

Original Article

Increased Risk of Atrial Fibrillation in Patients with Atopic Triad: A Nationwide Population-Based Study

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What is already known about this topic? Chronic inflammatory disease is associated with an increase in atrial fibrillation.

What does this article add to our knowledge? This article showed that the atopic triad is associated with an increased risk for atrial fibrillation. To the author's best knowledge, this is the first study to show that multiple atopic conditions cause a higher incidence of atrial fibrillation.

How does this study impact current management guidelines? The atopic triad conditions, including asthma, atopic dermatitis, and/or allergic rhinitis, are associated with an increased risk for atrial fibrillation. Increased vigilance for atrial fibrillation in atopic patients is warranted.

BACKGROUND: Despite a sharp increase in the global prevalence of allergy over the past decade, the relation between multiple atopic conditions and atrial fibrillation (AF) has not been fully elucidated.

OBJECTIVE: To determine whether there is an association between atopic diseases and AF and to examine the effect of multiple atopic diseases on the incidence of AF.

METHODS: This retrospective population-based study used the database from the 2009 National Health Insurance Services-Health Screening Cohort in Korea. A total of 6,748,564 subjects without a previous history of AF were included in the final analysis and observed until 2017. The atopic triad included asthma, allergic rhinitis, and atopic dermatitis. A total of 1,168,196 subjects (17.3%) with at least one atopic disease were

classified as the atopic group. The primary outcome was new-onset AF.

RESULTS: During a median 7.2 ± 1.0 years of follow-up, 136,253 subjects were given the new diagnosis of AF (30,300 in the atopic group and 105,953 in the nonatopic group). The incidence of AF was 3.63/1000 person-years in the atopic group and 2.64/1000 person-years in the nonatopic group. The risk for AF showed a positive correlation with the number of diseases in the atopic triad (adjusted hazard ratio [aHR], 95% confidence interval [CI]: one disease: aHR = 1.15, CI, 1.14-1.17; two diseases: aHR = 1.34, CI, 1.31-1.38; and three diseases: aHR = 1.35, CI, 1.11-1.66; P for trend < .001).

CONCLUSIONS: The atopic triad of asthma, allergic rhinitis, and atopic dermatitis was associated with an increased risk for AF. Moreover, multiple atopic conditions have a higher risk for AF. © 2021 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2021;■:■-■)

Key words: Atopic triad; Asthma; Allergic rhinitis; Atopic dermatitis; Allergy; Atrial fibrillation; Inflammation; Cardiovascular disease

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Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

This work was supported by the Korea Medical Device Development Fund grant funded by the Korea government (the Ministry of Science and ICT, the Ministry of Trade, Industry and Energy, the Ministry of Health & Welfare, Republic of Korea, the Ministry of Food and Drug Safety) (Project Number: 202013B14), and by the Korea National Research Foundation funded by the Ministry of Education, Science and Technology (grant 2020R1F1A106740).

Received for publication January 29, 2020; revised April 21, 2021; accepted for publication April 22, 2021.

Available online ■■

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2213-2198

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<https://doi.org/10.1016/j.jaip.2021.04.056>

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, with increasing trends in both prevalence and incidence.¹ For decades, many experimental and observational epidemiologic studies have yielded extensive data on the risk factors attributed to AF development by providing supporting evidence and insight into the pathogenesis of AF.²⁻⁴

Recently, there has been accumulating evidence on the association of inflammatory and immune responses with incident AF.⁵⁻⁷ As a consequence, chronic inflammatory diseases such as vasculitis, rheumatic arthritis, and inflammatory bowel disease have been newly identified as associated with an increase in AF

Abbreviations used

AF- Atrial fibrillation

CI- Confidence interval

HR- Hazard ratio

ICD-10-CM- International Classification of Disease, 10th
Revision, Clinical Modification

NHIS- National Health Insurance Services

NHIS-HEALS- National Health Insurance Services-National
Health Screening Cohort

PDGF-A- Platelet-derived growth factor

susceptibility.⁸⁻¹¹ Moreover, allergic diseases as part of immune dysfunction have emerged as potential risk factors for AF development.^{12,13}

In recent years, allergies have rapidly increased worldwide and are considered a major burden of chronic disease.¹⁴ Moreover, the presence of one allergic disease significantly increases the coexistence of other allergic diseases, which can result in multiple allergic conditions.¹⁵ Whereas allergic reactions often wax and wane, atopic march refers to the developmental progress of the atopic triad (ie, asthma, atopic dermatitis, and/or allergic rhinitis). In the infantile period, this presents as atopic dermatitis, which is the cutaneous manifestation of atopy, and progresses to allergic rhinitis and asthma in children.¹⁶ In contrast, in adults, atopic multimorbidity is more common than atopic march.^{17,18} Because the prevalence of atopic diseases is increasing worldwide, many studies have reported on the relation between atopic disease and cardiovascular disease.^{19,20} However, few have investigated the connection between multiple atopic conditions and the risk for incident AF. Therefore, we aimed to investigate whether there is an association between atopic diseases and AF and to clarify the effect of multiple atopic diseases on incident AF.

METHODS**Study design and database**

We conducted a population-based cohort study using a database from the National Health Insurance Services (NHIS) in Korea. The NHIS provides comprehensive medical care coverage to 97% of the Korean population, including a standardized National Health Screening program for enrollees aged 40 years and greater every 2 years. The participation rate of eligible subjects in the National Health Screening program was 74.8% in 2014^{21,22}; and the remaining 3% of the population with low income was covered by the Medical Aid program. The NHIS database includes the health care service claims database, which includes inpatient and outpatient use records and health information (demographic findings, socioeconomic variables, and death information).

The NHIS-National Health Screening Cohort (NHIS-HEALS) database was constructed by the Korean government in 2015 to offer comprehensive claims data for health research. The NHIS-HEALS database is composed of a complete set of the health care service claims data in addition to health screening data. The health screening data obtained through the NHIS program are composed of physical examinations, regular blood tests, and self-questionnaires on lifestyle and behavior. A detailed cohort profile of the NHIS-HEALS has been described elsewhere.²³

This study was approved by the institutional review board of Seoul National University Hospital and was conducted according to

the Declaration of Helsinki. The NHIS-HEALS has been made publicly available to facilitate the wider use of the health screening database with anonymous and deidentified information; thus, the requirement for informed consent was waived.

Study population

We extracted a sample cohort from the health screening participants in the NHIS-HEALS in 2009 (see [Figure E1](#) in this article's Online Repository at www.jaci-inpractice.org). The NHIS-HEALS consisted of 7,183,272 adults aged 40 to 79 years in 2009. After excluding 327,082 subjects with missing values, 6,856,190 subjects were eligible for inclusion. To include only newly diagnosed AF, subjects who had a history of previous AF before the diagnosis of atopic disease (n = 79,034) and those who had AF in the year after the diagnosis of atopic disease (n = 28,592) were excluded. A total of 6,748,564 subjects were included in the final analysis and were observed through 2017.

Definition of atopic diseases

We used the record of the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) code to define atopic diseases. The atopic triad, including asthma (J45-46), allergic rhinitis (J301-304), and atopic dermatitis (L20), was used to define atopic disease. Subjects with at least one disease of the atopic triad were classified into the atopic group. To improve accuracy, data on atopic diseases were refined by splitting subjects according to the atopic triad diagnosis and by the number of clinic visits (three or more times per year) to diagnose each disease. The nonatopic group consisted of subjects without atopic disease.

Primary outcome and follow-up

The primary outcome of this study was newly diagnosed AF, which was defined as a record of ICD-10-CM code I48. The diagnosis of AF was confirmed by one or more records during hospitalization or more than two records in the outpatient clinic. To include nonvalvular AF, we excluded subjects diagnosed with mitral stenosis (I050, I052, and I059) or those with mechanical heart valves (Z952-Z954) from the analysis. The cohort was observed until the occurrence of the primary end point, death, or emigration, or until the end of the study period (December 31, 2017), whichever came first. Death or emigration before the primary end point and the end of the study period was censored (right censoring).

Comorbidities and measurements performed during health examination

Baseline comorbidities (hypertension, diabetes mellitus, and dyslipidemia) were defined using ICD-10-CM codes and medical prescription data from the claim data and measurements of physical examination and laboratory test from the National Health Screening program (see [Table E1](#) in this article's Online Repository at www.jaci-inpractice.org). Laboratory tests for serum glucose and serum lipid profiles were performed after fasting overnight. Baseline demographic findings and socioeconomic variables were based on the NHIS-HEALS database. Self-questionnaires were used to classify previous medical history (previous stroke and previous ischemic heart disease), smoking status (nonsmoker, ex-smoker, or current smoker), drinking habit (none; mild intake, average <30 g/d; heavy intake, average ≥30 g/d), and regular physical activity. Regular physical activity was defined as performing moderate physical activity for more than 30 minutes, at least five times per week, or strenuous physical activity for more than 20 minutes, at least three

TABLE I. Baseline characteristics of study population*

Variable	Nonatopic group	Atopic group	Atopic diseases, n		
			1	2	3
Subjects, n	5,580,368	1,168,196	1,023,996	142,059	2141
Age, y	53.90 ± 10.29	56.13 ± 10.95	55.74 ± 10.86	58.94 ± 11.14	59.77 ± 11.48
<65 y, n (%)	4,614,602 (82.7)	875,466 (74.9)	781,093 (76.3)	93,062 (65.5)	1311 (61.2)
≥65 y, n (%)	965,766 (17.3)	292,730 (25.1)	242,903 (23.7)	48,997 (34.5)	830 (38.8)
Male sex, n (%)	2,897,464 (51.9)	483,164 (41.4)	427,367 (41.7)	54,907 (38.7)	890 (41.6)
Body mass index, kg/m ²	23.9 ± 3.01	24.1 ± 3.06	24.1 ± 3.04	24.3 ± 3.19	24.3 ± 3.18
BP measurements					
Systolic BP, mm Hg	124.23 ± 15.44	124.09 ± 15.31	123.95 ± 15.28	125.08 ± 15.48	125.69 ± 15.33
Diastolic BP, mm Hg	77.26 ± 10.18	76.80 ± 9.97	76.76 ± 9.98	77.08 ± 9.96	77.38 ± 9.89
Comorbidities, n (%)					
Hypertension	1,813,875 (32.5)	440,572 (37.7)	377,757 (36.9)	61,815 (43.5)	1000 (46.7)
Diabetes mellitus	634,409 (11.4)	148,865 (12.7)	127,614 (12.5)	20,882 (14.7)	369 (17.2)
Dyslipidemia	1,236,407 (22.2)	315,326 (27.0)	271,084 (26.5)	43,504 (30.6)	738 (34.5)
Previous stroke	73,246 (2.06)	15,432 (2.01)	13,497 (2.02)	1901 (1.96)	34 (2.27)
Previous ischemic heart disease	123,999 (3.49)	37,481 (4.88)	31,550 (4.71)	5847 (6.01)	84 (5.61)
Inflammatory bowel disease	3529 (0.06)	986 (0.08)	857 (0.08)	127 (0.09)	2 (0.09)
Psoriasis	32,165 (0.58)	10,357 (0.90)	8734 (0.85)	1564 (1.10)	59 (2.76)
Glomerular filtration rate, mL/min per 1.73 m ²	85.67 ± 36.67	84.45 ± 35.00	84.63 ± 35.29	83.24 ± 32.83	82.07 ± 33.53
Smoking, n (%)					
Never	3,464,901 (62.1)	822,881 (70.4)	719,419 (70.3)	101,962 (71.8)	1500 (70.1)
Ex-smoker	8,69,683 (15.6)	174,930 (15.0)	154,224 (15.1)	20,396 (14.4)	310 (14.5)
Current smoker	1,245,784 (22.3)	170,385 (14.6)	150,353 (14.7)	19,701 (13.9)	331 (15.5)
Drinking, n (%)					
No	3,175,483 (56.9)	772,589 (66.1)	669,751 (65.4)	101,252 (71.3)	1586 (74.1)
<30 g/d	2,032,785 (36.4)	346,573 (29.7)	310,225 (30.3)	35,864 (25.3)	484 (22.6)
≥30 g/d	372,100 (6.67)	566,562 (48.5)	44,020 (4.3)	4943 (3.48)	71 (3.32)
Low income, n (%)†	1,498,751 (26.9)	321,019 (27.5)	280,822 (27.4)	39,538 (27.8)	659 (30.8)
Regular physical activity	2,795,498 (50.1)	566,562 (48.5)	501,083 (48.9)	64,532 (45.4)	947 (44.2)

BP, blood pressure.

*Continuous variables are presented as mean ± SD and categorical variables as number (percentage). For baseline comparisons, Student *t* test or Mann-Whitney U test was used for continuous variables and chi-square test or Fisher exact test for categorical variables. All variables were significantly different between the nonatopic and atopic groups (all *P* < .001, except for previous stroke, at *P* = .024). All variables were significantly different according to the number of atopic diseases (all *P* < .001).

†Low income indicates the lowest quadrant of income level (25%).

times per week. A low income indicated the lowest quadrant (25%) of income level.

Statistical analysis

With regard to baseline characteristics, continuous variables are presented as means and SD and categorical variables as numbers and percentages. For baseline comparisons, Student *t* test or Mann-Whitney U test was performed for continuous variables and chi-square or Fisher exact test for categorical variables. The incidence rate of AF was calculated by dividing the number of incident cases by the total follow-up duration; it is presented as events per 1000 person-years. The hazard ratio (HR) and 95% confidence interval (CI) for new-onset AF were analyzed using the Cox proportional hazards model. The following multivariable adjusted Cox proportional hazards models were applied: model 1 was adjusted for age and sex; model 2 was adjusted for age, sex, smoking status, drinking habit, income level, diabetes mellitus, hypertension, and dyslipidemia; and model 3 was additionally adjusted for inflammatory bowel disease, and psoriasis. To estimate the effect size of the results, we used Cohen's *d* in the formula: $d = \ln(\text{HR}) \times \sqrt{6/\pi}$.²⁴ Although a formal sample size calculation was not conducted in the planning

stage, we performed a post hoc power analysis for the final Cox proportional hazards model.²⁵

In conjunction, we conducted subgroup analyses according to confounding factors: age strata (<65 years and ≥65 years), sex, body mass index (<25 kg/m² and ≥25 kg/m²), smoking status, presence of metabolic syndrome, previous stroke, and income level. Bonferroni correction was used for multiple comparisons in subgroups. A test for interaction was performed to determine statistically significant subgroup differences. Atrial fibrillation-free survival was estimated using the Kaplan-Meier method, log-rank test, and Cox proportional hazards model.

Statistical significance was defined as two-sided *P* values for interaction less than .05 and a two-sided *P* less than .05. All statistical analyses were performed using SAS (version 9.4, SAS Institute, Inc, Cary, NC, 2013) and R program (version 3.2.4, R Core Team, Vienna, Austria, 2017).

RESULTS

Baseline characteristics

Table I lists the baseline characteristics of the study population according to the presence and absence as well as the number of

TABLE II. Risk for atrial fibrillation according to presence of atopic disease*

Subgroups	Total n	Atrial fibrillation	Follow-up duration†	Incidence rate‡	Model 1	Model 2	Model 3
					HR (95% CI)	HR (95% CI)	HR (95% CI)
Nonatopic group	5,580,368	105,953	401,227,867	2.64	1 (reference)	1 (reference)	1 (reference)
Atopic group	1,168,196	30,300	8,349,903	3.63	1.31 (1.29-1.32)	1.25 (1.23-1.27)	1.18 (1.17-1.20)
One atopic disease	1,023,996	25,175	7,334,245	3.43	1.26 (1.24-1.27)	1.21 (1.19-1.23)	1.15 (1.14-1.17)
Asthma	111,874	4913	768,456	6.39	1.78 (1.73-1.83)	1.62 (1.57-1.66)	1.36 (1.32-1.40)
Atopic dermatitis	17,073	427	121,123	3.53	1.16 (1.06-1.28)	1.09 (0.99-1.20)	1.04 (0.95-1.13)
Allergic rhinitis	895,049	19,835	6,444,667	3.08	1.17 (1.16-1.19)	1.14 (1.12-1.16)	1.12 (1.10-1.14)
Two atopic diseases	142,059	5041	1,000,756	5.04	1.61 (1.57-1.66)	1.49 (1.45-1.54)	1.34 (1.31-1.38)
Asthma plus atopic dermatitis	923	55	6133	8.97	2.31 (1.77-3.01)	2.01 (1.55-2.62)	1.72 (1.34-2.21)
Asthma plus allergic rhinitis	132,982	4756	936,808	5.08	1.62 (1.58-1.67)	1.51 (1.46-1.55)	1.35 (1.31-1.39)
Allergic rhinitis plus atopic dermatitis	8154	230	57,814	3.98	1.33 (1.17-1.51)	1.24 (1.09-1.41)	1.17 (1.04-1.32)
Three atopic diseases	2141	84	14,902	5.64	1.70 (1.38-2.11)	1.55 (1.25-1.92)	1.35 (1.11-1.66)

CI, confidence interval; HR, hazard ratio.

*Model 1 is adjusted for age and sex. Model 2 is adjusted for age, sex, history of smoking, drinking level, low income, diabetes mellitus, hypertension, and dyslipidemia. Model 3 is adjusted for age, sex, history of smoking, drinking level, low income, diabetes mellitus, hypertension, dyslipidemia, inflammatory bowel disease, and psoriasis.

†Follow-up duration is in person-years.

‡Incidence rate is presented as 1000 person-years.

atopic diseases. Of the total 6,748,564 study subjects, 1,168,196 had one or more atopic diseases (17.3%). The atopic group (mean age, 56.1 ± 10.3 years; 41.4% men) was older and had a higher proportion of females than did the nonatopic group (mean age, 53.9 ± 11.0 years; 51.9% men). Comorbidities such as hypertension, diabetes mellitus, and dyslipidemia, and a history of ischemic heart disease were frequently observed in the atopic group. Conversely, the proportions of smokers and drinkers were higher in the nonatopic group. In the atopic group, subjects with multiple atopic diseases had a higher rate of comorbidities than did those with a single atopic disease. Table E2 (in this article's Online Repository at www.jaci-inpractice.org) shows the baseline characteristics of the atopic group according to each atopic disease.

Primary outcome: risk for AF

During a mean follow-up of 7.2 ± 1.0 years, new-onset AF occurred in 136,253 of study subjects. Of those, 30,300 were from the atopic group (3.63/1000 person-years) and 105,953 were from the nonatopic group (2.64/1000 person-years). After adjustment for confounding factors, the atopic group had a higher hazard rate of AF development compared with the nonatopic group (HR = 1.18; 95% CI, 1.17-1.20) (Table II). Kaplan-Meier analysis indicated that the atopic group was associated with worse AF-free survival compared with the nonatopic group (log-rank test, $P < .001$) (Figure 1, A). The adjusted AF-free survival curve showed a similar tendency (Figure 1, B).

Multiple atopic diseases led to a higher incidence rate of AF, indicating a positive correlation with the risk for incident AF (bar graphs in Figure 2). The HR for AF development was 1.15 (95% CI, 1.14-1.17) in the one-disease group, 1.34 (95% CI, 1.31-1.38) in the two-disease group, and 1.35 (95% CI, 1.11-1.65) in the three-disease group, compared with the nonatopic group (P for trend $< .001$) (line graphs in Figure 2). Cohen's d for AF was 0.11, 0.23, and 0.24 in the one-, two-, and three-disease groups, respectively, indicating a relatively small effect size.

Among subjects with a single atopic disease, those with asthma had the highest hazard rate of developing AF (HR = 1.36; 95%

CI, 1.14-1.40). Among subjects with multiple atopic diseases, those with asthma and atopic dermatitis had the highest hazard rate of AF (HR = 1.72; 95% CI, 1.34-2.21). Moreover, compared with a single atopic disease, subjects with two or three atopic diseases had worse AF-free survival (see Figure E2 in this article's Online Repository at www.jaci-inpractice.org). The risk for developing AF associated with the presence or absence of each atopic disease is listed in Table E3 (in this article's Online Repository at www.jaci-inpractice.org).

Subgroup analysis

In all subgroups, the atopic triad increased the risk for AF development (Table III). There were significant differences in the risk for AF development in the subgroups according to body mass index, smoking status, income level, and previous stroke, but the overall trend was consistent. There was no significant interaction in the age and sex subgroups. In the subgroup analysis for the number of atopic diseases, statistical significance was attenuated in the three-disease group of some subgroups, but the overall trend was maintained. Subgroup analysis according to each atopic disease and the combination of atopic diseases showed a similar tendency (see Table E4 in this article's Online Repository at www.jaci-inpractice.org).

DISCUSSION

In this large population-based study of more than 6 million individuals, we found that the atopic triad (asthma, atopic, and/or allergic rhinitis) was linked to an increased risk for AF development. Moreover, we demonstrated that multiple atopic conditions led to a higher risk for new-onset AF compared with a single atopic disease, indicating a directly proportional relation. Although previous studies showed a link between a single allergic disease and cardiovascular disease, to the best of our knowledge, this study is the first to elucidate the impact of multiple atopic conditions on cardiovascular diseases, especially AF. In addition, our findings showed the risk for incident AF in subjects with a single atopic disease or a combination of atopic diseases.

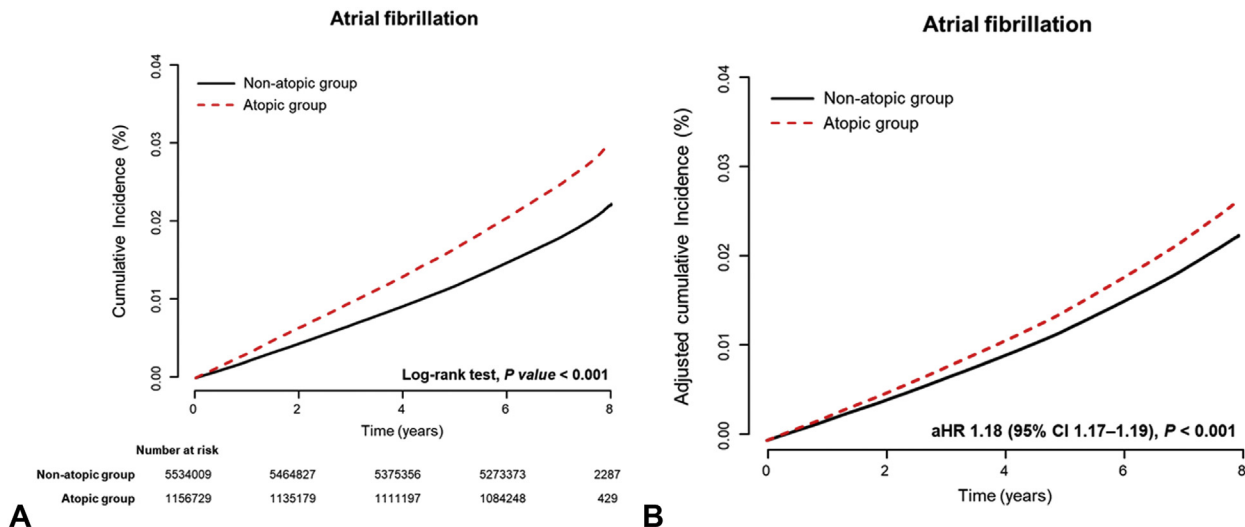


FIGURE 1. Cumulative incidence of overall new-onset atrial fibrillation development. Crude cumulative incidence curves of (A) atrial fibrillation and (B) adjusted cumulative incidence curves of atrial fibrillation. The atopic group was defined as those who had at least one disease of the atopic triad, which includes asthma, allergic rhinitis, and atopic dermatitis. aHR, adjusted hazard ratio; CI, confidence interval.

Together with the dramatic increase in the prevalence of allergic diseases globally, approximately one in four Korean adults has atopic disease.²⁶ A large-scale national epidemiology study conducted in England reported that the number of individuals with multiple atopic diseases surged from 4.72/1000 patient-years in 2001 to 6.28/1000 patient-years in 2005, indicating a growing burden of multiple allergic diseases.¹⁵ Above all, multiple allergic conditions are difficult to control and more clinically intractable than single conditions. Moreover, because allergic diseases constitute a considerable burden on global health care, there is a growing interest in the relation between allergic and cardiovascular diseases.^{19,20}

Because systemic inflammation and subsequent immune responses have reportedly been linked to the initiation and maintenance of AF, allergic diseases have attracted scientific interest as putative risk factors for AF. Atopic disease is the result of an allergic reaction caused by a T_H2 cell-associated inflammatory response to innocuous objects and affects specific organs such as the airway, skin, and nasal mucosa.²⁷ However, IgE sensitization, which is associated with T_H2 helper cells, accounts for only 38% of multiple morbidities, which suggests that a wider range of interrelated cellular mechanisms exist, including the presence of non- T_H2 cellular pathways.²⁸ Thus, the mechanisms responsible for the risk for AF in allergic multiple morbidities are not yet fully understood in terms of the host T_H1/T_H2 balance shift. Nevertheless, there are increasing experimental studies to enhance the comprehension of mechanisms underlying AF development in allergic diseases. Indeed, several studies have provided compelling evidence of an essential role of cardiac mast cells in the pathogenesis of cardiac fibrosis.^{20,29} In an animal study, cardiac mast cell infiltration in pressure-overloaded mouse hearts increased the synthesis of platelet-derived growth factor (PDGF-A) and resulted in atrial fibrosis as a result of the activation, proliferation, and differentiation of cardiac fibroblasts.³⁰ Moreover, cardiac fibrosis is attenuated by pharmacologic stabilization of activated mast cells and the PDGF-A pathway.³¹

These findings suggest a crucial role of mast cells in incident AF and address the relation between allergic response and AF.

Asthma is a well-known independent risk factor for AF; the association can be explained by a common pathogenesis.¹³ β_2 -Agonists and corticosteroids, which are the cornerstones of asthma treatment, are known to increase the risk for cardiovascular disease, including AF.^{32–34} Conversely, because hypoxia-induced catecholamines can lead to tachycardia, high blood pressure, and arterial wall shear stress, the beneficial effect of inhalers could improve asthma and result in a subsequent reduction in hypoxemia episodes.³⁵

Prior epidemiologic studies also showed ambiguous results and found that the impact of atopic dermatitis on cardiovascular disease is related to coexisting cardiovascular risk factors such as obesity, alcohol consumption, depression, and lower physical activity rather than to the inflammatory nature of atopic dermatitis.^{36–38} Moreover, although few studies directly examined the relation between allergic rhinitis and cardiovascular disease, serum IgE-positive allergic rhinitis was found to be associated with a lower cardiovascular risk and all-cause mortality.³⁹ Jaramillo et al⁴⁰ also demonstrated that patients with positive serum IgE test results were less likely to have a history of myocardial infarction. One plausible explanation for this protective effect is a pharmacologic intervention in allergic rhinitis, such as an intranasal steroid and an oral antihistamine, which leads to a reduction in systolic blood pressure and a decrease in C-reactive protein level. Immune-modulating therapy for IgE-mediated allergic diseases has also been reported to be associated with a low risk for myocardial infarction.⁴¹

However, serum total IgE is not a specific biomarker of atopic diseases; it is also known to increase with smoking and alcohol intake.⁴² Various inflammatory mediators, such as cytokines and growth factors, can induce the differential release of mast cell mediators.⁴³ Furthermore, previous studies showed that atopic dermatitis has a directly proportional relation to cardiovascular

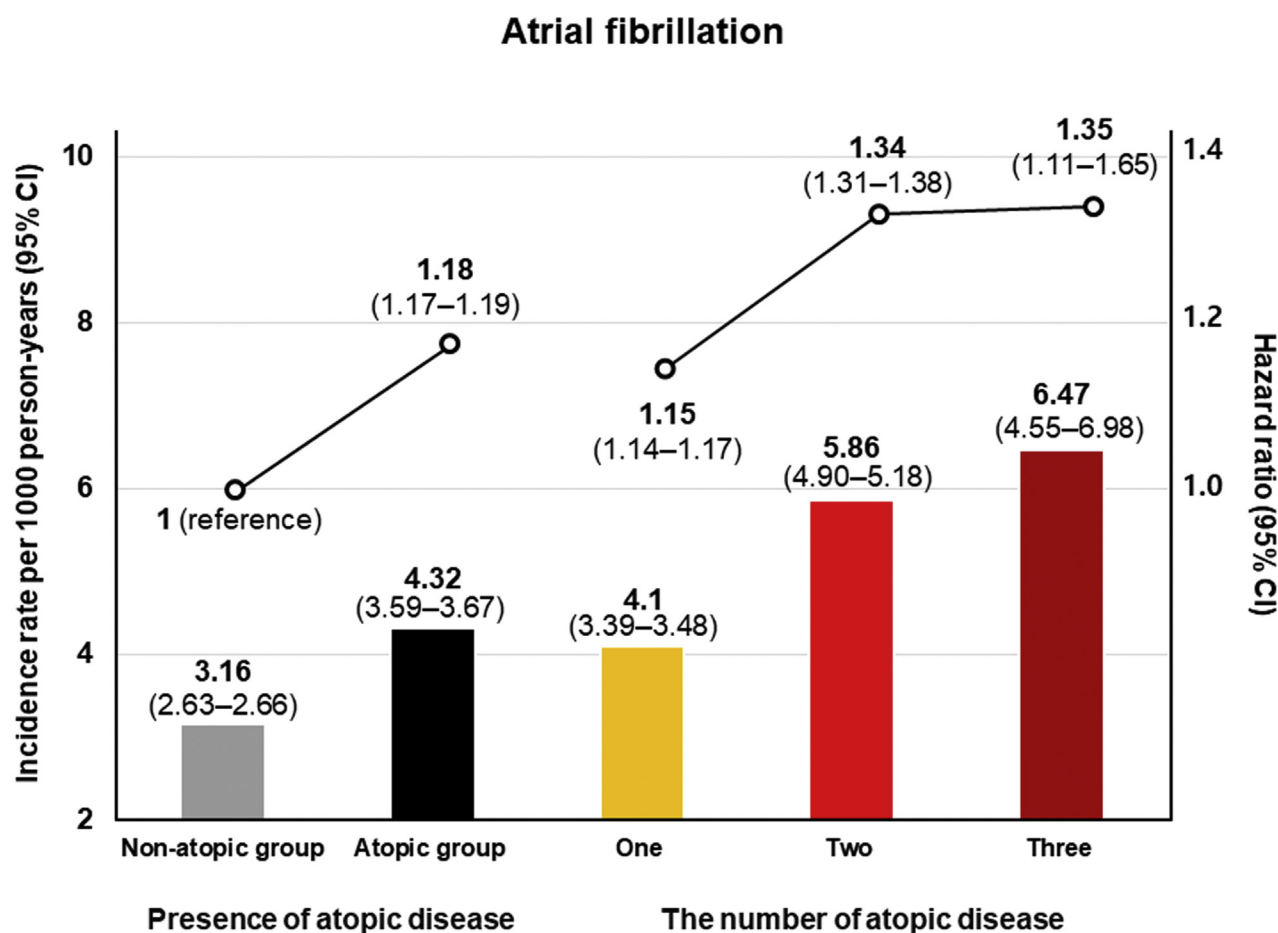


FIGURE 2. New-onset atrial fibrillation according to the presence and number of atopic diseases. The presence of multiple atopic conditions had a directly proportional relation to the hazard ratio of new-onset atrial fibrillation (P for trend $< .001$). Data are adjusted for age, sex, history of smoking, drinking level, low income, diabetes mellitus, hypertension, dyslipidemia, inflammatory bowel disease, and psoriasis. Atopic diseases include asthma, allergic rhinitis, and atopic dermatitis. *CI*, confidence interval.

diseases, including AF, which is consistent with our results.⁴⁴ The conflicting results of this relationship of atopic diseases with myocardial infarction and AF might result from differences in the mechanism of coronary vascular disease and AF. Whereas coronary artery disease in cases of inflammation involves atherosclerosis and/or coronary arterial spasms, AF development is associated with myocyte inflammation, atrial remodeling, and intracardiac conduction disturbance.^{20,45}

In the subgroup analysis, the risk for AF development was higher in current smokers and in those with lower income and lower body mass index. In patients with asthma, smoking damages the airway mucosa, which leads to sensitization of allergens and increases the concentration of serum IgE.⁴⁶ Smoking also increases oxidative stress, inflammation, and atrial fibrosis, all of which have the potential to enhance AF development.⁴⁷ Therefore, smokers might have a favorable condition for incident AF; as a result, they may show more pronounced effects of atopic diseases.

The role of socioeconomic status in the development of allergies is unclear. Based on the hygiene hypothesis, individuals with a high socioeconomic status are prone to allergic diseases

because of greater access to medication and immunization.⁴⁸ However, a previous systematic review suggested that asthma is associated with lower socioeconomic status, whereas the prevalence of allergies is associated with higher socioeconomic status.⁴⁹ The relation between allergic diseases and obesity is also unclear. Although pathologic mechanisms may explain how obesity could influence the immune system and promote the process of sensitization, evidence of a role of obesity in atopy development has been inconsistent.^{50,51} Thus, although the subgroup analysis is sufficient to support the consistent clinical association of atopic disease with AF, it requires further investigations to establish the risk factors for AF to develop preventive strategies for patients with atopic disease. In this large-scale population-based study, we provide crucial evidence for the association of the atopic triad with AF development. Moreover, our findings provide important insight into the fact that multiple atopic conditions are associated with a higher risk for AF development.

Limitations

This study had several strengths, including the large cohort of men and women, a stable multiple-year follow-up, and a high

TABLE III. Subgroup analysis

Subgroups	Atopic disease	HR (95% CI)*	P for interaction	Atopic diseases, n	HR (95% CI)*	P for interaction
Age, y						
<65	No	1 (reference)	.073	0	1 (reference)	.044
				1	1.172 (1.147-1.196)	
	Yes	1.176 (1.154-1.199)	2	1.343 (1.278-1.411)		
			3	1.447 (0.973-2.151)		
≥65	No	1 (reference)		0	1 (reference)	
				1	1.139 (1.116-1.162)	
	Yes	1.178 (1.158-1.199)	2	1.342 (1.292-1.395)		
			3	1.328 (1.001-1.761)		
Sex						
Male	No	1 (reference)	.535	0	1 (reference)	.700
				1	1.142 (1.119-1.165)	
	Yes	1.253 (1.231-1.275)	2	1.344 (1.287-1.404)		
			3	1.464 (1.080-1.984)		
Female	No	1 (reference)		0	1 (reference)	
				1	1.169 (1.144-1.193)	
	Yes	1.236 (1.212-1.259)	2	1.337 (1.282-1.395)		
			3	1.241 (0.875-1.762)		
Body mass index, kg/m ²						
<25	No	1 (reference)	.014	0	1 (reference)	.007
				1	1.177 (1.155-1.200)	
	Yes	1.268 (1.247-1.289)	2	1.346 (1.300-1.395)		
			3	1.654 (1.253-2.182)		
≥25	No	1 (reference)		0	1 (reference)	
				1	1.122 (1.097-1.148)	
	Yes	1.219 (1.195-1.244)	2	1.333 (1.274-1.396)		
			3	0.982 (0.652-1.479)		
Smoking						
No or ex-smoker	No	1 (reference)	.005	0		.007
				1	1.154 (1.136-1.172)	
	Yes	1.238 (1.220-1.255)	2	1.332 (1.289-1.376)		
			3	1.241 (0.952-1.616)		
Current	No	1 (reference)		0		
				1	1.151 (1.110-1.193)	
	Yes	1.293 (1.253-1.335)	2	1.383 (1.281-1.494)		
			3	1.891 (1.186-3.016)		
Previous stroke						
No	No	1 (reference)	.031	0	1 (reference)	.103
				1	1.145 (1.125-1.165)	
	Yes	1.097 (1.010-1.192)	2	1.341 (1.295-1.389)		
			3	1.335 (1.025-1.738)		
Yes	No	1 (reference)		0	1 (reference)	
				1	1.119 (1.018-1.230)	
	Yes	1.236 (1.217-1.254)	2	1.296 (1.059-1.587)		
			3	1.887 (0.517-6.879)		
Lower income						
No	No	1 (reference)	<.001	0	1 (reference)	<.001
				1	1.148 (1.130-1.168)	
	Yes	1.166 (1.149-1.184)	2	1.330 (1.285-1.377)		
			3	1.379 (1.061-1.792)		
Yes	No	1 (reference)		0	1 (reference)	
				1	1.177 (1.141-1.214)	
	Yes	1.286 (1.254-1.319)	2	1.382 (1.297-1.473)		
			3	1.287 (0.798-2.076)		

CI, confidence interval; HR, hazard ratio.

*Adjusted for age, sex, history of smoking, drinking level, low income, diabetes mellitus, hypertension, and dyslipidemia by Bonferroni correction.

participation rate. However, there were also several limitations. One major limitation stems from the nature of the study design using a claims database, which could lead to Berkson's bias. Although individuals with AF generally present with symptoms, and electrocardiogram screening is not regularly performed in patients with atopic diseases, intermittent symptoms associated with AF are more likely to be detected in patients who frequently visit health care facilities than in those who do not. Second, there is no reference standard for the diagnosis of atopic diseases. Therefore, to increase the diagnostic accuracy, we required atopic disease to be defined as having at least three records of diagnosis per year in the current study. Frequent visits to hospitals could help to enroll a higher number of subjects with active disease conditions. Third, no drug information was available for the atopic diseases; this is particularly important because the treatment of asthma with β_2 -agonists can affect the heart rate and increase the risk for arrhythmias. Therefore, these results should be interpreted with caution, particularly with regard to the relatively higher risk in subjects with asthma compared with subjects with other atopic diseases. Moreover, we did not provide objective indicators for the severity of atopic diseases, such as biomarker levels or skin prick test, or a detailed data set on echocardiography, electrocardiogram, and specific characteristics of AF. Finally, the observational study using the claims data limits causal inference with a possibility of residual confounding. Also, the choice and selection of sample size calculation would be considered. However, a prior sample size calculation was not performed in this study. Instead, we performed a post hoc power analysis. As a result, the power of this study to detect an HR of 1.25 was greater than 99% at a 0.05 significance level.

Conclusion

The atopic triad, including asthma, atopic dermatitis, and allergic rhinitis, is associated with an increased risk for incident AF. Moreover, multiple atopic conditions were associated with a higher risk for AF than the presence of a singular atopic disease or none. Extra vigilance for AF may be needed in patients with multiple atopic diseases. Further studies investigating this relation are warranted.

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TABLE E1. Definition of comorbidities

Diagnosis	ICD-10-Clinical Modification code and definition	Diagnostic definition
Hypertension	I10-I13, I15, and minimum of one prescription of antihypertensive drug (thiazide, loop diuretics, aldosterone antagonist, α -/ β -blocker, calcium-channel blocker, angiotensin-converting enzyme inhibitor, or angiotensin II receptor blocker)	Systolic blood pressure $\geq$ 140 mm Hg or diastolic blood pressure $\geq$ 90 mm Hg
Diabetes mellitus	E11-E14 and minimum of one prescription of antidiabetic drugs (sulfonylureas, metformin, meglitinides, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, α -glucosidase inhibitors, or insulin).	Fasting blood glucose $\geq$ 126 mg/dL
Dyslipidemia	E78 and minimum of one prescription of lipid-lowering drugs	Fasting total cholesterol $\geq$ 240 mg/dL

TABLE E2. Baseline characteristics of atopic group according to each disease*

Variable	Atopic dermatitis	Allergic rhinitis	Asthma
Subjects, n	111,874	895,049	132,982
Age, y	62.03 $\pm$ 11.16	54.92 $\pm$ 10.55	59.02 $\pm$ 11.13
<65, n (%)	61,510 (55.0)	707,306 (79.0)	86,863 (65.3)
$\geq$ 65, n (%)	50,364 (45.0)	187,743 (21.0)	46,119 (34.7)
Male sex, n (%)	46,724 (41.8)	372,152 (41.6)	50,776 (38.2)
Body mass index, kg/m ²	24.3 $\pm$ 3.41	24.0 $\pm$ 2.99	24.3 $\pm$ 3.20
BP measurements			
Systolic BP, mm Hg	126.63 $\pm$ 15.9	123.59 $\pm$ 15.16	125.09 $\pm$ 15.48
Diastolic BP, mm Hg	77.66 $\pm$ 10.02	76.64 $\pm$ 9.96	77.09 $\pm$ 9.95
Comorbidities, n (%)			
Hypertension	54,084 (48.3)	316,686 (35.4)	57,874 (43.5)
Diabetes mellitus	18,486 (16.5)	106,468 (11.9)	19,443 (14.6)
Dyslipidemia	33,003 (29.5)	233,144 (26.1)	40,732 (30.6)
Previous stroke	1973 (2.45)	11,241 (1.95)	6008 (7.46)
Previous ischemic heart disease	6008 (7.46)	25,016 (4.33)	5514 (6.05)
Glomerular filtration rate, mL/min per 1.73 m ²	82.46 $\pm$ 31.76	84.90 $\pm$ 35.60	83.18 $\pm$ 32.47
Smoking, n (%)			
Never	77,149 (69.0)	631,415 (70.6)	95,904 (72.1)
Ex-smoker	15,826 (14.2)	135,546 (15.1)	18,864 (14.2)
Current	18,899 (16.9)	128,088 (14.3)	18,214 (13.7)
Drinking, n (%)			
No	80,057 (71.6)	578,886 (64.7)	95,112 (71.5)
<30 g/d	27,114 (24.2)	277,701 (31.0)	33,320 (25.1)
$\geq$ 30 g/d	4703 (4.20)	38,462 (4.30)	4550 (3.42)
Low income, n (%)	31,018 (27.7)	245,030 (27.4)	36,960 (27.8)
Regular physical activity	45,710 (40.9)	447,138 (45.0)	60,128 (45.2)

BP, blood pressure.

*Continuous variables are presented as mean $\pm$ SD and categorical variables as number (percentage). For baseline comparisons, Student *t* test or Mann-Whitney U test was used for continuous variables and chi-square test or Fisher exact test for categorical variables. All variables were significantly different between the nonatopic and atopic groups (all *P* < .001).

TABLE E3. Risk for atrial fibrillation development according to presence of atopic diseases*

Category	Total n	Atrial fibrillation	Follow-up duration†	Incidence rate‡	Model 1	Model 2	Model 3
					HR (95% CI)	HR (95% CI)	HR (95% CI)
Non-asthma	6,500,644	126,445	46,746,391	2.70	1 (reference)	1 (reference)	1 (reference)
Asthma	247,920	9808	1,726,299	5.68	1.660 (1.627-1.695)	1.530 (1.498-1.561)	1.330 (1.305-1.357)
Nonatopic dermatitis	6,720,273	135,457	48,272,718	2.81	1 (reference)	1 (reference)	1 (reference)
Atopic dermatitis	28,291	796	199,972	3.98	1.229 (1.146-1.318)	1.154 (1.076-1.237)	1.087 (1.020-1.159)
Nonallergic rhinitis	5,710,238	111,348	41,018,498	2.71	1 (reference)	1 (reference)	1 (reference)
Allergic rhinitis	1,038,326	24,905	7,454,192	3.34	1.216 (1.199-1.233)	1.175 (1.159-1.191)	1.142 (1.128-1.157)

CI, confidence interval; HR, hazard ratio.

*Model 1 is adjusted for age and sex. Model 2 is adjusted for age, sex, history of smoking, drinking level, low income, diabetes mellitus, hypertension, and dyslipidemia. Model 3 is adjusted for age, sex, history of smoking, drinking level, low income, diabetes mellitus, hypertension, dyslipidemia, inflammatory bowel disease, and psoriasis.

†Follow-up duration is in person-years.

‡Incidence rate is presented as 1,000 person-years.

TABLE E4. Subgroup analysis according to each atopic disease and combination of atopic diseases*

Category	Atopic dermatitis	Allergic rhinitis	Asthma	Atopic dermatitis plus allergic rhinitis	Atopic dermatitis plus asthma	Allergic rhinitis plus asthma	Atopic dermatitis plus allergic rhinitis plus asthma
Age, y							
<65	1.394 (1.319-1.472)	1.632 (1.567-1.699)	1.700 (1.637-1.765)	1.739 (1.668-1.814)	1.615 (1.565-1.667)	1.578 (1.527-1.630)	1.373 (1.328-1.420)
≥65	1.128 (1.104-1.153)	1.145 (1.122-1.169)	1.157 (1.134-1.180)	1.165 (1.140-1.190)	1.131 (1.112-1.150)	1.123 (1.103-1.143)	1.093 (1.074-1.113)
Sex							
Male	1.356 (1.290-1.425)	1.545 (1.482-1.61)	1.510 (1.453-1.571)	1.615 (1.548-1.686)	1.481 (1.434-1.528)	1.502 (1.453-1.553)	1.349 (1.304-1.395)
Female	1.057 (0.913-1.224)	1.085 (0.960-1.227)	1.044 (0.919-1.186)	1.128 (0.983-1.295)	1.109 (0.998-1.231)	1.103 (0.989-1.230)	1.028 (0.921-1.148)
Body mass index, kg/m ²							
<25	1.361 (0.732-2.529)	2.408 (1.745-3.325)	1.966 (1.375-2.813)	2.466 (1.679-3.622)	1.909 (1.41-2.583)	1.791 (1.308-2.451)	1.522 (1.098-2.11)
≥25	1.267 (1.038-1.546)	1.142 (0.956-1.364)	1.236 (1.042-1.468)	1.103 (0.900-1.351)	1.21 (1.049-1.397)	1.261 (1.088-1.462)	1.084 (0.928-1.265)
Smoking							
No or ex-smoker	1.073 (1.050-1.096)	1.131 (1.106-1.157)	1.114 (1.088-1.141)	1.110 (1.086-1.134)	1.181 (1.137-1.227)	1.069 (0.969-1.178)	1.174 (1.140-1.210)
Current	1.365 (1.317-1.415)	1.448 (1.389-1.508)	1.490 (1.427-1.557)	1.404 (1.349-1.461)	1.618 (1.503-1.742)	1.183 (0.969-1.443)	1.537 (1.451-1.629)
Previous stroke							
No	0.985 (0.869-1.116)	1.101 (0.948-1.279)	1.158 (1.005-1.335)	1.056 (0.926-1.204)	1.015 (0.809-1.273)	0.982 (0.569-1.694)	1.041 (0.863-1.257)
Yes	1.934 (1.444-2.590)	1.471 (0.927-2.335)	2.078 (1.404-3.076)	1.720 (1.195-2.475)	2.404 (1.395-4.141)	2.691 (0.673-10.76)	2.640 (1.684-4.140)
Lower income							
No	1.072 (0.904-1.271)	1.373 (1.137-1.658)	1.241 (1.019-1.511)	1.344 (1.136-1.589)	1.380 (1.020-1.868)	0.397 (0.099-1.590)	1.445 (1.141-1.830)
Yes	1.397 (1.082-1.803)	1.389 (1.002-1.925)	1.135 (0.779-1.656)	1.393 (1.036-1.872)	2.129 (1.357-3.338)	1.391 (0.348-5.565)	1.521 (1.010-2.289)

*Data are presented as adjusted hazard ratio (95% confidence interval), adjusted for age, sex, history of smoking, drinking level, low income, diabetes mellitus, hypertension, and dyslipidemia. In the Cox proportional hazards regression model, the reference category was each subgroup of nonatopic subjects.

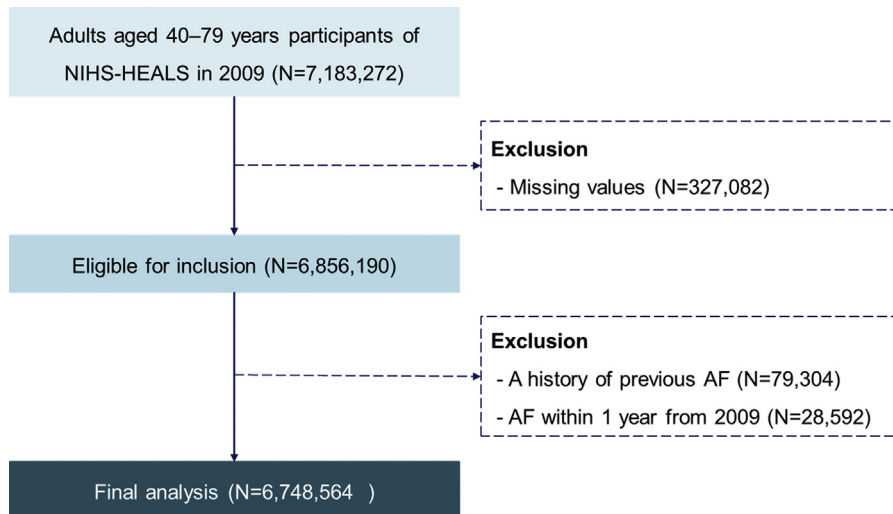


FIGURE E1. Study enrollment flow. *AF*, atrial fibrillation; *NIHS-HEALS*, National Health Insurance Services-Health Screening Cohort.

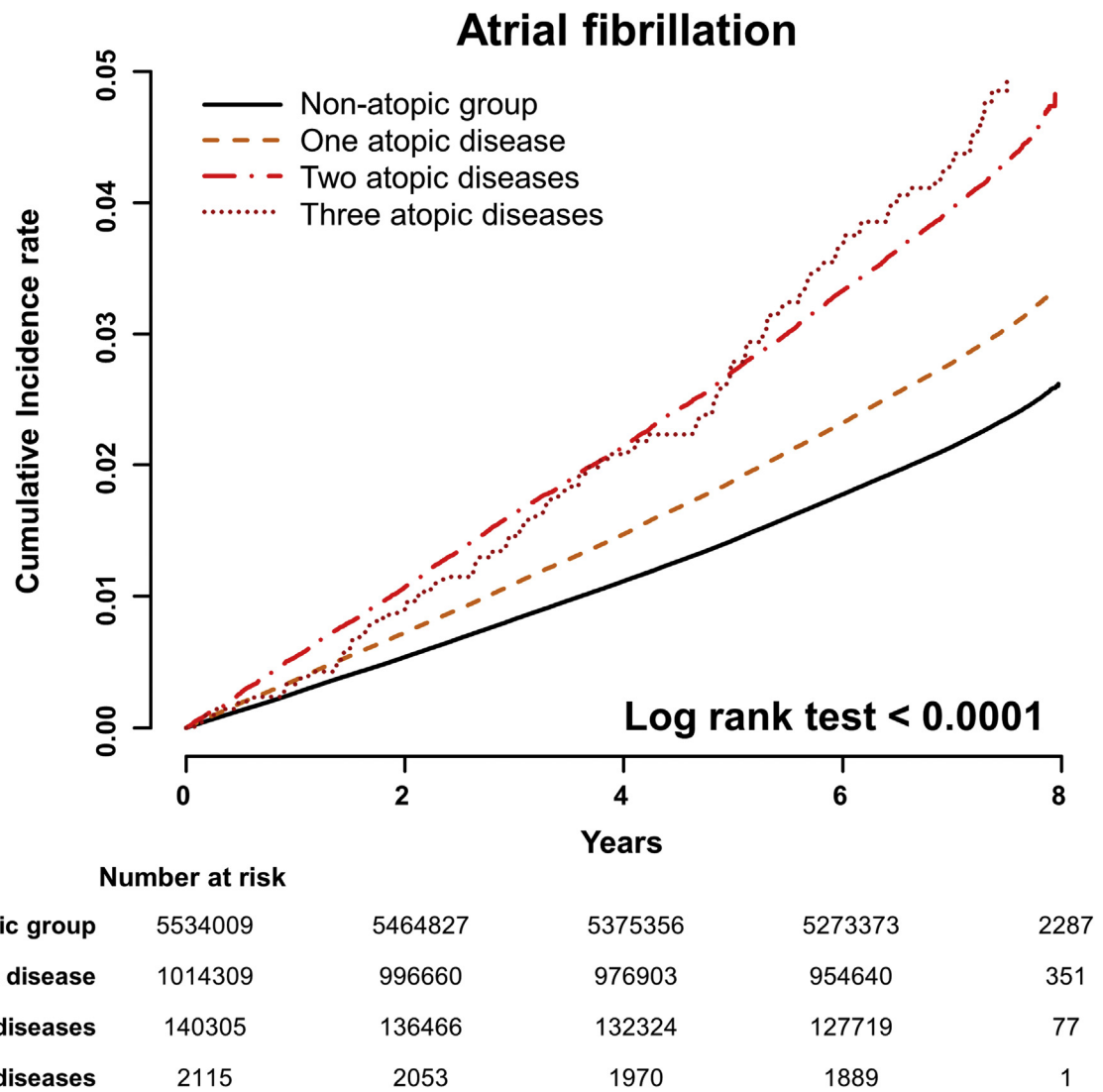


FIGURE E2. Kaplan-Meier curve for overall new-onset atrial fibrillation development according to the number of atopic diseases. Atopic diseases consist of asthma, allergic rhinitis, and atopic dermatitis.