

Original Article

Impact of the Combinations of Allergic Diseases on Myocardial Infarction and Mortality

Tae-Min Rhee, MD^a, Eue-Keun Choi, MD, PhD^b, Kyung-Do Han, PhD^b, So-Ryoung Lee, MD^a, and Seil Oh, MD, PhD, FHRS^a
Seoul, Korea

What is already known about this topic? Although patients with one of the triad diseases commonly have other allergic diseases, the effects of combinations of allergic diseases on the long-term risk of myocardial infarction and mortality are unknown.

What does this article add to our knowledge? In this population-based study with 9,548,939 adults, we found that the combination of atopic dermatitis and asthma in adults resulted in the highest risk of myocardial infarction and mortality among the combinations of allergic diseases.

How does this study impact current management guidelines? The prompt screening of the combination of other allergic conditions in allergic disease patients is important, as well as the evaluation and appropriate intervention for their future risk of myocardial infarction and mortality.

BACKGROUND: Allergic rhinitis (AR), atopic dermatitis (AD), and asthma, each by itself, are known to be associated with a higher risk of cardiovascular disease. Each of these diseases often coexists with one another, but the effect of combined allergic diseases on the long-term risk of myocardial infarction (MI) and mortality remains unknown.

OBJECTIVE: To evaluate the effects of various combinations of the allergic triad on the risk of MI and mortality.

METHODS: Adult allergic disease patients without prior MI were enrolled from the nationwide health check-up data provided by the Korean National Health Insurance Service in 2009. The primary and secondary end points were all-cause death and MI.

RESULTS: A total of 9,548,939 individuals older than 20 years were selected for analysis. The prevalence of allergic diseases was 13.9% for AR, 0.4% for AD, and 2.7% for asthma. During a median 8.2 years of follow-up, 105,659 MIs and 298,769 deaths

occurred. All allergic diseases were associated with an increased risk of MI (AR, adjusted hazard ratio [HR_{adjust}], 1.11, 95% CI, 1.10-1.13; AD, HR_{adjust} 1.14, 95% CI, 1.06-1.24; asthma, HR_{adjust} 1.37, 95% CI, 1.33-1.40), whereas mortality risk was increased only for patients with AD (HR_{adjust} 1.15; 95% CI, 1.10-1.20) or asthma (HR_{adjust} 1.41; 95% CI, 1.39-1.43).

Among the combinations of allergic diseases, patients with both AD and asthma had the highest risk of mortality (HR_{adjust} 1.71; 95% CI, 1.46-2.00) and MI (HR_{adjust} 1.57; 95% CI, 1.15-2.16). The results were significant after adjusting for demographic characteristics, comorbidities, socioeconomic status, and lifestyle factors.

CONCLUSIONS: Patients with both AD and asthma have the highest risk of MI and mortality among all allergic disease combinations. Physicians should evaluate combinations of allergic conditions in allergic disease patients and promptly assess and manage their future risk of MI and mortality. © 2020 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;■:■-■)

Key words: Asthma; Atopic dermatitis; Allergic rhinitis; Myocardial infarction; Mortality

^aDivision of Cardiology, Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea

^bDepartment of Statistics and Actuarial Science, Soongsil University, Seoul, Korea
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Corresponding author: Eue-Keun Choi, MD, PhD, Department of Internal Medicine, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea. E-mail: choiek17@snu.ac.kr.

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INTRODUCTION

The triad of chronic allergic diseases, namely allergic rhinitis (AR), atopic dermatitis (AD), and asthma, has been highlighted for its high prevalence and the accompanying disease burden in adults.¹ Cardiovascular disease is a major leading cause of morbidity and mortality around the world, and it is reportedly associated with various chronic inflammatory conditions.² The systemic inflammatory effects of chronic allergic diseases also affect the development and progression of atherosclerosis through various mechanisms.³ Asthma has been closely linked to diabetes mellitus and cardiovascular diseases, including coronary

Abbreviations used

AD- Atopic dermatitis

AR- Allergic rhinitis

BMI- Body mass index

HR_{adjust}- Adjusted hazard ratio

ICD-10- International Classification of Diseases, Tenth Revision

MI- Myocardial infarction

NHIS- National Health Insurance Service

heart disease, myocardial infarction (MI), and stroke.⁴⁻⁶ Evidence regarding the relationship of AD or AR with MI is limited, with few reports presenting controversial results.⁷⁻¹⁰ Furthermore, all 3 allergic diseases commonly present alongside each other,^{11,12} but the effect of multiple allergic diseases on MI and mortality is unknown. This is mainly due to the difficulty with establishing a large cohort with a sufficient follow-up duration to simultaneously cover several allergic diseases.¹³

Therefore, a large-scale cohort that covers all combinations of AR, AD, and asthma in adults was established in this study based on a nationwide claims database. Using this cohort, we investigated the impact of the combination of the atopic triad on the risk of MI and mortality.

METHODS

Data source and study population

The nationwide population data from the Korean National Health Insurance Service (NHIS) claims database were used for the study. The NHIS provides comprehensive data incorporating demographics, socioeconomic status, medical treatments and procedures, and disease diagnoses according to the *International Classification of Diseases, Tenth Revision (ICD-10)*. The profile of the data source was previously described.¹⁴

All subjects registered in the NHIS database are advised to undergo national health check-ups every 2 years. The categories of health check-ups include anthropometric data, blood pressure, and laboratory data, such as fasting glucose levels, cholesterol levels, and serum creatinine levels. Using standardized self-reporting questionnaires, data on previous medical history and lifestyle factors, including smoking habits, alcohol consumption, and physical activity, were collected.

Because the data were encrypted and completely anonymous, the study protocol was exempt from review by the Seoul National University Hospital Institutional Review Board (E-2005-093-1123). Informed consent could not be obtained because all records and information for patients were anonymized and deidentified before cohort establishment.

Establishment of study cohort

We initially selected 9,548,939 participants older than 20 years who had undergone the NHIS health check-up from January 1, 2009, to December 31, 2009. Participants with a history of MI that occurred before December 31, 2008, were excluded. Patients with a prevalence of 1 or more of the 3 allergic diseases investigated, that is, AD, AR, and asthma, were identified. Considering the practice pattern for allergic diseases in Korea, the prevalent allergic disease was defined as 3 or more occasions of diagnosis within 1 year with dedicated *ICD-10* codes registered by physicians at outpatient clinics, which was validated in a previous epidemiologic study in Korea.¹³

The analysis was performed in 2 parts. First, the entire cohort was analyzed as 3 separate sets divided by the presence of each allergic disease, that is, AR versus non-AR, AD versus non-AD, and asthma versus nonasthma. The prevalence of AR, AD, and asthma and the effect of each allergic disease on the development of long-term risk of MI and mortality were analyzed in Korean adults older than 20 years. Second, the participants were reclassified into 5 groups: none or 1 allergic disease, AR + AD, AR + asthma, AD + asthma, and AR + AD + asthma. The long-term outcomes were compared between groups with 2 or more allergic diseases and those with none or only 1 allergic disease. All participants in the study cohort had completed 8 years of follow-up by December 31, 2018.

Defining the study outcomes and comorbidities

The primary end point of this study was death by any cause during the follow-up period. The secondary end point was the occurrence of MI, defined using *ICD-10* codes (I21 and I22). Comorbidities including hypertension, diabetes mellitus, and dyslipidemia were also defined on the basis of *ICD-10* codes as described in our previous studies.¹⁵⁻¹⁷ The definitions of comorbidities are presented in Table E1 in this article's Online Repository at www.jaci-inpractice.org.

Statistical analysis

Categorical variables were presented as numbers and relative frequencies (percentages) and compared using the χ^2 test. Normally distributed continuous variables were expressed as the mean $\pm$ SD and analyzed using the independent sample *t* test or the ANOVA test. Annual event rates were described as the number of events per 1000 person-years. A comparison of the cumulative event rates between allergic disease and control groups was based on Kaplan-Meier censoring estimates and was performed with the log-rank test. Hazard ratios and the corresponding 95% CIs were calculated using univariate and multivariate Cox proportional hazard models. The first model was a univariate Cox proportional hazard model unadjusted for any covariates to evaluate the crude risk ratios. The second multivariate model was adjusted for age and sex, and the final multivariate model included smoking habit, alcohol consumption level, regular physical activity, low socioeconomic status, body mass index (BMI), hypertension, diabetes mellitus, and dyslipidemia in addition to the second model. Bonferroni correction was performed for multiple comparisons. Subgroup analyses divided by multiple risk factors were subsequently performed. All *P* values were 2-sided, and a value less than .05 was considered statistically significant. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC), Stata statistical software release 12 (StataCorp, College Station, Texas), and SPSS statistical package version 19.0 (SPSS Inc, Chicago, Ill).

RESULTS

Baseline characteristics of the study population

Tables I and II present the baseline characteristics according to the presence and combination of allergic diseases in the study population. The mean age of the study population, corresponding to a total of 9,548,939 participants, was 46.5 ± 13.8 years, and 55.0% were males. The prevalence of allergic diseases was 13.9% for AR, 0.4% for AD, and 2.7% for asthma in 2009. Individuals in the allergic disease group were older than those in the control group; the former group also had a significantly lower proportion of men. Among the 2 groups, the proportions of heavy alcohol drinkers, current smokers, and individuals who

TABLE I. Baseline characteristics according to presence of allergic disease

Characteristic	Total population (N = 9,548,939)	AR (N = 1,325,699)	Non-AR (N = 8,223,240)	P	AD (N = 38,223)	Non-AD (N = 9,510,716)	P	Asthma (N = 261,722)	Non-asthma (N = 9,287,217)	P
Sex: men	5,247,352 (55.0)	574,959 (43.4)	4,672,393 (56.8)	<.001	18,557 (48.6)	5,228,795 (55.0)	<.001	108,041 (41.3)	5,139,311 (55.3)	<.001
Age (y)	46.5 ± 13.8	48.8 ± 13.9	46.1 ± 13.8	<.001	48.6 ± 15.7	46.5 ± 13.8	<.001	56.3 ± 14.0	46.2 ± 13.7	<.001
BMI (kg/m ²)	23.7 ± 3.2	23.7 ± 3.2	23.7 ± 3.2	<.001	23.6 ± 3.3	23.7 ± 3.2	.024	24.1 ± 3.4	23.7 ± 3.2	<.001
Waist circumference (cm)	80.1 ± 9.1	80.0 ± 9.1	80.1 ± 9.1	<.001	80.2 ± 9.5	80.1 ± 9.1	.122	81.9 ± 9.2	80.0 ± 9.1	<.001
Smoking habit				<.001			<.001			<.001
Nonsmoker	5,652,994 (59.2)	906,550 (68.4)	4,746,444 (57.7)		24,262 (63.5)	5,628,732 (59.18)		181,649 (69.4)	5,471,345 (58.9)	
Ex-smoker	1,354,204 (14.2)	190,512 (14.4)	1,163,692 (14.2)		5,605 (14.7)	1,348,599 (14.2)		36,500 (14.0)	1,317,704 (14.2)	
Current smoker	2,541,741 (26.6)	228,637 (17.3)	2,313,104 (28.1)		8,356 (21.9)	2,533,385 (26.64)		43,573 (16.7)	2,498,168 (26.9)	
Alcohol consumption				<.001			<.001			<.001
Never	4,841,163 (50.7)	783,925 (59.1)	4,057,238 (49.3)		22,149 (58.0)	4,819,014 (50.7)		176,541 (67.5)	4,664,622 (50.2)	
Mild drinker	4,042,630 (42.3)	479,925 (36.2)	3,562,705 (43.3)		14,116 (36.9)	4,028,514 (42.4)		74,234 (28.4)	3,968,396 (42.7)	
Heavy drinker	665,146 (7.0)	61,849 (4.7)	603,297 (7.3)		1,958 (5.1)	663,188 (7.0)		10,947 (4.2)	654,199 (7.04)	
Regular physical activity	4,943,160 (51.8)	672,130 (50.7)	4,271,030 (51.9)	<.001	19,210 (50.3)	4,923,950 (51.77)	<.001	117,619 (44.9)	4,825,541 (52.0)	<.001
Low socioeconomic status	2,524,568 (26.4)	361,020 (27.2)	2,163,548 (26.3)	<.001	10,675 (27.9)	2,513,893 (26.4)	<.001	73,681 (28.2)	2,450,887 (26.4)	<.001
Hypertension	2,300,421 (24.1)	362,952 (27.4)	1,937,469 (23.6)	<.001	11,330 (29.6)	2,289,091 (24.1)	<.001	102,319 (39.1)	2,198,102 (23.7)	<.001
Diabetes mellitus	771,277 (8.1)	118,680 (9.0)	652,597 (7.9)	<.001	4,040 (10.6)	767,237 (8.1)	<.001	34,131 (13.0)	737,146 (7.9)	<.001
Dyslipidemia	1,644,242 (17.2)	272,355 (20.5)	1,371,887 (16.7)	<.001	8,394 (22.0)	1,635,848 (17.2)	<.001	67,754 (25.9)	1,576,488 (17.0)	<.001
SBP (mm Hg)	122.2 ± 14.9	121.7 ± 14.9	122.3 ± 14.9	<.001	122.2 ± 15.1	122.2 ± 14.9	.984	124.4 ± 15.6	122.1 ± 14.8	<.001
DBP (mm Hg)	76.2 ± 10.0	75.8 ± 9.9	76.3 ± 10.0	<.001	75.9 ± 9.9	76.2 ± 10.0	<.001	76.8 ± 10.0	76.2 ± 10.0	<.001
Fasting glucose (mg/dL)	96.8 ± 22.5	96.7 ± 21.6	96.8 ± 22.6	<.001	96.9 ± 23.2	96.8 ± 22.5	.678	99.2 ± 23.9	96.7 ± 22.5	<.001
Triglyceride (mg/dL)	113.1 (113.1-113.2)	111.3 (111.2-111.4)	113.4 (113.4-113.5)	<.001	112.9 (112.3-113.5)	113.1 (113.1-113.2)	.506	116.9 (116.7-117.2)	113.0 (113.0-113.1)	<.001
eGFR (mL/min/1.73 m ²)	88.7 ± 44.4	87.7 ± 43.3	88.8 ± 44.6	<.001	88.6 ± 49.2	88.7 ± 44.4	.743	84.8 ± 37.8	88.8 ± 44.6	<.001

DBP, Diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.
Values are described as numbers (%), mean ± SD, or median (Q1-Q3).

TABLE II. Baseline characteristics according to combination of multiple allergic diseases

Characteristic	None or 1 allergic disease (N = 9,390,212)	AR + AD (N = 10,353)	AR + asthma (N = 144,983)	AD + asthma (N = 973)	AR + AD + asthma (N = 2,418)	P
Sex: Men	5,183,804 (55.2)	4,605 (44.5)	57,456 (39.6)	477 (49.0)	1,010 (41.8)	<.001
Age (y)	46.3 ± 13.8	49.6 ± 15.0	54.4 ± 13.9	58.6 ± 15.3	53.6 ± 15.3	<.001
BMI (kg/m ²)	23.7 ± 3.2	23.7 ± 3.2	24.1 ± 3.3	24.1 ± 3.4	24.0 ± 3.3	<.001
Waist circumference (cm)	80.1 ± 9.1	80.2 ± 9.4	81.4 ± 9.2	83.0 ± 9.3	81.5 ± 9.3	<.001
Smoking habit						<.001
Nonsmoker	5,541,113 (59.0)	6,925 (66.9)	102,674 (70.8)	603 (62.0)	1,679 (69.4)	
Ex-smoker	1,331,924 (14.2)	1,582 (15.3)	20,217 (13.9)	147 (15.1)	334 (13.8)	
Current smoker	2,517,175 (26.8)	1,846 (17.8)	22,092 (15.2)	223 (22.9)	405 (16.8)	
Alcohol consumption						<.001
Never	4,735,377 (50.4)	6,336 (61.2)	97,102 (67.0)	679 (69.8)	1,669 (69.0)	
Mild drinker	3,995,782 (42.6)	3,542 (34.2)	42,391 (29.2)	254 (26.1)	661 (27.3)	
Heavy drinker	659,053 (7.0)	475 (4.6)	5,490 (3.8)	40 (4.1)	88 (3.6)	
Regular physical activity	4,868,500 (51.9)	5,267 (50.9)	67,875 (46.8)	398 (40.9)	1,120 (46.3)	<.001
Low socioeconomic status	2,479,848 (26.4)	2,978 (28.8)	40,684 (28.1)	293 (30.1)	765 (31.6)	<.001
Hypertension	2,243,358 (23.9)	3,209 (31)	52,505 (36.2)	464 (47.7)	885 (36.6)	<.001
Diabetes mellitus	752,409 (8.0)	1,115 (10.8)	17,266 (11.9)	169 (17.4)	318 (13.2)	<.001
Dyslipidemia	1,603,618 (17.1)	2,372 (22.9)	37,286 (25.7)	295 (30.3)	671 (27.8)	<.001
SBP (mm Hg)	122.2 ± 14.9	122 ± 15.0	123.6 ± 15.4	126.1 ± 15.2	123.4 ± 15.3	<.001
DBP (mm Hg)	76.2 ± 10.0	75.8 ± 10.0	76.5 ± 10.0	77.4 ± 9.7	76.5 ± 10.0	<.001
Fasting glucose (mg/dL)	96.8 ± 22.5	97.0 ± 22.6	98.3 ± 22.9	100.9 ± 28.8	97.7 ± 23.5	<.001
Triglyceride (mg/dL)	113.1 (113.0-113.1)	113.4 (112.2-114.7)	115.4 (115.1-115.7)	120.8 (116.7-125.0)	115.7 (113.2-118.2)	<.001
eGFR (mL/min/1.73 m ²)	88.7 ± 44.5	88.1 ± 44.2	85.5 ± 40.4	83.7 ± 25.2	84.6 ± 33.3	<.001

DBP, Diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.

Values are described as numbers (%), mean ± SD, or median (Q1-Q3).

TABLE III. Clinical outcomes according to the presence of allergic disease

Clinical outcome	Disease group		Control group		Unadjusted HR (95% CI)	Age/sex-adjusted HR (95% CI)	MV-adjusted HR (95% CI)
	No. of events/N	Incidence rate (per 1000 p-y)	No. of events/N	Incidence rate (per 1000 p-y)			
All-cause death							
AR	45,235/1,325,699	4.13	253,534/8,223,240	3.73	1.11 (1.09-1.12)	0.92 (0.91-0.93)	0.95 (0.94-0.96)
AD	1,960/38,223	6.25	296,809/9,510,716	3.78	1.66 (1.59-1.73)	1.16 (1.11-1.21)	1.15 (1.10-1.20)
Asthma	23,552/261,722	11.12	275,217/9,287,217	3.59	3.10 (3.06-3.14)	1.43 (1.41-1.45)	1.41 (1.39-1.43)
MI							
AR	18,096/1,325,699	1.66	87,563/8,223,240	1.29	1.28 (1.26-1.30)	1.12 (1.10-1.14)	1.11 (1.10-1.13)
AD	628/38,223	2.02	105,031/9,510,716	1.34	1.51 (1.40-1.63)	1.21 (1.12-1.31)	1.14 (1.06-1.24)
Asthma	6,877/261,722	3.28	98,782/9,287,217	1.29	2.53 (2.47-2.60)	1.44 (1.41-1.48)	1.37 (1.33-1.40)

HR, Hazard ratio; MV, multivariate; p-y, person-years.

TABLE IV. Clinical outcomes according to the combination of multiple allergic diseases

Clinical outcome	No. of events/N	Incidence rate (per 1000 p-y)	Unadjusted HR (95% CI)	Age/sex-adjusted HR (95% CI)	MV-adjusted HR (95% CI)
All-cause death					
None or 1 allergic disease	287,997/9,390,212	3.71	1 (reference)	1 (reference)	1 (reference)
AR + AD	505/10,353	5.94	1.60 (1.47-1.75)	1.10 (1.01-1.20)	1.12 (1.02-1.22)
AR + asthma	9,917/144,983	8.37	2.25 (2.21-2.30)	1.24 (1.21-1.26)	1.24 (1.22-1.27)
AD + asthma	155/973	20.29	5.49 (4.69-6.42)	1.80 (1.53-2.10)	1.71 (1.46-2.00)
AR + AD + asthma	195/2,415	9.92	2.67 (2.32-3.08)	1.33 (1.16-1.54)	1.29 (1.12-1.49)
MI					
None or 1 allergic disease	102,097/9,390,212	1.32	1 (reference)	1 (reference)	1 (reference)
AR + AD	146/10,353	1.73	1.31 (1.11-1.54)	1.02 (0.87-1.20)	0.97 (0.82-1.14)
AR + asthma	3,307/144,983	2.82	2.13 (2.06-2.20)	1.37 (1.32-1.42)	1.31 (1.27-1.36)
AD + asthma	39/973	5.18	4.01 (2.94-5.47)	1.81 (1.32-2.48)	1.57 (1.15-2.16)
AR + AD + asthma	70/2,418	3.60	2.73 (2.16-3.45)	1.71 (1.35-2.16)	1.56 (1.23-1.97)

HR, Hazard ratio; MV, multivariate; p-y, person-years.

performed regular physical activity were significantly lower in the allergic disease group. Cardiovascular risk factors, such as hypertension, diabetes mellitus, and dyslipidemia, were higher in the allergic disease group.

Compared with the none or 1 allergic disease group, age and the proportion of hypertension, diabetes mellitus, and dyslipidemia were significantly higher in the AR + AD, AR + asthma, AD + asthma, and AR + AD + asthma groups. The AD + asthma group had the highest systolic and diastolic blood pressure, serum levels of fasting glucose, and serum triglyceride levels and the lowest level of the estimated glomerular filtration rate. The results were consistent after correction for multiple comparisons (see Table E2 in this article's Online Repository at www.jaci-inpractice.org).

Incidence and risk of mortality and MI in patients with allergic disease

Table III presents the incidence and relative risks of the primary and secondary end points according to the presence of the 3 allergic diseases evaluated. The incidence rates of all-cause death in patients with AR, AD, and asthma were 4.13, 6.25, and 11.12 per 1000 person-years, respectively. The incidence rates of MI were generally lower than those of all-cause death and were 1.66, 2.02, and 3.28 per 1000 person-years in the AR, AD, and asthma groups, respectively. Compared with the control group, all 3 allergic diseases increased the risk of all-cause death and MI in the analysis with no adjustments (see Figure E1 in this article's

Online Repository at www.jaci-inpractice.org). However, in the multivariate model adjusted for possible confounders, only AD (adjusted hazard ratio [HR_{adjusted}], 1.15; 95% CI, 1.10-1.20) and asthma (HR_{adjusted}, 1.41; 95% CI, 1.39-1.43) were identified as significant risk factors that increased the mortality rate. The risks of MI were significantly higher in AR (HR_{adjusted}, 1.11; 95% CI, 1.10-1.13), AD (HR_{adjusted}, 1.14; 95% CI, 1.06-1.24), and asthma (HR_{adjusted}, 1.37; 95% CI, 1.33-1.40) groups than in the control groups in both the crude and multivariate models.

Incidence and risk of outcomes according to combination of multiple allergic diseases

The outcomes for patients with 2 or more allergic diseases were analyzed (Table IV). For both all-cause death and MI, all groups with 2 or more allergic diseases showed higher incidence rates than the none or 1 allergic disease group. After separating the control group (see Table E3 in this article's Online Repository at www.jaci-inpractice.org), the group with 2 or more allergic diseases also showed a significantly higher risk of mortality and MI than the group with 1 allergic disease. In addition, those without allergic disease showed lower risks of MI and mortality compared with those with 1 allergic disease. Among the combinations, the AR + AD group had the lowest risk of death and MI, whereas the AD + asthma group had the highest risk. The incidence rates of all-cause death and MI in the AD + asthma group were 20.29 and 5.18 per 1000 person-years, respectively. Compared with the none or 1

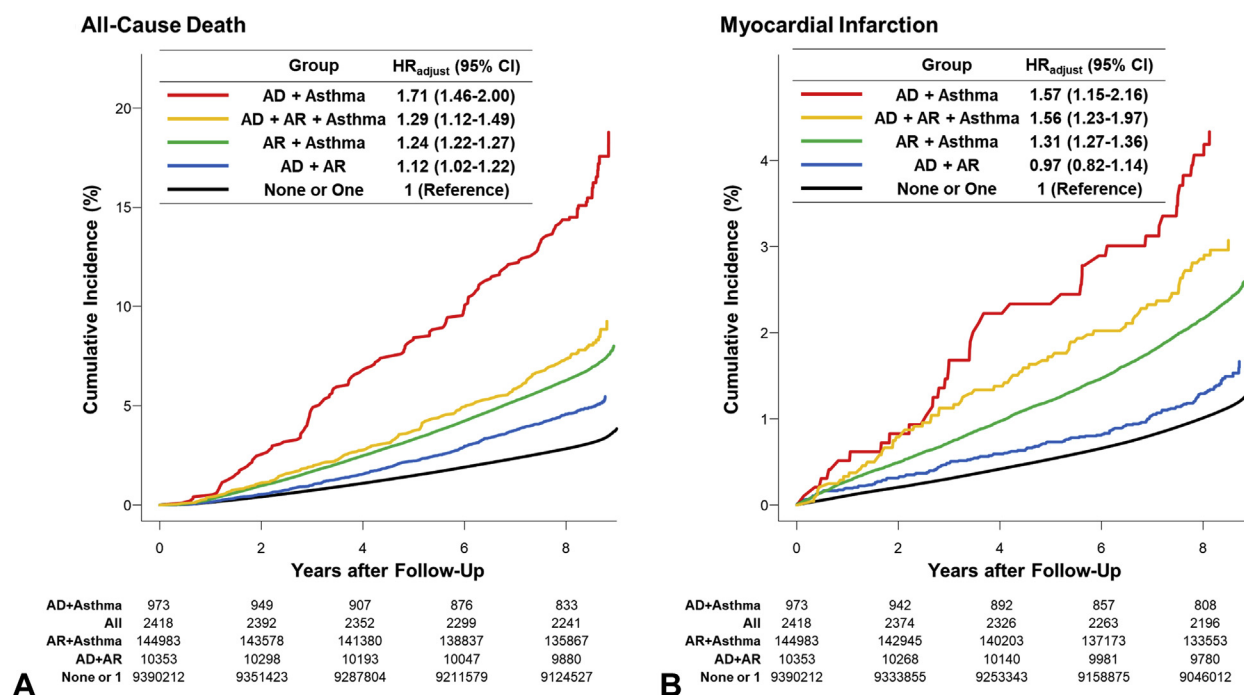


FIGURE 1. Comparison of cumulative incidence of all-cause death and MI according to the combinations of multiple allergic diseases. Kaplan-Meier curves with cumulative hazards of (A) all-cause death and (B) MI compared on the basis of combinations of allergic diseases.

allergic disease group, the multivariate-adjusted risk for all-cause death in the AD + asthma group was 1.71 (95% CI, 1.46-2.00) and the risk for MI was 1.57 (95% CI, 1.15-2.16), which was the highest among all the multiple allergic disease groups (Figure 1). After correction for multiple comparisons, the risks of all-cause death and MI were significantly higher in AR + asthma, AD + AR + asthma, and AD + asthma groups than in the none or 1 allergic disease group. For all-cause death, the risk of AD + asthma group was significantly higher than that of AR + AD and AR + asthma groups (see Figure E2 in this article's Online Repository at www.jaci-inpractice.org).

Subgroup analyses

Subgroup analyses for all-cause death risk are summarized in Figure 2. The incidence of all-cause death was higher in participants who were older, male, or current smokers, in those with BMI lower than 25 kg/m², and in those who had hypertension or diabetes mellitus, but who did not have dyslipidemia. The AD + asthma group had the highest mortality risk among all combinations regardless of age, sex, BMI, smoking habits, or presence of cardiovascular risk factors.

DISCUSSION

The epidemiology of 3 major allergic diseases and the long-term risk of MI and mortality according to the copresentation of multiple allergic diseases were analyzed in this study using a cohort of nearly 10 million adults who underwent national routine health check-ups. The prevalence of allergic diseases in Korean adults was 13.9% for AR, 0.4% for AD, and 2.7% for asthma. AD and asthma were independent risk factors for mortality and MI, but AR only increased the risk of MI, not

mortality. Among the various combinations of allergic diseases, adult patients with AD + asthma had the highest mortality and MI risk. The higher incidence of all-cause death in the AD + asthma group was particularly pronounced in older individuals, men, smokers, and normal/underweight groups.

Large epidemiological data on allergic diseases among adults are limited, and several reports have presented diverse numbers.¹³ The reported prevalence of AR was 3% to 34.5%,¹⁸ varying according to the disease definition, whereas that of AD was 2% to 4%¹⁹ and that of asthma was 0.7% to 5.4%.^{20,21} In the most recent epidemiological study of allergic diseases based on Korean nationwide claims data, the prevalence of AR, AD, and asthma was reported to be 11.0%, 1.2%, and 2.7%, respectively.¹³ In this study, the prevalence of the 3 diseases was calculated on the basis of cases wherein the diagnosis code (ICD-10) was electronically input by the clinical physician when the patient visited the clinic at least 3 times within 1 year. Based on these data, the prevalence in this study was 13.9% for AR, 0.4% for AD, and 2.7% for asthma, which showed a similar tendency as previous reports. Because of the lack of a universal definition of these diseases and the lack of well-designed epidemiological studies in the adult population, this large-scale epidemiological data can provide valuable evidence for future researchers and physicians.

Chronic allergic diseases, including AR, AD, and asthma, have a high prevalence, are closely interrelated, and have long durations of morbidity. Because cardiovascular disease, including MI, is a major disease entity that affects morbidity and mortality in adults globally, future MI and mortality risks from allergic diseases and their combinations have clinical significance.² The studies performed to date had insufficient

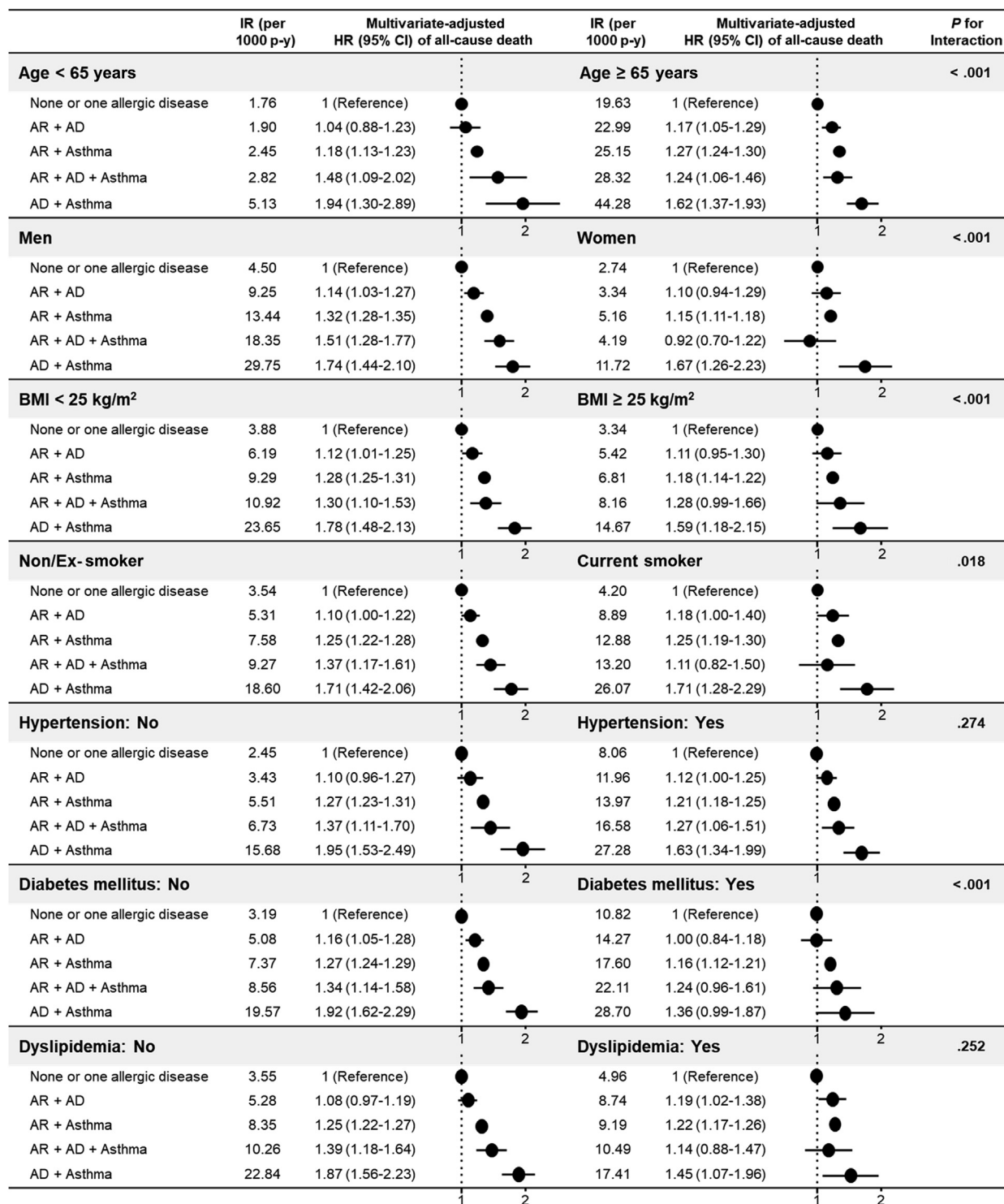


FIGURE 2. Subgroup analyses for all-cause death among combinations of multiple allergic diseases. The effects of the combinations of multiple allergic diseases on the risk of all-cause death in adults are presented according to the exploratory subgroups. *HR*, Hazard ratio; *IR*, incidence rate.

follow-up durations, did not cover a sufficient number of patients, and most often overlooked lifestyle and anthropometric factors that may significantly affect the occurrence of MI or mortality.⁹ The definitions of the target allergic disease in many

studies were also based on self-reporting questionnaires rather than on the physician's objective judgment.²² Furthermore, the 3 allergic diseases share some of the same pathophysiology and are closely related: 10% to 40% of AR cases are accompanied by

asthma^{18,23} and 15% to 61% of AD cases are complicated by AR.^{24,25} However, MI and mortality risks are not well known for patients with 2 or more allergic diseases compared with the risks for those with only 1 allergic disease. In this regard, the present study provides nationwide, large-scale, long-term follow-up data covering all 3 allergic diseases and their combinations. Furthermore, a comprehensive multivariate analysis including metabolic risk, anthropometric factors, and lifestyle factors was used to adjust for possible confounding bias that may affect the long-term outcomes of chronic allergic diseases. Notably, the allergic disease group in this study presented a higher proportion of traditional cardiovascular risk factors, such as hypertension, diabetes mellitus, and dyslipidemia, than the nonallergic disease group, which could predominantly be due to the significantly higher mean age in the former. Patients in the allergic disease group were significantly older than those in the nonallergic disease group (AR 48.8 vs non-AR 46.1 years, $P < .001$; AD 48.6 vs non-AD 46.5 years, $P < .001$; asthma 56.3 vs nonasthma 46.2 years, $P < .001$). Furthermore, it is likely that additional laboratory tests may have been performed at the time of the patient being diagnosed with an allergic disease in the clinic, which may have led to the detection bias.

It is well known that asthma is associated with cardiovascular diseases, including coronary heart disease.⁴⁻⁶ The results of the present study reconfirmed the significant adverse effects of asthma on the occurrence of MI and mortality. In agreement with some previous studies,^{8,9} AD showed a weaker but significant increase in MI and mortality risk compared with asthma. After adjustments for confounding factors, AR showed a modestly higher risk of MI but a lower risk of mortality. In addition, the risks of MI and mortality were lower in the combination of allergic diseases that included AR than in those without AR. This result was consistent with previous reports that suggested the possible protective effect of AR in terms of cardiovascular disease and long-term mortality.^{10,26} However, considering the confounding effects by other baseline factors in the present study, further clinical and preclinical studies to clarify the protective effect of AR are necessary.

Most importantly, this study is the first to systematically analyze the effects of combinations of the allergic triad on the long-term risk of MI and mortality. The results showed that the presentation of AD with asthma resulted in a higher risk of 71% for all-cause death and 57% for MI. In addition, among patients with AD and asthma, higher annual mortality was prominent in specific subgroups: 4.4% in the elderly population (vs 0.5% for patients aged <65 years), 3.0% in men (vs 1.2% in women), 2.4% in the normal or underweighted group (vs 1.5% in the obese group), and 2.6% in current smokers (vs 1.9% in non- or ex-smokers). In the study population, 1.3% of patients with asthma also presented with AD and 8.9% of patients with AD also had asthma. Given the above results, patients with AD who also have asthma should be screened promptly, and it would be necessary for physicians to assess their future risk of MI and mortality and for patients to make appropriate lifestyle modifications early.

The pathophysiology that underlies the relationship between allergic diseases and MI has not been established yet. Several hypotheses have been proposed, particularly focusing on asthma. The first is that allergic disease and MI share the same risk factors. Allergic diseases are well known to be related to individual components of metabolic risk, such as elevated blood

pressure, blood glucose, and high cholesterol levels,^{6,27} which may partly explain the increased incidence of MI and mortality in allergic disease patients. Second, all 3 diseases are susceptible to respiratory microbial infection or chronic local skin infection.^{22,28,29} Increased susceptibility to infection naturally increases the frequency and exposure time of systemic inflammatory responses, and this will adversely affect the long-term cardiovascular outcomes by triggering dysregulated inflammation and thrombosis.³⁰ Third, allergic disease and MI also share the same inflammatory pathogenesis.³¹ As like diseases related to adaptive immunity mediated by T lymphocytes, AR, AD, and asthma are T_H2-predominant allergic diseases.⁵ Conversely, T_H1-mediated inflammation, represented by intracellular IFN- γ expression, is known to have a significant effect on atherosclerosis, plaque progression, and MI.³ However, even localized allergic diseases can induce interactions with vascular endothelial cells and promote atherosclerosis through the release of vasoactive peptides and cytokines.³² An increase in serum total IgE, the surrogate marker of atopy, was also reportedly associated with atherosclerotic disease.³³ Furthermore, proinflammatory substances, such as leukotrienes, are important mediators of both asthmatic bronchiole and atherosclerotic plaques.³⁴ The 5-lipo-oxygenase enzymatic pathway, which mediates parts of the asthmatic inflammation process, also appears to be common in the progression of atherosclerotic plaques, plaque instability, and the development of MI.³⁵ In summary, a number of complex mechanisms are expected to interact and affect the inconsistent outcomes in patients with AD and AR as well as the significantly greater risk of MI and mortality in the AD + asthma group. The epidemiology and pathophysiology of AD, AR, and multiple allergic diseases related to cardiovascular outcomes need to be identified in future studies.

Several limitations of the present study should be discussed. First, this retrospective, observational cohort study could not reveal the causality of the relationship among allergic diseases, MI, and mortality. Second, because this was a nationwide study conducted in a single country, it should be noted that the results may not be generalizable to all populations. Further studies in various populations are necessary to clarify whether the results of the present study are applicable to other populations. Third, because of the limitations in the investigation for covariates, bias from unmeasured confounding factors was not considered. Although the multivariate analysis was performed using known confounders, there could be residual confounding effects. Fourth, because the working definition using the ICD-10 diagnostic code was included in claims data, misclassification bias and the possibility of underreporting or overreporting cannot be excluded. This study used the definition of prevalent allergic diseases considering 3 or more encounters a year; thus, we may have consequently selected more severely ill patients than we would have with a definition considering 1 or 2 encounters a year. However, the methodology of this study was firmly validated through several previous studies by our group.¹⁴⁻¹⁶ Finally, because of the lack of data on drug use, patients could not be classified according to the severity of each allergic disease. In addition, it is unknown whether medications could be a causative factor in the elevated risk of MI and mortality in this study, considering the possible unmeasured confounding bias by medications.

CONCLUSIONS

Long-term follow-up data in the national claims database revealed that the allergic triad increased the incidence of MI in adults and that the mortality risk was significantly higher in patients with AD or asthma than in the control group. Patients with AD + asthma had the highest MI and mortality risks among all allergic disease combinations. Adult allergic disease patients require screening for a combination of other allergic conditions and active surveillance for future risk of MI and mortality.

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ONLINE REPOSITORY

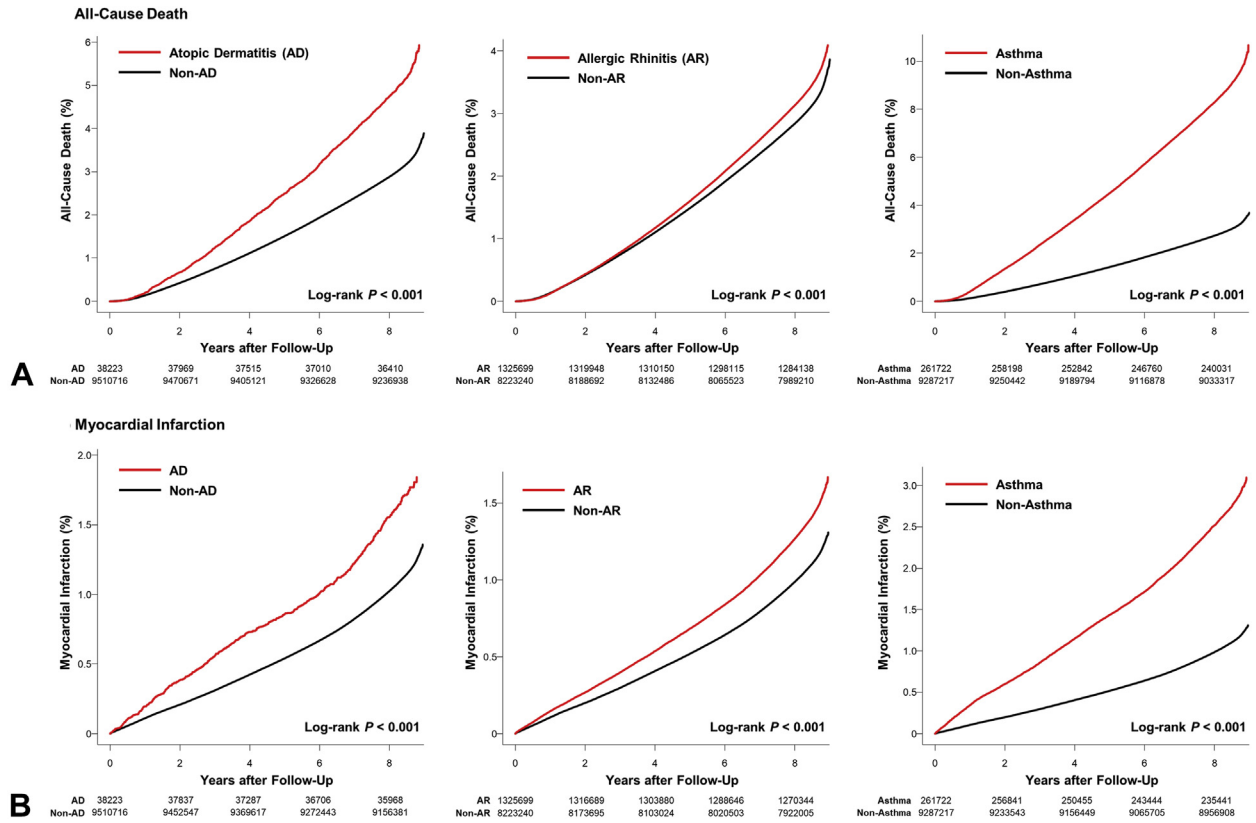


FIGURE E1. Cumulative incidence of all-cause death and MI in adult allergic disease patients. Kaplan-Meier curves with cumulative hazards of (A) all-cause death and (B) MI compared by the presence of allergic diseases.

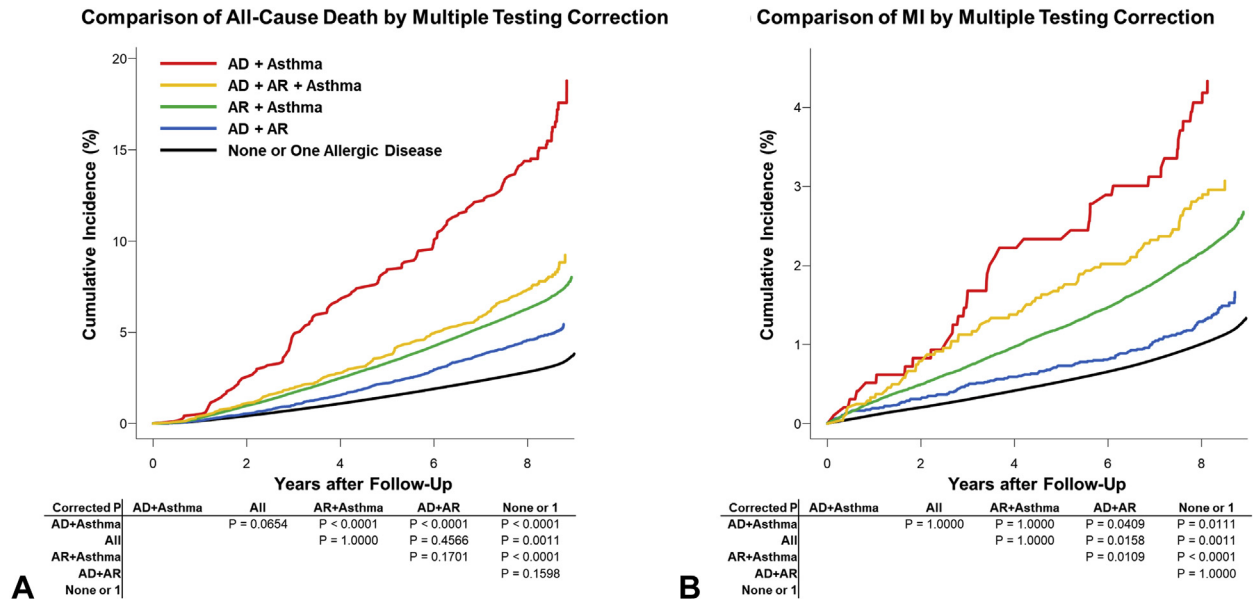


FIGURE E2. Comparison of all-cause death and MI according to combination of allergic diseases using Bonferroni correction. Kaplan-Meier curves with cumulative hazards of (A) all-cause death and (B) MI compared by the combination of allergic diseases and the corrected *P* values by Bonferroni correction for multiple comparison. The risks of all-cause death and MI were significantly higher in AR + asthma, AD + AR + asthma, and AD + asthma groups than in the none or 1 allergic disease group. For all-cause death, the risk of the AD + asthma group was significantly higher than that of AR + AD and AR + asthma groups.

TABLE E1. List of definitions of comorbidities and lifestyle factors

Comorbidities	ICD-10 codes	Additional definitions
Hypertension	I10-I15	Hospitalization ≥ 1 or outpatient visit ≥ 2
Diabetes mellitus	E11-E14	Hospitalization ≥ 1 or outpatient visit ≥ 2 With additional claims for the oral antidiabetic agents or insulin
Dyslipidemia	E78	Any of hospitalization or outpatient visit ≥ 1
Lifestyle factors	Definitions	
Alcohol consumption	Mild drinker	The average amount of alcohol consumption < 30 g/d
	Heavy drinker	The average amount of alcohol consumption ≥ 30 g/d
Regular physical activity	Moderate-intensity physical activity for ≥ 30 min at a time and at least 1 d a week, or high-intensity physical activity for ≥ 20 min at a time and at least 1 d a week	
Low socioeconomic status	Paying the lowest quartile of national health insurance premium or being covered by the national medical care system	

TABLE E2. Comparison of baseline characteristics according to combination of multiple allergic diseases using Bonferroni correction for multiple comparisons

Characteristic	<i>P</i> values by Bonferroni correction									
	None or 1 allergic disease (N = 9,390,212)				AR + AD (N = 10,353)			AR + asthma (N = 144,983)		AR + AD + asthma (N = 2,418)
	AR + AD (N = 10,353)	AR + asthma (N = 144,983)	AR + AD + asthma (N = 2,418)	AD + asthma (N = 973)	AR + asthma (N = 144,983)	AR + AD + asthma (N = 2,418)	AD + asthma (N = 973)	AR + AD + asthma (N = 2,418)	AD + asthma (N = 973)	AD + asthma (N = 973)
Age	<.0001	<.0001	<.0001	<.0001	.0589	<.0001	<.0001	<.0001	<.0001	<.0001
BMI	<.0001	<.0001	.0012	>.9999	>.9999	>.9999	<.0001	>.9999	<.0001	<.0001
Waist circumference	<.0001	<.0001	<.0001	>.9999	>.9999	<.0001	<.0001	.0001	<.0001	<.0001
Smoking habit	<.0001	<.0001	<.0001	<.0001	<.0001	.2273	.004	.4485	<.0001	.0001
Alcohol consumption	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	.1686	.5619	>.9999
Regular physical activity	.5171	<.0001	<.0001	<.0001	<.0001	.0005	<.0001	>.9999	.0014	.0285
Low socioeconomic status	<.0001	<.0001	<.0001	.0062	>.9999	.1502	>.9999	.0179	.9149	>.9999
Hypertension	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	>.9999	<.0001	<.0001
Diabetes mellitus	<.0001	<.0001	<.0001	<.0001	.0078	.0117	<.0001	.6742	<.0001	.0147
Dyslipidemia	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	.1972	.0101	>.9999
SBP	<.0001	.0002	<.0001	>.9999	>.9999	<.0001	<.0001	<.0001	.0002	<.0001
DBP	<.0001	.0302	<.0001	.0002	>.9999	.0288	<.0001	.1076	1.0000	.0014
Fasting glucose	<.0001	>.9999	<.0001	>.9999	>.9999	.0019	<.0001	.0016	.2857	<.0001
Triglyceride	.0435	>.9999	.0142	>.9999	>.9999	.1543	<.0001	.5457	.4261	.0037
eGFR	<.0001	.0047	.0257	>.9999	>.9999	>.9999	<.0001	>.9999	<.0001	.0031

DBP, Diastolic blood pressure; *eGFR*, estimated glomerular filtration rate; *SBP*, systolic blood pressure.

TABLE E3. Clinical outcomes according to the combination of multiple allergic diseases

Outcome	No. of events/N	Incidence rate (per 1000 p-y)	Unadjusted HR (95% CI)	Age/sex-adjusted HR (95% CI)	MV-adjusted HR (95% CI)
All-cause death					
No allergic disease	238,404/8,124,729	3.65	0.78 (0.78-0.79)	1.00 (0.99-1.01)	0.98 (0.97-0.99)
One allergic disease	49,593/1,313,026	4.67	1 (reference)	1 (reference)	1 (reference)
Two or more allergic diseases	10,772/158,724	8.51	1.83 (1.79-1.86)	1.24 (1.21-1.26)	1.22 (1.19-1.24)
MI					
No allergic disease	83,480/8,124,729	1.28	0.73 (0.72-0.74)	0.87 (0.85-0.88)	0.88 (0.86-0.89)
One allergic disease	18,617/1,313,026	1.75	1 (reference)	1 (reference)	1 (reference)
Two or more allergic diseases	3,562/158,724	2.85	1.62 (1.57-1.68)	1.22 (1.18-1.26)	1.17 (1.13-1.21)

HR, Hazard ratio; MV, multivariate; p-y, person-years.