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Association between lung function and the risk of atrial fibrillation in a nationwide population cohort study

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We investigated the association between lung function and atrial fibrillation (AF) in 21,349 adults without AF aged ≥ 40 years who underwent spirometry. The study participants were enrolled from the Korean National Health and Nutritional Examination Survey between 2008 and 2016. The primary outcome was new-onset non-valvular AF identified from the National Health Insurance Service database. During the median follow-up of 6.5 years, 2.15% of participants developed new-onset AF. The incidence rate of AF per 1000 person-years was inversely related to the forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), and FEV_1/FVC quartile. After adjustment for multiple variables, the AF risk in the lowest FEV_1 quartile was 1.64-fold higher than that in the highest quartile (hazard ratio (HR) 1.64 (95% confidence interval (CI) 1.26–2.12) for lowest FEV_1 quartile). The lowest quartile of FVC had 1.56-fold higher AF risk than the highest quartile (HR 1.56 (95% CI 1.18–2.08) for lowest FVC quartile). Although the lowest FEV_1/FVC quartile was associated with an increased risk of AF in the unadjusted model, this increased risk was not statistically significant in the multivariable analysis. Compared to those with normal lung function, participants with restrictive or obstructive lung function had 1.49 and 1.42-fold higher AF risks, respectively. In this large nationwide cohort study, both obstructive and restrictive patterns of reduced lung function were significantly associated with increased AF risk.

Abbreviations

AF	Atrial fibrillation
DM	Diabetes mellitus
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
FEV_1	Forced expiratory volume in 1 s
FVC	Forced vital capacity
IHD	Ischemic heart disease
KNHANES	Korean National Health and Nutrition Examination Survey
NHIS	National Health Insurance Service
BMI	Body mass index
WC	Waist circumference
ICD	International classification of disease
eGFR	Estimated glomerular filtration rate
HR	Hazard ratio
CI	Confidence interval

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ARIC	Atherosclerosis risk in communities
MESA	Multi-ethnic study of atherosclerosis study

Atrial fibrillation (AF) is the most common arrhythmia in adults worldwide¹. AF is associated with increased risks of stroke, heart failure, and death, leading to a high economic burden². AF occurs in an estimated 2–4% of adults¹. And the incidence rate is expected to gradually increase with the increasing age of the population. Therefore, undiagnosed AF should be recognized in the general population to prevent AF-related complications³. The risk of AF is increased by several factors, including age, male sex, obesity, smoking, alcohol consumption, hypertension, diabetes mellitus (DM), chronic kidney disease (CKD), coronary artery disease, valvular heart disease, heart failure, obstructive sleep apnea, and chronic obstructive pulmonary disease (COPD)².

AF frequently occurs in patients with airway diseases, such as COPD and asthma. Patients with asthma and COPD have approximately 1.5- and twofold higher AF risks than those without asthma and COPD, respectively^{4,5}. Several factors, such as smoking, hypoxia, inflammation, and increased use of beta-2 agonists, contribute to the development of AF in patients with airway diseases⁶. Reduced lung function, i.e., low forced expiratory volume in 1 s (FEV₁) and forced vital capacity (FVC), is associated with heart failure and ischemic heart disease (IHD), which are risk factors for AF. In addition, reduced lung function is associated with stroke, which is the most common complication of AF^{7–9}. Previous studies have reported that lung function is inversely related to AF risk^{10–12}. However, these studies focused on FEV₁ and FVC instead of lung function categories, and were conducted in Western populations.

We analyzed a nationwide population-based cohort to investigate the association between reduced lung function and the AF risk in an adult population using two linked Korean National Health Databases: Korean National Health and Nutrition Examination Survey (KNHANES) and National Health Insurance Service (NHIS). To the best of our knowledge, this is the first study to investigate the association between restrictive or obstructive lung function impairment and AF in a nationwide population-based cohort with detailed anthropometric and laboratory results.

Results

Baseline characteristics. Table 1 presents the baseline characteristics of the 21,349 participants. Among the study population, 10.2% and 13.1% had restrictive and obstructive lung function impairments, respectively. Compared to those with normal lung function, participants with restrictive or obstructive lung function impairment had higher prevalence of old age, male sex, current smoking, heavy alcohol consumption, low household income, unemployment, low education, DM, hypertension, dyslipidemia, asthma, prior stroke and prior IHD. Obesity and abdominal obesity were significantly more common in participants with restrictive lung function impairment than the other groups.

Among the study population, 2.15% had new-onset AF during a median follow-up of 6.5 years (interquartile range = 4.5–8.5 years) (Table 2). Compared to those without AF, participants with new-onset AF were more likely to exhibit old age, male sex, current smoking, heavy alcohol consumption, unemployment, obesity, and low income and education levels. Participants with AF had significantly worse baseline lung function and were more likely to have DM, hypertension, asthma, stroke, CKD, and IHD than those without AF.

Lung function quartile and AF. The incidence of AF was inversely related to FEV₁, FVC, and FEV₁/FVC quartiles. From the highest to lowest quartiles, the incidence rates were 2.82, 2.55, 3.10, and 5.08 for FEV₁; 2.11, 2.64, 3.52, and 5.32 for FVC; 1.87, 2.60, 3.51, and 5.71 for FEV₁/FVC (Table 3). Therefore, lung function quartiles were inversely associated with AF risk. After adjustment for multiple variables, the AF risks were 1.64-fold higher for the lowest compared to the highest FEV₁ quartile (HR 1.64 (95% CI 1.26–2.12) for the lowest FEV₁ quartile), and 1.56-fold higher for the lowest compared to the highest FVC quartile (HR 1.56 (95% CI 1.18–2.08) for the lowest FVC quartile), respectively. Although the lowest FEV₁/FVC quartile was associated with increased AF risk in the unadjusted model, this inverse association was not statistically significant in the multivariable analysis. Figure 1 shows the AF incidence rates and HRs by lung function deciles.

Restrictive or obstructive lung function impairment and AF. Among participants with restrictive and obstructive lung function impairment, the incidence rates of newly diagnosed AF were 5.92 and 6.96 per 1000 person-years, respectively (Table 4). The age- and sex-adjusted HR for AF according to lung function impairment was 1.64 (95% CI 1.27–2.11) for restrictive lung function impairment and 1.42 (95% CI 1.11–1.81) for obstructive lung function impairment. After adjusting for age, sex, BMI, household income, education, exercise, alcohol consumption, smoking, hypertension, DM, dyslipidemia, stroke, IHD, asthma, white blood cell and eGFR, AF was significantly associated with reduced lung function (HR 1.49 (95% CI 1.15–1.92) for restrictive lung function impairment, HR 1.42 (95% CI 1.11–1.82) for obstructive lung function impairment, respectively) (Table 4, Fig. 2).

Subgroup analysis. Figure 3 shows the results of the subgroup analysis of reduced lung function and AF risk according to age, sex, smoking, alcohol consumption, DM, hypertension, CKD, stroke, and IHD. The association between reduced lung function and AF risk did not vary according to any of these factors. There were no significant interactions observed in any subgroup.

Variable	Normal (n = 16,365)	Restrictive (n = 2178)	Obstructive (n = 2806)	p-value
Age ≥ 65 years	3479 (21.3)	873 (40.1)	1652 (58.9)	<.0001 ^{a,b,c}
Male	6294 (38.5)	1031 (47.3)	2058 (73.3)	<.0001 ^{a,b,c}
Smoking				<.0001 ^{a,b,c}
Nonsmoker	10,734 (65.6)	1280 (58.8)	889 (31.7)	
Ex-smoker	2978 (18.2)	497 (22.8)	1078 (38.4)	
Current smoker	2653 (16.2)	401 (18.4)	839 (29.9)	
Alcohol consumption				<.0001 ^{a,b,c}
None	4768 (29.1)	793 (36.4)	898 (32.0)	
Mild to moderate	10,342 (63.2)	1208 (55.5)	1607 (57.3)	
Heavy	1255 (7.7)	177 (8.1)	301 (10.7)	
Moderate physical activity	6417 (39.2)	796 (36.6)	1208 (43.1)	<.0001 ^{a,b,c}
Household income (lowest quartile)	2713 (16.6)	540 (24.8)	888 (31.7)	<.0001 ^{a,b,c}
Occupation, yes	10,590 (64.7)	1214 (55.7)	1596 (56.9)	<.0001 ^{a,b}
High education	9693 (59.2)	1037 (47.6)	1166 (41.6)	<.0001 ^{a,b,c}
Diabetes mellitus	1768 (10.8)	503 (23.1)	520 (18.5)	<.0001 ^{a,b,c}
Hypertension	5712 (34.9)	1130 (51.9)	1379 (49.1)	<.0001 ^{a,b,c}
Dyslipidemia	3221 (19.7)	521 (23.9)	532 (19.0)	<.0001 ^{a,c}
Asthma	311 (1.9)	90 (4.1)	246 (8.8)	<.0001 ^{a,b,c}
Prior stroke	219 (1.3)	68 (3.1)	74 (2.6)	<.0001 ^{a,b}
Prior ischemic heart disease	338 (2.1)	106 (4.9)	118 (4.2)	<.0001 ^{a,b}
Anthropometric measurements				
Obesity	5920 (36.2)	1150 (52.8)	837 (29.8)	<.0001 ^{a,b,c}
Abdominal obesity	6841 (41.8)	1302 (59.8)	991 (35.3)	<.0001 ^{a,b,c}
Height (cm)	155.9 ± 9.1	155.7 ± 9.0	158.7 ± 8.9	<.0001 ^{b,c}
Weight (kg)	57.7 ± 10.6	60.6 ± 11.4	58.6 ± 10.4	<.0001 ^{a,b,c}
Body mass index (kg/m ²)	24.1 ± 2.9	25.3 ± 3.2	23.7 ± 2.7	<.0001 ^{a,b,c}
Waist circumference (cm)	77.5 ± 9.0	81.9 ± 9.6	79.7 ± 8.8	<.0001 ^{a,b,c}
SBP (mmHg)	120.8 ± 16.4	126.7 ± 17.3	125.6 ± 16.7	<.0001 ^{a,b}
DBP (mmHg)	77.7 ± 10.2	78.0 ± 10.4	76.1 ± 10.5	<.0001 ^{b,c}
Laboratory findings				
Fasting blood glucose (mg/dL)	100.2 ± 22.4	108.2 ± 30.3	103.6 ± 22.8	<.0001 ^{a,b,c}
Serum creatinine (mg/dL)	0.8 ± 0.2	0.9 ± 0.3	0.9 ± 0.4	<.0001 ^{a,b,c}
eGFR (mL/min/1.73m ²)	90.4 ± 16.6	87.7 ± 18.3	85.8 ± 17.0	<.0001 ^{a,b,c}
White blood cell (× 10 ⁹ /L)	6.0 ± 1.7	6.4 ± 1.8	6.5 ± 1.8	<.0001 ^{a,b}
Hemoglobin (g/dL)	13.9 ± 1.5	14.0 ± 1.6	14.4 ± 1.4	<.0001 ^{a,b,c}
Total cholesterol (mg/dL)	195.9 ± 35.9	193.0 ± 37.2	188.8 ± 36.4	<.0001 ^{a,b,c}
HDL cholesterol (mg/dL)	49.5 ± 11.8	46.5 ± 11.1	47.0 ± 11.6	<.0001 ^{a,b}
Triglyceride (mg/dL)	118.7 (117.6–119.7)	132.8 (129.8–136.0)	126.0 (123.5–128.7)	<.0001 ^{a,b,c}
ALT (IU/L)	19.0 (18.9–19.2)	21.4 (21.0–21.9)	19.4 (19.0–19.7)	<.0001 ^{a,c}
AST (IU/L)	21.5 (21.4–21.6)	23.1 (22.7–23.4)	22.7 (22.4–23.0)	<.0001 ^{a,b}

Table 1. Baseline characteristics of the study population. Values are presented as *n* (%) or mean ± standard deviation. SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein; AST, aspartate transaminase; ALT, alanine transaminase. ^aSignificant for Normal vs Restrictive, ^bsignificant for Normal vs Obstructive, ^csignificant for Restrictive vs Obstructive.

Discussion

In this large national cohort study, we found that reduced lung function was associated with increased AF risk, with similar risks for obstructive and restrictive lung function impairments. Lung function quartiles were inversely related to the AF risk. The main finding of the present study was that individuals with obstructive or restrictive lung function impairments had approximately 1.4-fold higher AF risk than those with normal lung function.

Most studies of pulmonary function and AF risk have been multicenter cohort studies that mainly focused on the FEV₁ and FVC values, rather than categories of lung function impairment^{11–14}. Moreover, previous studies had significant differences in the FEV₁ and FVC categories, follow-up duration and study design. A large Swedish population-based cohort study with a long follow-up duration of 24.8 years showed an inverse relationship between lung function and AF incidence by gender, but many patients were treated in an outpatient rather than an inpatient setting, hospitalized patients were excluded from the study¹⁰. The Atherosclerosis Risk

Variable	No AF (n = 20,890)	AF (n = 459)	p-Value
Age ≥ 65 years	5746 (27.51)	258 (56.21)	< .0001
Male	9147 (43.79)	236 (51.42)	0.0011
Smoking			0.0003
Nonsmoker	12,654 (60.57)	249 (54.25)	
Ex-smoker	4420 (21.16)	133 (28.98)	
Current smoker	3816 (18.27)	77 (16.78)	
Alcohol consumption			< .0001
None	6280 (30.06)	179 (39.00)	
Mild to moderate	12,929 (61.89)	228 (49.67)	
Heavy	1681 (8.05)	52 (11.33)	
Moderate physical activity	8227 (39.38)	194 (42.27)	0.2112
Household income (lowest quartile)	3978 (19.04)	163 (35.51)	< .0001
Occupation, yes	13,160 (63.00)	240 (52.29)	< .0001
High education	11,728 (56.14)	168 (36.60)	< .0001
Diabetes mellitus	2708 (12.96)	83 (18.08)	0.0013
Hypertension	7948 (38.05)	273 (59.48)	< .0001
Dyslipidemia	4191 (20.06)	83 (18.08)	0.2945
Asthma	618 (2.96)	29 (6.32)	< .0001
Prior stroke	344 (1.65)	17 (3.70)	0.0007
Prior ischemic heart disease	529 (2.53)	33 (7.19)	< .0001
Lung function			< .0001
Normal	16,105 (77.09)	260 (56.64)	
Restrictive	2096 (10.03)	82 (17.86)	
Obstructive	2689 (12.87)	117 (25.49)	
Anthropometric measurements			
Obesity	7712 (36.9)	195 (42.3)	0.0146
Abdominal obesity	8887 (42.5)	247 (53.8)	< .0001
Height (cm)	156.28 ± 9.09	156.27 ± 9.99	0.9986
Weight (kg)	58.10 ± 10.68	59.48 ± 10.66	0.0061
Body mass index (kg/m ²)	24.19 ± 2.91	24.67 ± 3.05	0.0004
Waist circumference (cm)	78.21 ± 9.10	81.07 ± 9.37	< .0001
SBP (mmHg)	121.85 ± 16.63	128.25 ± 17.98	< .0001
DBP (mmHg)	77.49 ± 10.25	77.49 ± 10.92	0.9964
Laboratory findings			
Fasting blood glucose (mg/dL)	101.47 ± 23.55	102.12 ± 20.02	0.5616
Serum creatinine (mg/dL)	0.84 ± 0.24	0.89 ± 0.35	< .0001
eGFR (mL/min/1.73 m ²)	89.58 ± 16.84	85.37 ± 19.14	< .0001
White blood cell (× 10 ⁹ /L)	6.07 ± 1.70	6.04 ± 1.66	0.7651
Hemoglobin (g/dL)	14.00 ± 1.53	14.05 ± 1.62	0.4956
Total cholesterol (mg/dL)	194.75 ± 36.14	189.93 ± 36.20	0.0047
HDL cholesterol (mg/dL)	48.90 ± 11.77	46.89 ± 11.80	0.0003
Triglyceride (mg/dL)	120.91 (119.97–121.86)	124.99 (118.61–131.71)	0.2239
ALT (IU/L)	19.31 (19.18–19.44)	19.12 (18.31–19.97)	0.6678
AST (IU/L)	21.81 (21.71–21.90)	23.00 (22.30–23.71)	0.0006

Table 2. Baseline characteristics according to the development of AF. Values are presented as *n* (%) or mean ± standard deviation. AF, atrial fibrillation; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein; AST, aspartate transaminase; ALT, alanine transaminase.

In Communities (ARIC) study also reported an inverse relationship between lung function and AF, with a relatively high rate of AF development (11%) during the follow-up of 11 years. However, in the ARIC study, 73.8% of participants were White, who have a higher AF risk than Asians^{12,13}. In addition, the ARIC investigators reported that obstructive lung function impairment was associated with increased AF incidence. However, they did not analyze restrictive lung function impairment in the study. In the Multi-Ethnic Study of Atherosclerosis (MESA) study, the AF incidence varied by race and was significantly lower in non-White patients compared to White patients¹⁵. In a cohort study conducted in specific regions of Korea, new-onset AF was identified in 1.7%

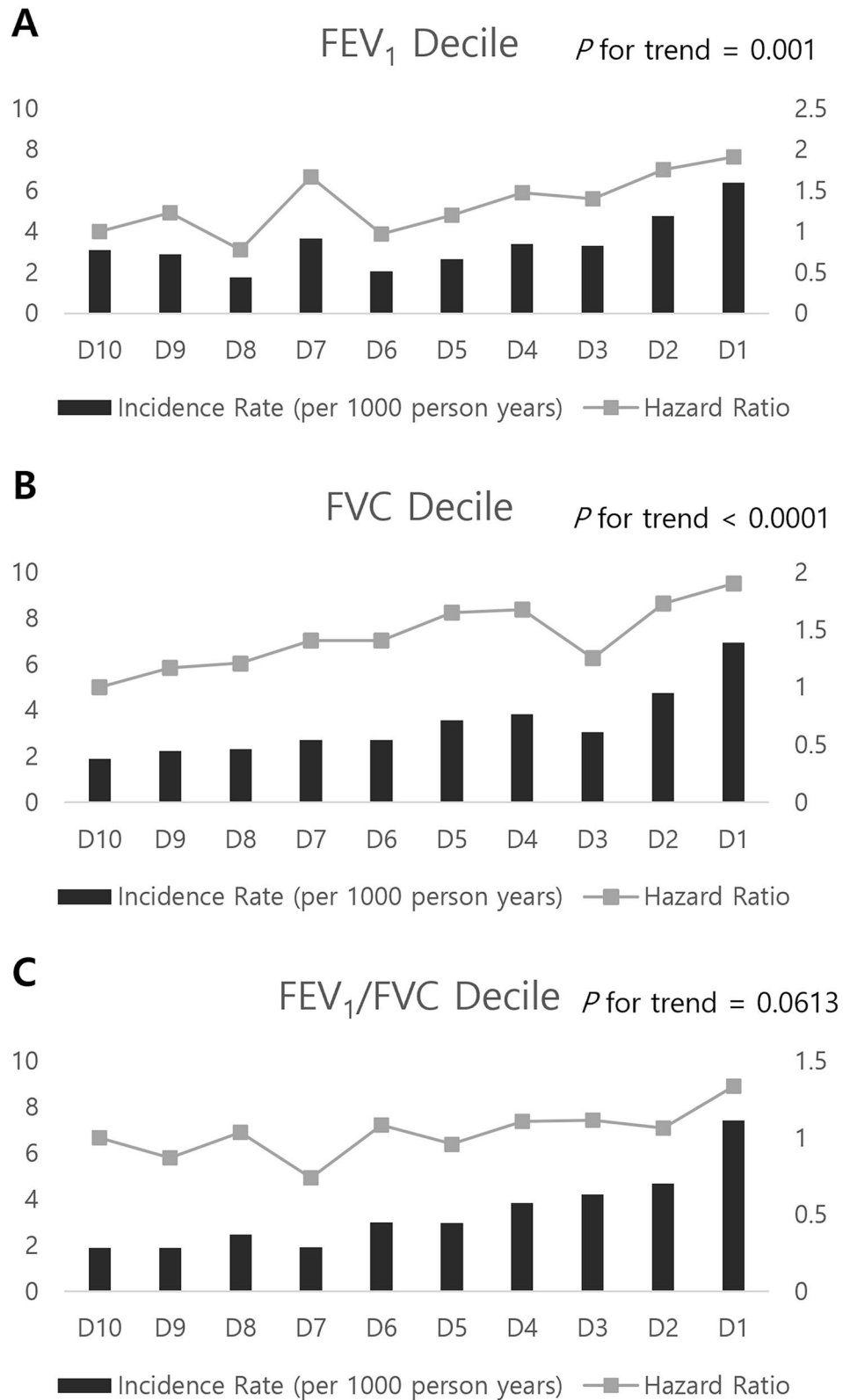


Figure 1. Incidence rate and hazard ratio of atrial fibrillation according to the decile of lung function measurements. **(A)** FEV₁, **(B)** FVC, and **(C)** FEV₁/FVC. All HRs adjusted for covariates including age, sex, BMI, household income, education, exercise, alcohol consumption, smoking, hypertension, DM, dyslipidemia, white blood cell count, eGFR, stroke, IHD, and asthma.

	Number of case	Number of AF	IR of AF (per 1000 person years)	Hazard ratio (95% CI)			
				Unadjusted	Model 1	Model 2	Model 3
FEV₁							
Q4 (highest)	5337	97	2.82	1	1	1	1
Q3	5337	87	2.55	0.91 (0.68–1.21)	1.13 (0.85–1.52)	1.13 (0.85–1.52)	1.11 (0.83–1.49)
Q2	5339	105	3.10	1.10 (0.83–1.45)	1.32 (1.00–1.74)	1.30 (0.98–1.72)	1.28 (0.96–1.69)
Q1 (lowest)	5336	170	5.08	1.80 (1.41–2.32)	1.71 (1.33–2.21)	1.70 (1.32–2.19)	1.64 (1.26–2.12)
FVC							
Q4 (highest)	5337	73	2.11	1	1	1	1
Q3	5338	90	2.64	1.25 (0.92–1.70)	1.27 (0.93–1.73)	1.25 (0.92–1.71)	1.24 (0.91–1.68)
Q2	5338	119	3.52	1.67 (1.25–2.24)	1.53 (1.14–2.05)	1.44 (1.07–1.94)	1.41 (1.05–1.90)
Q1 (lowest)	5336	177	5.32	2.53 (1.93–3.32)	1.75 (1.33–2.31)	1.60 (1.21–2.13)	1.56 (1.18–2.08)
FEV₁/FVC							
Q4 (highest)	5337	66	1.87	1	1	1	1
Q3	5338	89	2.60	1.40 (1.02–1.92)	1.09 (0.79–1.51)	1.1 (0.80–1.52)	1.10 (0.80–1.51)
Q2	5350	119	3.51	1.89 (1.40–2.56)	1.14 (0.84–1.56)	1.16 (0.85–1.59)	1.15 (0.84–1.57)
Q1 (lowest)	5324	185	5.71	3.11 (2.35–4.12)	1.31 (0.96–1.79)	1.37 (1.00–1.88)	1.32 (0.96–1.82)

Table 3. Incidence rate and hazard ratios for the risk of atrial fibrillation according to quartiles of FEV₁, FVC, and FEV₁/FVC ratio. Model 1: Adjust by age, sex. Model 2: Adjust by age, sex, body mass index, household income, education, alcohol consumption, smoking, diabetes mellitus, hypertension, dyslipidemia. Model 3: Adjust by age, sex, body mass index, household income, education, alcohol consumption, smoking, diabetes mellitus, hypertension, dyslipidemia, white blood cell, estimated glomerular filtration rate, prior stroke, prior ischemic heart disease, asthma. FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; AF, atrial fibrillation; IR, incidence rate (events/1000 person years); CI, confidence interval.

	Number of case	Number of AF	IR of AF (per 1000 person years)	Hazard ratio (95% CI)			
				Unadjusted	Model 1	Model 2	Model 3
Normal	16,365	260	2.47	1	1	1	1
Restrictive or obstructive	4984	199	6.49	2.64 (2.16–3.18)	1.51 (1.24–1.85)	1.48 (1.21–1.82)	1.45 (1.18–1.78)
Normal	16,365	260	2.47	1	1	1	1
Restrictive	2178	82	5.92	2.39 (1.86–3.06)	1.64 (1.27–2.11)	1.52 (1.17–1.96)	1.49 (1.15–1.92)
Obstructive	2806	117	6.96	2.86 (2.30–3.55)	1.42 (1.11–1.81)	1.46 (1.14–1.86)	1.42 (1.11–1.82)

Table 4. Incidence rate and hazard ratios for the risk of atrial fibrillation according to restrictive or obstructive lung function impairment. Model 1: Adjust by age, sex. Model 2: Adjust by age, sex, body mass index, household income, education, alcohol consumption, smoking, diabetes mellitus, hypertension, dyslipidemia. Model 3: Adjust by age, sex, body mass index, household income, education, alcohol consumption, smoking, diabetes mellitus, hypertension, dyslipidemia, white blood cell, estimated glomerular filtration rate, prior stroke, prior ischemic heart disease, asthma. AF, atrial fibrillation; IR, incidence rate (events/1000 person years); CI, confidence interval.

of the population, and individuals in the lowest FEV₁ quartile had 1.59-fold higher AF risk than those in the highest quartile, which is in line with the results of our study. However, in the previous study, AF was not defined using the ICD-10 code¹⁴. In the present nationwide population cohort study, including data from the baseline physical examination, laboratory findings, outpatient visits, hospitalization, and medication claims, the AF risk was significantly inversely associated with FEV₁ and FVC quartiles after multivariable adjustment. Interestingly, patients with obstructive or restrictive lung function impairment had a 1.4-fold higher AF incidence than those with normal lung function.

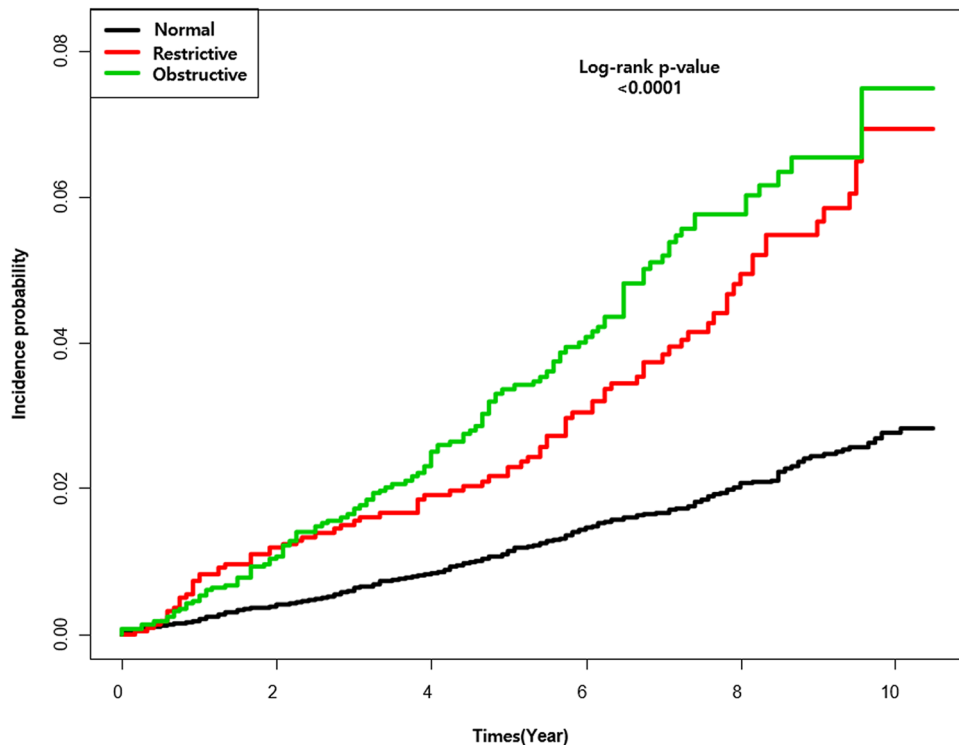


Figure 2. Clinical outcomes according to lung function.

The mechanisms underlying the association between decreased lung function and AF are unclear. However, previous studies have suggested several mechanisms, including hypoxia, systemic inflammation, increased sympathetic nerve activation, and the use of COPD treatments, such as beta-2 agonists and oral steroids⁶. Hypoxia is common in individuals with decreased lung function and causes pulmonary vasoconstriction, which leads to pulmonary hypertension and increased afterload to the right side of the heart^{16,17}. Moreover, chronic hypoxia regulates the expression of hypoxia-inducible factors 1 and 2, the production of reactive oxygen species, blood pressure, and vascular inflammation¹⁸. Atrial structural remodeling plays a key role in the development of AF in patients with impaired lung function. In addition, elevated white blood cell count and C-reactive protein levels are associated with increased AF incidence¹⁹. Fogarty et al.²⁰ reported that the C-reactive protein level is inversely related to lung function. The present study also showed that the white blood cell count was elevated in individuals with restrictive and obstructive lung function impairments, in line with previous studies. Sympathetic nerve activation, which is related to AF progression, is often found in patients with reduced lung function²¹. Inhaled beta-2 agonists and anticholinergics, the main treatments for COPD, are highly associated with tachyarrhythmia²². In addition, oral corticosteroids and theophylline increase the risk of AF²³.

The present study of nationwide population showed increased AF incidence in patients with reduced lung function. Therefore, individuals with reduced lung function may be potential candidates for more meticulous screening of AF. To the best of our knowledge, this was the first study to investigate the association between obstructive or restrictive lung function impairment and AF risk using detailed anthropometric and laboratory results in a nationwide cohort.

This study has several limitations. First, clinical outcomes relied only on claims data and there might be missed diagnoses of asymptomatic and paroxysmal AF. Second, the pulmonary function tests used in this study could not assess the severity of COPD because of the pre-bronchodilator results. Third, this study was conducted with a single Asian ethnic group. Fourth, we measured lung function using only one method, spirometry without chest computed tomography, which indicates the presence or absence of bronchiectasis or emphysema. However, spirometry is a simple and easy method to check lung function, and trained examiners measured lung function with a predefined protocol. Fifth, medications that could increase the incidence of AF, such as beta-2 agonists and oral steroids were not considered. Sixth, compared to population without lung function impairment, those with obstructive or restrictive lung function impairment may have higher detection rate of AF, due to this group tends to get more medical attention and examination. Last, in this study, more subjects had minor reduced lung function than severely reduced lung function, because KNHANES data were obtained from subjects participating in a national survey. However, the KNHANES data can represent the public health of the entire population of Korea, which has significant implications in many respects²⁴.

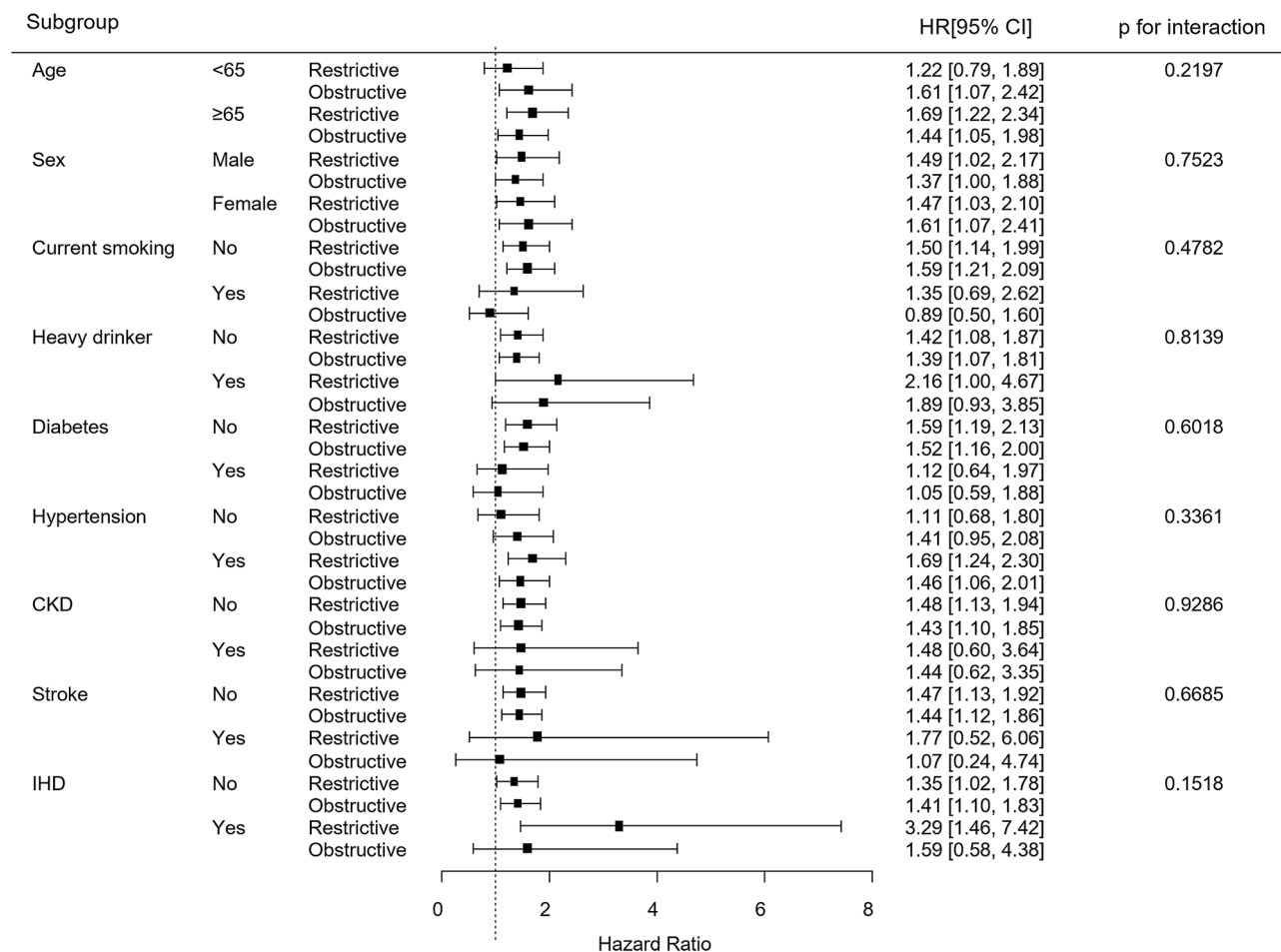


Figure 3. Subgroup analysis for atrial fibrillation risk. All HRs adjusted for covariates including age, sex, BMI, household income, education, exercise, alcohol consumption, smoking, hypertension, DM, dyslipidemia, white blood cell count, eGFR, stroke, IHD, and asthma. CKD chronic kidney disease, IHD ischemic heart disease.

Conclusions

We found that reduced lung function was an independent risk factor for AF in a nationwide population cohort study. Subjects with impaired lung function have a high risk of AF, and both obstructive and restrictive lung function impairment have similar AF risks. Future prospective research is needed to clarify the mechanism of association between reduced lung function and AF.

Methods

Source of the database and study population. We derived the data by cross-referencing KNHANES and NHIS. In this study, we used KNHANES data to collect study population and NHIS data to determine clinical outcomes. The KNHANES has been performed by the Korean Centers for Disease Control and Prevention at 3-year intervals since 1998 to monitor the general health and nutritional status of the civilian, noninstitutionalized Korean population²⁵. Sampling units were households selected via a stratified, multistage probability-sampling design that considered geographic area, sex, and age group, by reference to household registries. NHIS is a social insurance payment system that covers approximately 97% of the Korean population. The Korean NHIS data include all national health checkup data and claim data, including drug prescriptions, diagnostic codes for the International Classification of Disease-10 (ICD-10) disease coding system, and claimed treatment details²⁶. All KNHANES participants provided written informed consent for participation.

In this study, data from the KNHANES between 2008 and 2016 were used. We excluded participants among the 40,279 sample individuals as follow, aged < 40 years ($n = 4772$), participants without spirometry results ($n = 10,705$), participants who were already diagnosed with AF during wash-out period for 1 year ($n = 458$), or missing data ($n = 2995$) (Fig. 4).

The institutional review board of the Catholic University of Korea (IRB no: VC21ZISI0041) approved this study. The study was conducted in compliance with the Declaration of Helsinki. Informed consent was obtained from all participants at the time of survey collection.

Clinical and laboratory measurements. Details of the KNHANES regarding health surveys, standardized physical examinations, laboratory tests, and definitions of risk factors have been described in a previous

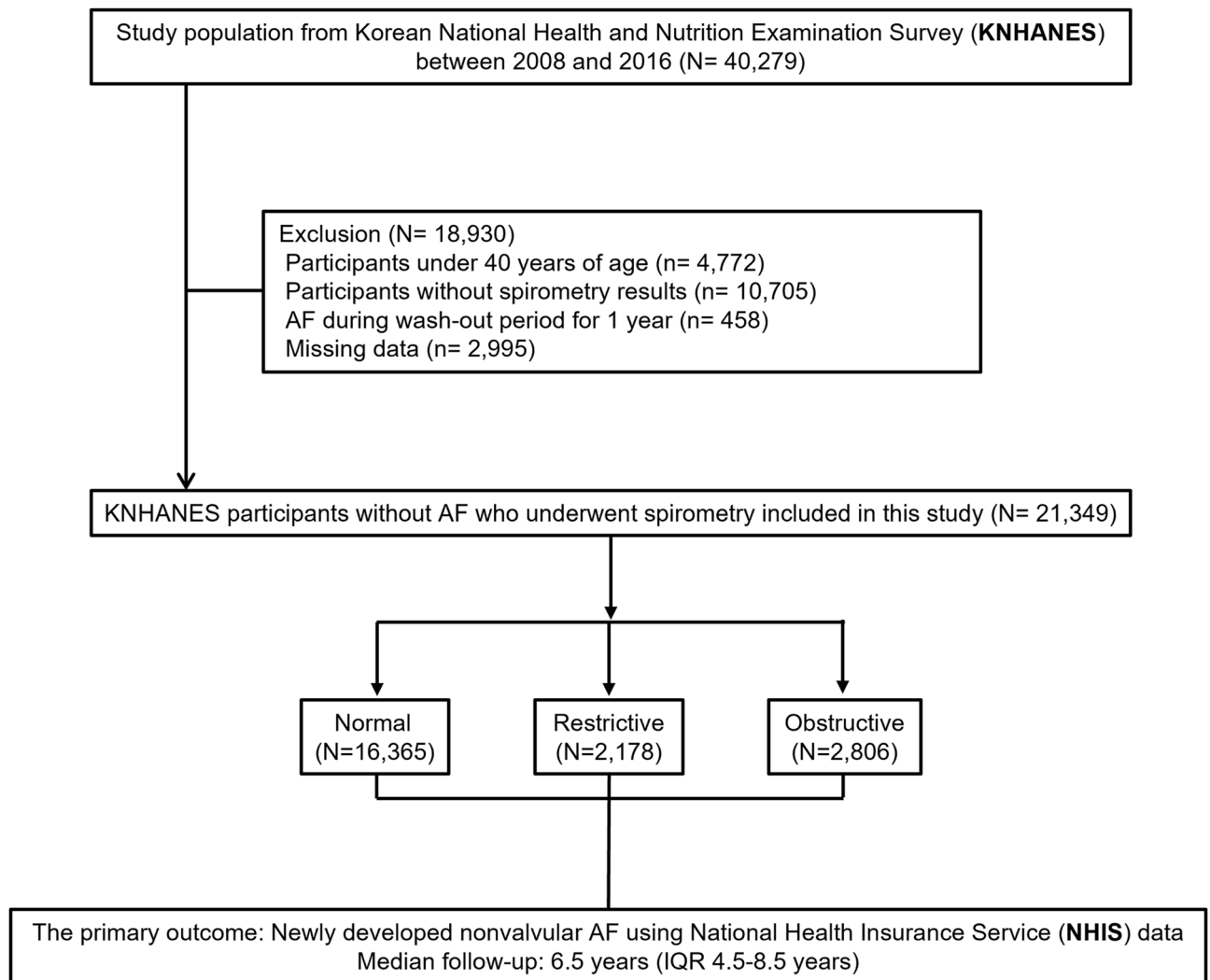


Figure 4. Sample recruitment from the database.

paper²⁵. Specially trained examiners performed the physical examination by a standardized method. Body mass index (BMI) was calculated as participant body weight in kilograms divided by the square of height in meters. Obesity was defined as subjects with BMI more than 25 kg/m²²⁷. Waist circumference (WC) was measured at the midpoint between the lowest rib and the anterior iliac crest in the standing position. Abdominal obesity was defined as subjects with WC more than 90 cm in men and more than 80 cm in women. The definition of abdominal obesity was a WC \geq 90 cm in men and \geq 85 cm²⁸. However, our data were provided by masking in 10 cm increments, and the standard of 80 cm in women has been applied. The health-related behavior surveys included well-established questionnaires to determine the demographic and socioeconomic characteristics of the population. Smoking status was divided into three categories: nonsmoker, ex-smoker, or current smoker. Alcohol consumption was assessed based on the average number of alcoholic beverages and frequency of drinking. Heavy drinkers were defined as subjects who drank more than 30 g/day, and subjects drinking less than 30 g/day were classified as mild to moderate drinkers²⁹. Moderate physical activity was defined as walking at least 150 min per week²⁹. Household income was divided into quartile groups: lowest, lower middle, higher middle, and highest. Occupation status was divided into yes or no. High education level was defined as subjects who finished high school education or more.

DM was defined as a fasting glucose level \geq 126 mg/dL, current use of antidiabetic medications, or a self-reported physician diagnosis of DM³⁰. Hypertension was defined as systolic blood pressure \geq 140 mmHg or diastolic blood pressure \geq 90 mmHg, the current use of antihypertensive medications, or a self-reported physician diagnosis of hypertension³¹. Dyslipidemia was defined as total cholesterol \geq 240 mg/dL, use of cholesterol-lowering medications, or a self-reported physician diagnosis of dyslipidemia. Asthma, prior stroke, and prior IHD were defined as a self-reported diagnosis by a physician in the health interview surveys³¹.

After overnight fasting, blood samples were collected from participants' antecubital veins. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Renal Diet equation from baseline serum creatinine³². CKD was defined as eGFR $<$ 60 mL/min/1.73 m² for 3 months or more.

Spirometry. Spirometry was performed in individuals aged ≥ 40 years, except those for whom accurate results could not be obtained, such as those with history of laparotomy, ophthalmic surgery, open heart surgery, stroke, myocardial infarction, or cardiac arrest within the past 3 months; aortic aneurysm, retinal detachment, pneumothorax, urinary incontinence, or pulmonary tuberculosis; hemoptysis within the past 1 month; chest or abdominal pain; pain in the mouth or face when biting the mouthpiece; systolic blood pressure > 200 mmHg; diastolic blood pressure > 140 mmHg; dementia; reduced consciousness. Spirometry was performed by four technicians, each of whom underwent two education sessions on lung function tests and quality control. Trained technicians measured the FEV₁, FVC and FEV₁/FVC ratio using a dry rolling-seal spirometer (model 2130; Sensor Medics, Yorba Linda, CA, USA) and the American Thoracic Society/European Respiratory Society criteria for the standardization of lung function tests³³. All of the spirometry values were described as prebronchodilator results³⁴. Normal predictive values were derived taking into account age, sex, height, and ethnicity in large population studies of healthy subjects³⁵. Analyses were performed only on data that met the following criteria: (i) 2 acceptable spirometry curves showing correct test initiation and expiration for at least 6 s and (ii) a greatest difference between two measurements of FEV₁ or FVC of < 150 mL. The spirometry results were classified into three groups: normal and restrictive and obstructive lung function impairment. Participants with FEV₁/FVC ≥ 0.7 and FVC $\geq 80\%$ of the normal predicted value were considered normal. A restrictive pattern was defined as FEV₁/FVC ≥ 0.7 and FVC $< 80\%$ predicted. An obstructive pattern was defined as FEV₁/FVC < 0.7 ^{36,37}.

Clinical outcomes. The primary outcome was newly diagnosed non-valvular AF, either one diagnosis (ICD-10 code of I48.0–I48.4, I48.9) during hospitalization or more than two diagnoses in the outpatient clinics, until censoring or death³⁸. A washout period of 1 year was set to ensure AF was newly diagnosed. To evaluate newly diagnosed AF, we used data derived from a 2007 cohort of the NHIS with clinical follow-up for the primary outcome through December 31, 2018.

Statistical analysis. Summary statistics are expressed as the means and standard deviations for continuous variables and as numbers and percentages for categorical variables. Continuous variables were compared using Student's t-test or analysis of variance, as appropriate. Categorical variables were compared using the chi-square test. Multiple comparisons were assessed using the Bonferroni correction. The IR of AF was calculated by dividing the number of AF cases by the sum of the follow-up duration and is presented as the rate per 1000 person-years. Participants were followed until the first diagnosis of AF, censoring by death, or December 31, 2018. Clinical outcomes were determined using the Kaplan–Meier method and compared using the log-rank test. Cox-proportional-hazard models were performed to analyze the impact of lung function on AF risk. The hazard ratio (HR) and 95% confidence interval (CI) were also calculated. A p value < 0.05 was considered statistically significant. To account for potentially confounding clinical covariates and to adjust the established risk factors for AF, multivariable Cox regression models were adjusted for age and sex (model 1); age, sex, BMI, household income, education, exercise, alcohol consumption, smoking, hypertension, DM, and dyslipidemia (model 2); and the variables in model 2 plus white blood cell count, eGFR, stroke, IHD, and asthma (model 3). Time-scale of the models was time on study. Statisticians confirmed the proportional hazard assumption through statistical tests based on Schoenfeld residuals and graphical diagnosis through log–log plots. In Fig. 1, p for trend was calculated through cox proportional regression analysis by considering the decile as a continuous variable. We also conducted subgroup analyses stratified by the confounding factors for the sensitivity analysis. The potential effect of modifications by the subgroups was evaluated using stratified analysis and interaction testing with a likelihood ratio test. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

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Author contributions

S.N.L. and S.H.K. take full responsibility for the content of this manuscript, including the data and analyses. S.H.H. made substantial contributions to the concept and design of the study. K.D.H. developed the design of the methodology. D.G.M., S.K.K., K.D.Y., and Y.B.A. made substantial contributions to the analysis and interpretation of data. S.N.L., S.H.K. and S.K.K. drafted the initial manuscript. All authors discussed the results and reviewed the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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