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Association between non-cystic fibrosis bronchiectasis and the risk of incident dementia: A nationwide cohort study

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Abstract

Background: Chronic lung diseases, such as chronic obstructive pulmonary disease or asthma, are associated with an increased risk of dementia. However, few data are available regarding the risk of dementia in individuals with bronchiectasis.

Objectives: To explore the association between bronchiectasis and the risk of incident dementia using a longitudinal population-based cohort.

Methods: A total of 4,068,560 adults older than 50 years without previous dementia were enrolled from the Korean National Health Insurance Service database in 2009. They were followed up until the date of the diagnosis of dementia or December 31, 2020. The study exposure was the diagnosis of bronchiectasis, and the primary outcome was incident dementia comprising Alzheimer's disease and vascular dementia.

Results: During the median follow-up duration of 9.3 years, the incidence of all-cause dementia was 1.6-fold higher in individuals with bronchiectasis than in those without bronchiectasis (15.0 vs. 9.3/1000 person-years, $p < .001$). In the multivariable Cox regression analysis, the risk of all dementia was significantly higher in individuals with bronchiectasis than in those without bronchiectasis (adjusted hazard ratio [aHR] 1.09, 95% confidence interval [CI] 1.04–1.14). In a subgroup analysis by dementia type, individuals with bronchiectasis had an increased risk of Alzheimer's disease compared to those without bronchiectasis (aHR 1.07, 95% CI 1.01–1.12); the risk of vascular dementia did not significantly differ between the two groups (aHR 1.05, 95% CI 0.90–1.21).

Conclusion: Bronchiectasis was associated with an increased risk of dementia, especially Alzheimer's disease.

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Bronchiectasis, dementia, epidemiology, Alzheimer disease, vascular dementia

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Introduction

The global burden of dementia is substantial, with a worldwide trend of aging.[1] Unfortunately, despite the huge socioeconomic burden of dementia,[2] risk factors for dementia have not been fully elucidated. Although aging is the most significant factor affecting the development of dementia, it is not modifiable, and current disease-modifying therapy for dementia remains insufficient.[3] Therefore, exploring risk factors and identifying potentially modifiable risk factors for dementia is important and may guide dementia prevention strategies. Chronic inflammatory diseases, including hypertension,[4] diabetes mellitus,[5] dyslipidemia,[6] and chronic obstructive pulmonary disease (COPD),[7] are good examples of this because previous studies revealed a positive association between these diseases and dementia. Hence, the prevention of chronic inflammatory diseases or the control of inflammation may reduce the risk of dementia.

Associations between chronic respiratory diseases and dementia have been increasingly recognized. Individuals with chronic lung diseases accompanied by impaired lung function are at increased risk of developing dementia.[8–10] Reduced lung function is considered an important risk factor for the development of cognitive disorders, possibly due to systemic inflammation and tissue hypoxia.[11] The risk of cognitive impairment escalates with a severe decline in lung function.[12] Consequently, individuals with airway diseases, such as COPD or asthma, have a higher incidence of dementia than those without.[7,13]

Non-cystic fibrosis bronchiectasis (referred to hereafter as bronchiectasis) is a chronic inflammatory respiratory disease, exhibiting a rising global prevalence.[14] The prevalence of bronchiectasis has steadily increased since the early 21st century, with an estimated annual increase of 8%–9% in the USA until the early 2010s.[15] Although specific pathways might vary among diseases, oxygen deprivation and underlying systemic inflammatory processes might contribute to neurodegeneration in individuals with various chronic respiratory conditions.[16] In this regard, bronchiectasis may also be associated with an increased risk of dementia. Although individuals with bronchiectasis had more cognitive dysfunction than healthy controls in one study,[17] small population (30 individuals with bronchiectasis and 20 healthy controls) and cross-sectional design may limit the study findings.

To the best of our knowledge, the risk of dementia in individuals with bronchiectasis has not been investigated through a large-scale longitudinal database. Therefore, this study aimed to explore the association between bronchiectasis and the risk of dementia using a longitudinal population-based cohort.

Methods

Data source

We used the Korea National Health Insurance Service (NHIS) database. About 97% of all Korean citizens are covered by universal, single-payer mandatory health insurance. Therefore, the NHIS provides data representative of the entire Korean population. The NHIS database includes demographic information (e.g., age, sex, and income level), insurance claim data (e.g., all reimbursed inpatient and outpatient visits, procedures, and prescriptions), and data from health screening exams. A general health examination is conducted annually or biennially for all adults free of charge by the Ministry of Health and Welfare. Health examinations included anthropometric measurements (body mass index [BMI], waist circumference, and blood pressure), laboratory data, and questionnaires on smoking, alcohol consumption, and physical activity. More detailed information on the NHIS and health exam screening items has been provided in the previous study.[18,19]

Study population

This study initially enrolled 10,628,070 individuals who underwent health exam in 2009. We excluded 6,156,826 individuals aged < 50 years and 234,495 with missing data about any baseline characteristics. We excluded younger individuals because early-onset Alzheimer's disease accounts for a small proportion of dementia with other risk factors, including genetic risk factors. Of the remaining 4,236,749, we further excluded 111,114 who were diagnosed with bronchiectasis more than a year prior to the 2009 health examination, 420 who were diagnosed with cystic fibrosis, 22,426 who were previously diagnosed with dementia, and 34,229 who were diagnosed with dementia within 1 year after the 2009 examination. Specific conditions for exclusion were established based on at least one relevant record. The final analytic cohort included 4,068,560 individuals including 14,722 diagnosed with bronchiectasis and 4,053,838 who were healthy or had other chronic respiratory diseases. The cohort was followed up from the date of a health examination during 2009 (index

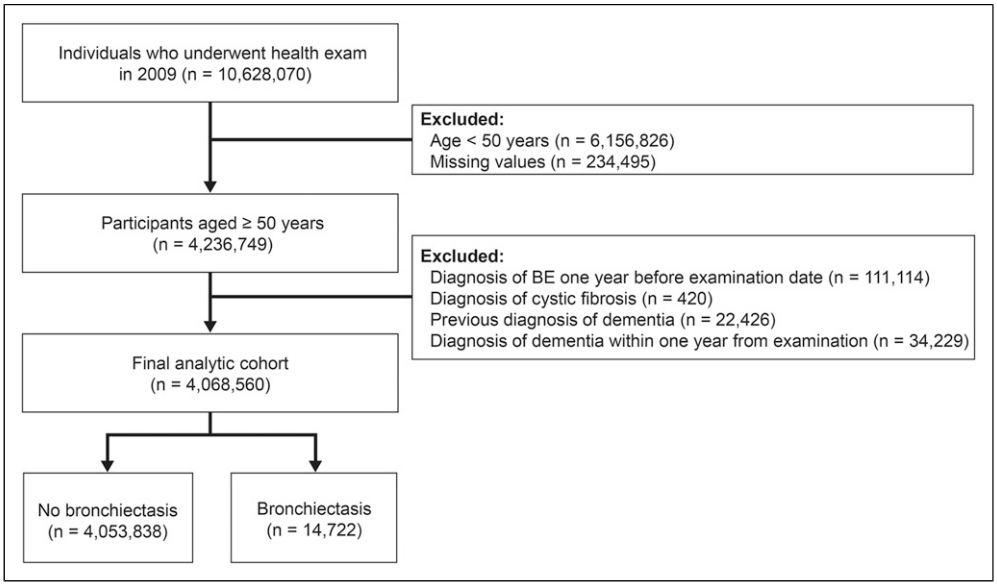

Figure 1. Flowchart of the study population. BE: bronchiectasis.

date) until whichever of the following came first: a diagnosis of dementia, death, or the study ended (December 31, 2020) (Figure 1).

Exposures: Diagnosis of bronchiectasis

Bronchiectasis was defined by at least one claim under 10th revision of the International Classification of Disease (ICD-10) code J47, excluding those with cystic fibrosis (ICD-10 diagnosis code E84).[20,21]

Outcomes: Incidence of dementia

The primary outcome was dementia. Dementia was defined using the following ICD-10 diagnosis codes: dementia in Alzheimer's disease (F00), vascular dementia (F01), dementia in Pick's disease (F02), unspecified dementia (F03), and Alzheimer's disease (G30).[22]

Covariates

BMI was calculated by dividing the weight by the square of height and categorized by Asian-specific criteria: underweight (<18.5 kg/m^2), normal weight (18.5–22.9 kg/m^2), overweight (23.0–24.9 kg/m^2), or obese (≥25.0 kg/m^2).[23] Low income was defined as income in the lowest 25% among the entire Korean population or receiving Medicaid. Smoking status and alcohol consumption were assessed using a self-questionnaire. Alcohol consumption was classified as never, mild to moderate (<30 g of alcohol/d), and heavy drinkers (≥30 g of alcohol/d). Regular exercise was defined as ≥ 30 min of moderate physical activity ≥5 times per week, or ≥20 min of vigorous physical activity ≥3 times per week.[24,25] Moderate-intensity physical activity was defined as causing mild shortness of breath and consisted of brisk walking, tennis doubles, or leisurely bicycling. Vigorous-intensity physical activity consisted of running, climbing, fast cycling, or aerobics, which caused more significant shortness of breath than moderate-intensity activities.[26] Regarding comorbidities, diabetes mellitus was defined as the prescription of anti-diabetic drugs with ICD-10 codes E11–E14 or a fasting blood glucose level ≥ 126 mg/dL. Hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or at least one annual claim for an antihypertensive drug with ICD-10 codes I10–I13 or I15. Dyslipidemia was defined as a total cholesterol level ≥ 240 mg/dL or at least one annual claim for an antihyperlipidemic drug with ICD-10 code E78. Other comorbidities were defined using the following ICD-10 codes: COPD (J42–J44, except J43.0 [unilateral emphysema]), asthma (J45–J46), ischemic heart disease (I20–I25), myocardial infarction (I21–I22), congestive heart failure (I50), stroke (I63–I64), and pulmonary tuberculosis (TB) (A15–A19 plus the specific NHIS code for TB, V000, V206, or V246).[19,27–33]

Statistical analysis

Continuous variables are expressed as the mean ± standard deviation and categorical variables are expressed as numbers (percentages). The differences between individuals with and without bronchiectasis were analyzed using Student's *t* test for continuous variables, and Pearson's chi-square test for categorical variables. The incidence of dementia was determined by dividing the number of persons with a newly diagnosed (incident) dementia by the total duration of follow-up

(1,000 person-years [PY]). We adopted the standardized measure of 1,000 PY to facilitate comparisons with published findings of dementia incidence.[34,35] A cumulative incidence plot was used to compare the incidence of dementia in individuals with and without bronchiectasis. Cox regression analysis was used to determine the risk of dementia in individuals with bronchiectasis compared to those without bronchiectasis. Sex and BMI were included as covariates in the multivariable model as possible confounders that consistently affect the development of dementia.[3,36] Therefore, demographic variables (age, sex, and BMI), socioeconomic status (low income), personal habits (smoking status, alcohol consumption, and regular exercise), and comorbidities (hypertension, dyslipidemia, diabetes mellitus, asthma or COPD, and pulmonary TB) were included for the adjustment. Values with two-sided $p < .01$ were considered statistically significant due to the large sample size. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA).

Results

Baseline characteristics

Individuals with bronchiectasis were older (64 ± 9 vs. 61 ± 8 years) and had a lower BMI (23.7 ± 3.2 vs. 24.1 ± 3.0 kg/m^2) than those without bronchiectasis ($p < .001$ for all). The proportion of never smokers was higher (67.4% vs. 66.6%, $p < .001$) in individuals with bronchiectasis, but the proportions of low income (20.3% vs. 21.5%, $p < .001$), heavy drinking (5.0% vs. 6.4%, $p < .001$) and regular exercise (19.7% vs. 21.3%, $p < .001$) were lower in individuals with bronchiectasis than in those without bronchiectasis. Individuals with bronchiectasis had a higher rate of all comorbidities than those without bronchiectasis ($p < .001$ for all) (Table 1).

Incidence and risk of dementia in individuals with and without bronchiectasis

During the median follow-up duration of 9.3 years (interquartile range, 9.1–9.6 years), the incidence of all-cause dementia was 1.6-fold higher in individuals with bronchiectasis than in those without bronchiectasis (15.0 vs. 9.3/1000 PY). In line with this result, there was a significant difference in the cumulative incidence probability of dementia between the two groups (Figure 2). In the multivariable model, the risk of dementia was significantly higher in individuals with bronchiectasis than in those without bronchiectasis (adjusted hazard ratio [aHR] 1.09, 95% confidence interval [CI] 1.04–1.14) (Table 2).

In a subgroup analysis by dementia type, individuals with bronchiectasis had an increased risk of Alzheimer's disease compared with those without bronchiectasis (aHR 1.07, 95% CI 1.01–1.12); however, the risk of vascular dementia did not significantly differ between the two groups (aHR 1.05, 95% CI 0.90–1.21).

Stratified analyses

The risk of all dementia among individuals with bronchiectasis was stratified by age, sex, BMI, low income, smoking status, alcohol consumption, regular exercise, and asthma or COPD. There was no significant interaction in the association between bronchiectasis and all dementia (p for interaction > .05 for all) (Figure 3).

In the subgroup analysis according to dementia type, there was no significant factor interacting with the association between bronchiectasis and Alzheimer's dementia. However, interaction effects by gender (p for interaction = .036) and low income (p for interaction = .010) were found for the association between bronchiectasis and vascular dementia. Individuals with bronchiectasis had 20% and 47% higher risks of vascular dementia among women and those with low-income, respectively than the corresponding individuals without bronchiectasis. More detailed information is provided in Supplementary Table 1.

Discussion

In this large-scale longitudinal cohort study, we revealed that individuals with bronchiectasis had an increased risk for dementia by 9% more than those without bronchiectasis during a 10-year follow-up duration. In addition, a subgroup analysis showed that the risk of dementia associated with Alzheimer's disease was especially high among individuals with bronchiectasis. Although there was no significant association between bronchiectasis and the risk of vascular dementia in the overall population, bronchiectasis increased the risk of vascular dementia in the female and low-income groups.

Chronic lung diseases, such as asthma and COPD, were previously found to be associated with an increased risk of dementia compared with their control group.[7,13] Extending the previous findings, we showed that bronchiectasis is a chronic respiratory illness with an increasing prevalence and disease burden, which might be associated with the development of dementia. The major strength of our study is that we used a nationally representative database, and the follow-up duration was as long as approximately 10 years. Another strength is that we minimized the effect of potential bias in evaluating the association of bronchiectasis with dementia by adjusting for risk factors for dementia (e.g., age, sex, smoking, and physical activity)[3] and other respiratory diseases (e.g., asthma, COPD, and TB).

Notably, in individuals with bronchiectasis, Alzheimer's disease accounted for more than three-fourths of incident

Table 1. Baseline characteristics of the study population.

	Total (n = 4,068,560)	No bronchiectasis (n = 4,053,838)	Bronchiectasis (n = 14,722)	p value
Age, years	61±8	61±8	64±9	<0.001
50–59	2,071,689 (51)	2,066,490 (51)	5,199 (35)	
60–69	1,304,154 (32)	1,298,678 (32)	5,476 (37)	
70–79	605,949 (15)	602,508 (15)	3,441 (23)	
≥80	86,768 (2)	86,162 (2)	606 (5)	
Sex				0.169
Male	1,970,669 (48)	1,963,455 (48)	7,214 (49)	
Female	2,097,891 (52)	2,090,383 (52)	7,508 (51)	
Body mass index, kg/m^2	24.1±3.0	24.1±3.0	23.7±3.2	<0.001
<18.5	88,868 (2.2)	88,189 (2.2)	679 (4.6)	
18.5–22.9	1,367,587 (33.6)	1,362,105 (33.6)	5,482 (37.2)	
23–24.9	1,115,619 (27.4)	1,111,918 (27.4)	3,701 (25.1)	
≥25	1,496,486 (36.8)	1,491,626 (36.8)	4,860 (33.1)	
Low income[a]	875,152 (21.5)	872,164 (21.5)	2,988 (20.3)	<0.001
Smoking status				<0.001
Never smoker	2,708,048 (66.6)	2,698,119 (66.6)	9,929 (67.4)	
Past smoker	645,070 (15.8)	642,451 (15.8)	2,619 (17.8)	
Current smoker	715,442 (17.6)	713,268 (17.6)	2,174 (14.8)	
Alcohol consumption				<0.001
Never	2,637,718 (64.8)	2,627,068 (64.8)	10,650 (72.3)	
Mild (<30 g/day)	1,169,595 (28.8)	1,166,252 (28.8)	3,343 (22.7)	
Heavy (≥30 g/day)	261,247 (6.4)	260,518 (6.4)	729 (5.0)	
Regular exercise	865,483 (21.3)	862,587 (21.3)	2,896 (19.7)	<0.001
Comorbidities				
Hypertension	1,850,612 (45.5)	1,843,247 (45.5)	7,365 (50.0)	<0.001
Dyslipidemia	1,091,827 (26.8)	1,087,659 (26.8)	4,168 (28.3)	<0.001
Diabetes mellitus	611,701 (15.0)	609,339 (15.0)	2,362 (16.0)	<0.001
Asthma or COPD	453,965 (11.2)	446,734 (11.0)	7,231 (49.1)	<0.001
Ischemic heart disease	328,170 (8.1)	325,753 (8.0)	2,417 (16.4)	<0.001
Myocardial infarction	28,426 (0.7)	28,131 (0.7)	295 (2.0)	<0.001
Congestive heart failure	47,437 (1.2)	46,956 (1.2)	481 (3.3)	<0.001
Stroke	128,275 (3.2)	127,513 (3.2)	762 (5.2)	<0.001
Pulmonary tuberculosis	1,235 (0.03)	1,201 (0.03)	34 (0.2)	<0.001

Data are presented as the number (percentage) or mean ± standard deviation.
[a]Low income was defined as income in the lowest 25% among the entire Korean population or receiving Medicaid.
COPD, chronic obstructive pulmonary disease.

dementia, while less than one-fourth of dementia was caused by vascular dementia. In addition, while individuals with bronchiectasis had a 7% increased risk of developing Alzheimer's disease compared to those without bronchiectasis, the risk of developing vascular dementia did not differ between the two groups. These results suggest that screening and early detection of Alzheimer's disease would be very important in improving cognitive dysfunction among individuals with bronchiectasis, which is also in line with a previous study.[17]

Two major hypotheses exist for the mechanism linking bronchiectasis with Alzheimer's disease. First, systemic inflammation associated with bronchiectasis may promote neurodegeneration. Inflammatory mediators such as tumor necrosis factor-α and interleukin-6 that are similar to those in COPD and asthma, are released in bronchiectasis.[37,38] An increasing body of human and animal studies have demonstrated that these systemic inflammation can cause neurodegeneration by inducing hyperphosphorylation, β-amyloid oligomerization, and complement activation.[39] Therefore, mechanisms underlying chronic respiratory diseases and the development of dementia might be linked. Second, hypoxia, common in individuals with bronchiectasis, may lead to dementia. A prospective study of older women showed a deleterious effect of decreased oxygen saturation on cognitive function.[40] Chronic hypoxia leads to several pathological changes, such as neuroinflammation, increased oxidative stress, and synaptic dysfunction, all resulting in

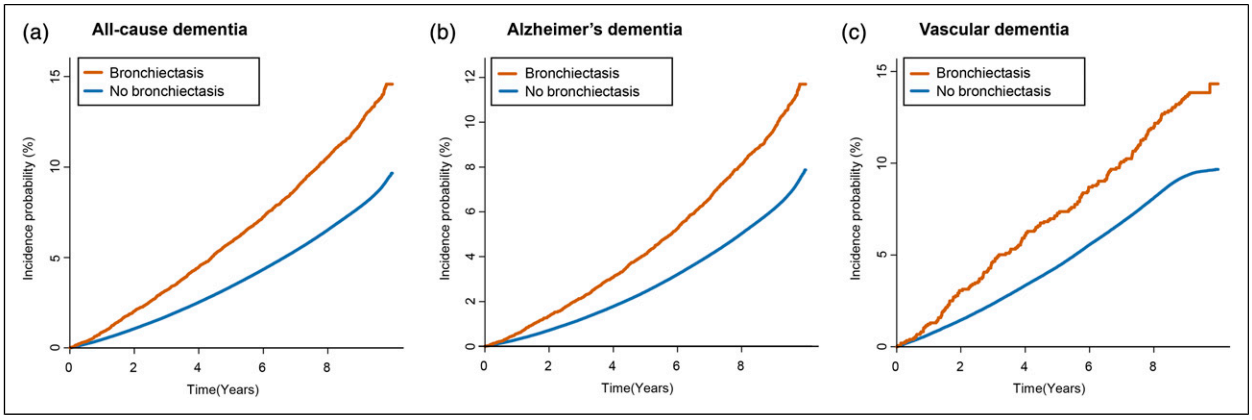

Figure 2. Cumulative incidence probability (%) of dementia in participants with and without bronchiectasis: (a) All-cause dementia, (b) Alzheimer's dementia and (c) Vascular dementia.

Table 2. Incidence and risk of dementia in individuals with and without bronchiectasis.

	No. of events	IR (/1,000 PY)	Unadjusted HR (95% CI)	Adjusted HR[a] (95% CI)
All-cause dementia				
No bronchiectasis (*n* = 4,053,838)	329,276	9.3	1 (Reference)	1 (Reference)
Bronchiectasis (*n* = 14,722)	1,829	15.0	1.63 (1.56–1.71)	1.09 (1.04–1.14)
Alzheimer's dementia				
No bronchiectasis (*n* = 4,053,838)	258,711	7.3	1 (Reference)	1 (Reference)
Bronchiectasis (*n* = 14,722)	1,416	11.6	1.61 (1.53–1.70)	1.07 (1.01–1.12)
Vascular dementia				
No bronchiectasis (*n* = 4,053,838)	35,877	1.0	1 (Reference)	1 (Reference)
Bronchiectasis (*n* = 14,722)	181	1.5	1.48 (1.28–1.72)	1.05 (0.90–1.21)

[a]Age, sex, body mass index, smoking status, alcohol consumption, regular exercise, low income, hypertension, dyslipidemia, diabetes mellitus, asthma or chronic obstructive pulmonary disease, and pulmonary tuberculosis were adjusted.
IR, incidence rate; PY, person-years; HR, hazard ratio; CI, confidence interval.

neurodegeneration.[41] Taken together, bronchiectasis seems to deteriorate cognitive function slowly and gradually through neurodegeneration.

It is well known that individuals with bronchiectasis have an increased risk of developing cerebrovascular diseases such as ischemic stroke compared with those without bronchiectasis.[42] Unexpectedly, our findings revealed no increased risk of vascular dementia in individuals with bronchiectasis compared to the control group. However, we found that sex and income modulated the effect of bronchiectasis on vascular dementia, which denotes a significantly increased risk of vascular dementia in the female and low-income groups. This phenomenon is not fully explainable because our study is observational, but there are a few possibilities. First, in the general population, it is believed that men have a slightly higher risk for vascular dementia than women.[43] However, studies have suggested that women with certain sex-specific risk factors (e.g., menopause, poorly timed hormone replacement therapy, etc.) may be at a higher risk of developing dementia.[43] Considering that bronchiectasis is associated with earlier menopause and a shorter duration of hormone replacement therapy in women,[44] this higher burden of female-specific risk factors for vascular dementia might have influenced our results. Second, female sex and low socioeconomic status are associated with bronchiectasis severity or exacerbations.[45,46] Increased severity expressed as frequent exacerbation is closely linked to systemic inflammation, which can damage vascular endothelial cells.[47] Chronic hypoxia resulting from repeated exacerbations is also associated with elevated blood viscosity.[48] These factors might contribute to an increased risk of cerebrovascular diseases.

There are academic and clinical implications of our study. First, few studies have evaluated cognitive dysfunction and dementia in individuals with bronchiectasis. Because we provided solid evidence that bronchiectasis can be a risk factor for dementia, it would be helpful to promote future research to reduce the burden of cognitive impairment in this population. Second, our study suggests that screening for cognitive dysfunction would be important in individuals with bronchiectasis. Particularly, the risk of dementia is

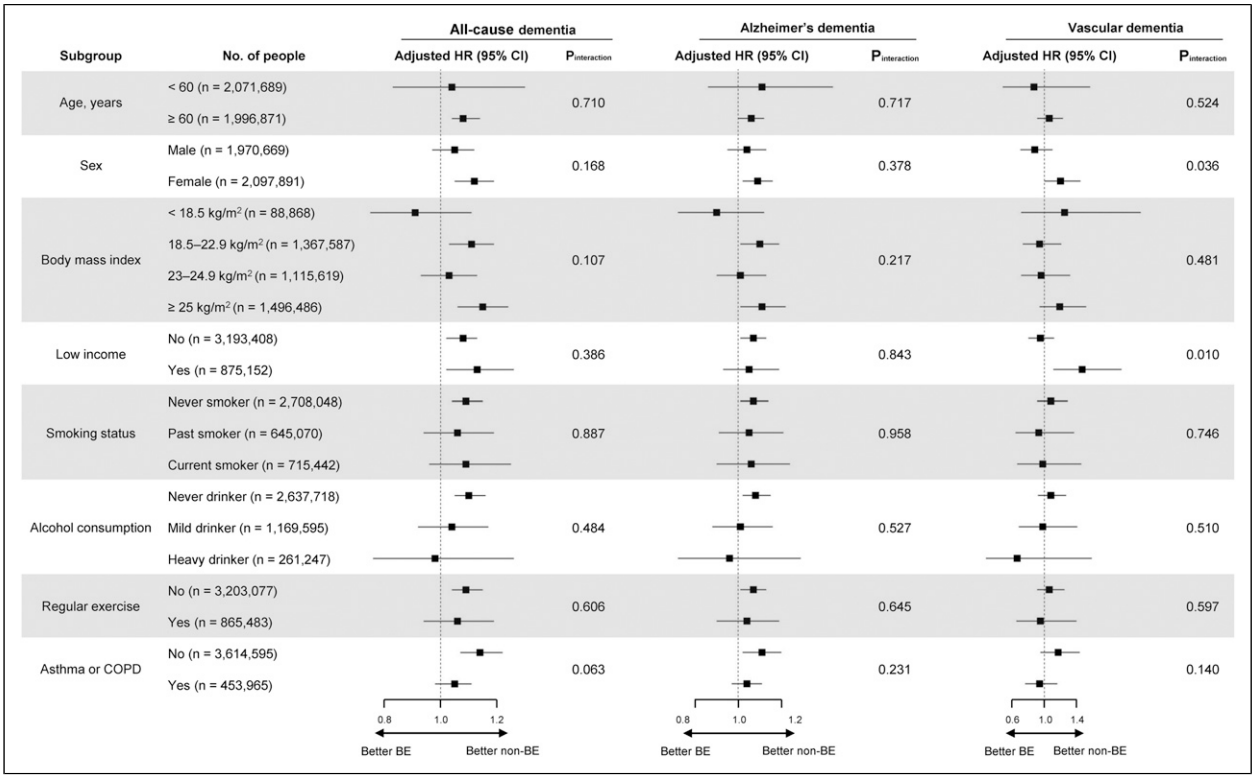

Figure 3. Subgroup analysis of the study outcome. Forest plots show the hazard ratio of individuals with bronchiectasis compared to those without bronchiectasis. COPD, chronic obstructive pulmonary disease; BE, bronchiectasis; aHR, adjusted hazard ratio; CI, confidence interval.

significantly increased in individuals with bronchiectasis than those without bronchiectasis regardless of stratification with clinically important variables. Therefore, preventive management and screening for dementia could be considered for all individuals with bronchiectasis. Potential preventive measures include respiratory symptom control, regular physical activity, cognitive training, and managing concurrent respiratory infections. However, as factors related to cognitive dysfunction are not well elucidated yet in bronchiectasis, we hope that well-designed studies focusing on cognitive dysfunction in individuals with bronchiectasis will be performed soon.

This study has some limitations. First, the prevalence of dementia may have been under- or over-estimated because the definition is solely dependent on the ICD-10 codes without several tools to guide dementia diagnoses, such as brain imaging and various rating scales. Additionally, a follow-up of about 10 years might be insufficient to capture all individuals with potential dementia. However, a longer follow-up was not feasible within the restrictions of the available dataset. Second, a one-year lag time might be insufficient to evaluate the causal relationship between bronchiectasis and dementia, considering the slow progression of Alzheimer's dementia. Third, possible measurement bias should be considered in the interpretation of our results. Further information in medical records, which may help with dementia diagnosis, could not be obtained. Additionally, misclassification was possible because some variables, including smoking status, were assessed using questionnaires. Fourth, our results should be cautiously generalized to other ethnicities because only a Korean population was included in this study.

Conclusion

Bronchiectasis was associated with an increased risk of dementia, especially Alzheimer's disease. Clinicians should be aware of the risk of dementia in individuals with bronchiectasis and provide adequate preventive management.

Acknowledgments

This study was performed using the National Health Insurance System database, and the results do not necessarily represent the opinion of the National Health Insurance Corporation.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical statement

Ethical approval

This study was approved by the institutional review board of Hallym University Kangnam Sacred Heart Hospital (application no. 2022-08-088). The requirement for informed consent was waived because the NHIS database was constructed the after anonymization of patients.

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Data availability statement

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Supplemental Material

Supplemental material for this article is available online.

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