	893 (86.0)	213.5 (88.6)	

*missing data (age, education, asthma, persistent coughing=1 missing, physical illness=7 missing). WHODAS: The World Health Organization Disability Assessment Schedule

The association between depression and mean FEV_1 was less significant, as compared to dementia (OR=1.32; 95% CI=1.10 −1.58) (Table 4). The association was not significant after adjusting for age, gender, and years of education. The association was no longer significant following gender stratification.

Table 3. Models for association between forced expiratory volume in one second (FEV_1) and dementia status

Models	Dementia×FEV_1		
	All participants	Male	Female
Model 1	2.02 (1.64−2.48)‡	1.63 (1.07−2.47)*	1.96 (1.52−2.53)‡
Model 2	1.39 (1.10−1.75)†	1.29 (0.81−2.04)	1.45 (1.10−1.91)†
Model 3	1.35 (1.06−1.72)*	1.21 (0.75−1.97)	1.41 (1.06−1.88)*
Model 4	1.34 (1.05−1.72)*	1.06 (0.62−1.80)	1.42 (1.06−1.90)*
Model 5	1.31 (1.03−1.68)*	1.04 (0.61−1.77)	1.37 (1.02−1.84)*
Model 6	1.34 (1.05−1.72)*	1.04 (0.61−1.80)	1.40 (1.04−1.89)*

Model 1: Unadjusted, Model 2: Model 1+age (75< or not), gender, education years, Model 3: Model 2+marital status, religion, accommodation, past occupation, current occupation, Model 4: Model 3+asthma, persistent cough, current smoking, Model 5: Model 4+WHODAS score, Model 6: Model 5+depression status. *p<0.05, †p<0.01, ‡p<0.001

Table 4. Models for association between forced expiratory volume in one second (FEV_1) and depression status

Models	Depression×mean FEV_1		
	All participants	Male	Female
Model 1	1.32 (1.10−1.58)†	1.33 (0.92−1.92)	1.17 (0.93−1.47)
Model 2	0.97 (0.78−1.21)	1.08 (0.72−1.63)	0.94 (0.73−1.22)
Model 3	0.95 (0.76−1.18)	1.09 (0.72−1.64)	0.91 (0.70−1.17)
Model 4	0.91 (0.72−1.14)	0.92 (0.59−1.45)	0.87 (0.67−1.14)
Model 5	0.87 (0.69−1.10)	0.86 (0.54−1.37)	0.83 (0.63−1.09)
Model 6	0.84 (0.67−1.07)	0.86 (0.54−1.37)	0.78 (0.59−1.04)

Model 1: Unadjusted, Model 2: Model 1+age (75< or not), gender, education years, Model 3: Model 2+marital status, religion, accommodation, past occupation, current occupation, Model 4: Model 3+asthma, persistent cough, current smoking, Model 5: Model 4+WHODAS score, Model 6: Model 5+depression status. *p<0.05, †p<0.01, ‡p<0.001

DISCUSSION

Principal findings of this cross-sectional study in a community-dwelling older Korean population were that poorer pulmonary function, as measured by FEV_1, was associated with dementia, independently of covariates, including pulmonary disease and smoking status. This association was only significant in women. However, no significant association was found between FEV_1 and depression in either sex.

Several plausible possibilities could explain the significant association between lower FEV_1 and dementia. One possibility is that decreased pulmonary function leads to insufficient oxygenation and other biological consequences that affect the brain. The brain is one of the most metabolically active organs, consuming 20% of bodily energy due to oxygen consumption,[36] and cerebral oxygenation is fundamental for proper functioning. Decreased brain oxygenation could lead to neuronal damage that could further manifest as cognitive decline. Chronic hypoxia, whether continuous or intermittent, reportedly interfered with myelination in the cerebral cortex and hippocampus in a mouse model.[37] In severe COPD with hypoxia, increased risk of cognitive decline was reported, suggesting hypoxia-induced neuronal damage.[27] Hypoperfusion in specific brain areas was detected using single photon emission computed tomography (SPECT) in COPD. More hypoperfusion was detected in demented groups, suggesting a correlation between cognitive decline and pulmonary function.[26] Second, an inflammation-related mechanism has also been suggested. It was demonstrated that even acute hypoxia could induce lung inflammation.[38] An Alzheimer's disease study demonstrated the presence of inflammation, providing evidence of various inflammatory markers and their involvement in cognitive deterioration.[39] In prospective studies, baseline inflammatory markers predict later cognitive performance.[40,41] Inflammation due to pulmonary insufficiency could directly or indirectly influence developmental processes of dementia by increasing other risk factors for dementia. Third, a brain-derived neurotrophic factor (BDNF) hypothesis of dementia was proposed. Physical activity was examined in association with BDNF expression, which is presumed to promote neuroplasticity.[42] Elderly individuals with decreased pulmonary function are less likely to be involved in physical activity that could sustain or promote cognitive function, thus increasing dementia risk. Our study indicates that the association between pulmonary function and cognitive function is not explained by functional disability alone, given that the association was significant even after controlling for WHODAS score. However, whether individuals were involved in regular exercise in spite of having a certain functional disability was unknown. Further, it is possible that a higher WHODAS score resulted from different dimensions of disability other than physical activity alone.

Reverse causality might also be possible, in that dementia could affect pulmonary function through certain physiological changes, although this hypothesis is less popular. Subjects with dementia may have limited capability to prevent, detect early and treat pulmonary disorder. Decreased pulmonary function in the dementia group may indicate that their mental health condition hindered them from engaging in sustaining their physical health. Pulmonary problems could be considered to be not only a respiratory but also a systemic condition associated with other physical causes and consequences. In this study, subjects with dementia were more likely to have persistent coughing and more physical illness (data not shown). However, the association was still significant after adjusting for these factors, even after including the number of physical illnesses (data not shown), indicating

that the effect cannot be explained by a physically-ill state.

Interestingly, the association was only significant in females in our study. In males, the association disappeared after controlling for age and education. Specifically, adjusting for education alone did not change the significance in either sex, but the significance disappeared after taking age into consideration in males. Considering the previously mentioned possible mechanisms, females may have a different sensitivity to hypoxia or other physical changes associated with decreased pulmonary function, as compared to males. de Leeuw and colleagues[43] reported a higher incidence of subcortical and periventricular white matter lesions in females, as compared to males, related to a higher incidence of dementia among the female population. Increased susceptibility to cerebral hypoxia due to hormonal changes after menopause (decrease in estrogen level) was suggested to be the reason. A lesser protective role of sex hormones in elderly females may provide a clue to understand the sex specific association in the present study. There are also studies reporting anthropometric measures, such as shorter leg length and smaller head circumference, associated with dementia, also only in females, similar to our study.[44,45] The reason for the sex difference needs to be further elucidated, but the gender specific association is in line with results of the present study. It is also generally acknowledged that females are at a higher risk for dementia.

Regarding depression, we found no association between its incidence and pulmonary function. Although we did not detect a statistically significant association between pulmonary function and depression, most studies support an increased risk of depression in pulmonary disorder.[24] However, there are reports that failed to find an association between FEV_1 and depression status.[23,28] Unlike dementia, which is more related to biophysiological processes, depression may be more related to psychological and emotional conditions in pulmonary disorders, which could explain our results. Pulmonary function is reportedly a predictor of quality of life in relation to functional impairment and depression.[3] In this study, quality of life was not measured; taking quality of life into consideration may have revealed a moderating effect. The prevalence of depression in this study was approximately 10%, which is similar to results from other studies using the same depression diagnosis tool.[46] It is also possible that the pulmonary dysfunction was not severe enough to detect the association in this population, considering that previous studies reporting a correlation between pulmonary function and depression were mostly executed in patients with specific pulmonary disorders.

The strength of this study lies in its large, community-based population from a well-validated database. Instead of relating pulmonary and cognitive function using various ranges of age groups, a relatively narrow age group was used to reduce individual differences in cognition due to age, specifically focusing on dementia. Since cognitive function, affective conditions and disability are interrelated,[34] disability was considered and dementia and depression status were entered in the analysis to remove potentially confounding effects. In addition, pulmonary function is known to differ among ethnic groups, resulting in different reference ranges,[47] in that FEV_1 and FVC values are lower in Asians, as compared to Western populations, suggesting true physiologic differences.[48] Previous studies concerning dementia and pulmonary function have been mostly conducted in Western countries. To our knowledge, this is the first study to evaluate the relationship in an Asian elderly population.

The major limitation of the present study is related to its cross-sectional design, in that the direction of causality cannot be concluded. Hypoxic state or oxygen saturation level was not monitored in the present study; thus, a direct correlation could not be determined. Further study measuring both peripheral and cerebral oxygenation would be needed to enhance our mechanistic understanding. In addition, although lung disease covariates such as asthma, persistent coughing, and smoking histories were evaluated, but other important variables could have effects on pulmonary function (especially on FEV_1) were not considered in our study. These factors are not only symptoms (wheezing without cough, chest discomfort without cough, and so on) but also diseases (chronic rhinitis, gastro-esophageal reflux disease, chronic bronchiolitis, emphysema, and so on).

An increase in the elderly population results in various issues, including an increase in both physical and mental disorders, with an accompanying rise in health costs. Dementia is considered to be a devastating disorder of deterioration without a cure. Although dementia treatment trials have been conducted, most studies of the disease are limited to reporting risk factors and preventions. This study presents an association between decreased pulmonary function and dementia without proposing a causal relationship. However, this result may be important, as pulmonary function is a manageable condition. Patients with pulmonary disorders would be considered an at-risk population in which regular evaluation of cognitive function should be recommended and an emphasis placed on pulmonary condition treatment. Also, public education regarding the importance of preserving and sustaining pulmonary health in relation to cognitive decline would be necessary. Future research utilizing a longitudinal design or clinical trials enhancing pulmonary health to improve dementia prevalence and outcomes are needed to clarify this association.

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