Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Original Article

Impact of Allergic Rhinitis and Asthma on COVID-19 Infection, Hospitalization, and Mortality

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What is already known about this topic? In different studies, whether asthma and allergic rhinitis acting as independent risk factors for corona virus disease 2019 (COVID-19) remains controversial.

What does this article add to our knowledge? AR (all ages) and asthma (aged <65) act as protective factors against COVID-19 infection, whereas asthma increases the risk for hospitalization. None of the long-term medications had a significant association with infection, severity, and mortality of COVID-19 among patients with AR and/or asthma.

How does this study impact current management guidelines? We provided new insights on the association between allergic diseases and COVID-19 prevalence and outcomes. We suggested that more attention should be paid to the education and primary care of elderly asthmatic patients diagnosed with COVID-19, including active treatment of comorbidities.

BACKGROUND: It remains unclear if patients with allergic rhinitis (AR) and/or asthma are susceptible to corona virus disease 2019 (COVID-19) infection, severity, and mortality.
OBJECTIVE: To investigate the role of AR and/or asthma in COVID-19 infection, severity, and mortality, and assess whether long-term AR and/or asthma medications affected the outcomes of COVID-19.
METHODS: Demographic and clinical data of 70,557 adult participants completed SARS-CoV-2 testing between March 16 and December 31, 2020, in the UK Biobank were analyzed. The rates of COVID-19 infection, hospitalization, and mortality in relation to pre-existing AR and/or asthma were assessed based on adjusted generalized linear models. We further analyzed the impact of long-term AR and/or asthma medications on the risk of COVID-19 hospitalization and mortality.
RESULTS: Patients with AR of all ages had lower positive rates of SARS-CoV-2 tests (relative risk [RR]: 0.75, 95% confidence interval [CI]: 0.69-0.81, $P < .001$), with lower susceptibility in males (RR: 0.74, 95% CI: 0.65-0.85, $P < .001$) than females (RR: 0.8, 95% CI: 0.72-0.9, $P < .001$). However, similar effects of asthma against COVID-19 hospitalization were only major in participants aged <65 (RR: 0.93, 95% CI: 0.86-1, $P = .044$)

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Abbreviations used
ACE2- Angiotensin-converting enzyme 2
AR- Allergic rhinitis
BMI- Body mass index
CI- Confidence interval
CNS- Corticosteroid nasal sprays
COPD- Chronic obstructive pulmonary disease
COVID-19- Corona virus disease 2019
ICD- International Classification of Diseases
RR- Relative risk
SD- Standard deviation
UKB- UK Biobank

instead of elderlies. In contrast, patients with asthma tested positively had higher risk of hospitalization (RR: 1.42, 95% CI: 1.32-1.54, $P < .001$). Neither AR nor asthma had an impact on COVID-19 mortality. None of conventional medications for AR or asthma, for example, antihistamines, corticosteroids, or β2 adrenoceptor agonists, showed association with COVID-19 infection or severity.
CONCLUSION: AR (all ages) and asthma (aged <65) act as protective factors against COVID-19 infection, whereas asthma increases risk for COVID-19 hospitalization. None of the long-term medications had a significant association with infection, severity, and mortality of COVID-19 among patients with AR and/or asthma. **(J Allergy Clin Immunol Pract 2022;10:124-33)**

Key words: *COVID-19; Allergic rhinitis; Asthma; Long-term medications; Glucocorticoids*

The emergence of corona virus disease 2019 (COVID-19) has had a huge impact on population health globally. As of May 9, 2021, there have been more than 157 million confirmed COVID-19 cases worldwide and over 3.2 million deaths were attributed to the pandemic (https://covid19.who.int./). It has been reported that some underlying diseases such as dementia, pneumonia, depression, diabetes, atrial fibrillation, chronic obstructive pulmonary disease (COPD), and hypertension,[1] as well as high cytokine, lactate dehydrogenase level,[2] and ages, could affect the prevalence and outcomes of COVID-19.

Allergic rhinitis (AR) and asthma are common and underestimated respiratory diseases and often simultaneously occur as united airway disease.[3-5] Whether AR and asthma acting as independent risk factors for the infection, hospitalization, and mortality of COVID-19 remains controversial. It was reported that patients with AR and/or asthma were often exacerbated by viral respiratory infections.[6,7] A Korean nationwide cohort study reported that AR and asthma increased the susceptibility and severity of COVID-19.[8] On the contrary, other reports suggested that asthma did not pose a threat to the diagnosis and severity of COVID-19.[9-12] Moreover, some meta-analyses even concluded that asthma was considered as an independent protective factor for the death of patients with COVID-19.[13-15]

Our current study aimed to explore the role of AR and/or asthma in the risk of infection, severity, and mortality of COVID-19 based on a large prospective cohort in UK Biobank (UKB), and to evaluate whether long-term medications for AR and/or asthma would affect the clinical manifestation and outcomes of COVID-19.

METHODS

Database information

UKB is a national prospective cohort with very large and detailed data from over 500,000 participants aged 40 to 69 years when recruited at baseline (in 2006-2010), which ensured a wide distribution across all exposures to provide reliable associations between personal characteristics and health outcomes.[16] SARS-CoV-2 testing result data were offered to UKB by Public Health England. UKB ethical approval was from the North West Multi-centre Research Ethics Committee. The current analysis was approved under the UKB application (Applicant Number: 69718).

Study population

UKB participants with matching SARS-CoV-2 results (whether reported as positive or negative for SARS-CoV-2) tested between March 16, 2020, and December 31, 2020, in England were examined. We excluded individuals (1) who died before the pandemic (set as February 1, 2020), (2) whose location belonged to UKB assessment centers in Scotland and Wales (where no SARS-CoV-2 testing data were available), and (3) who were diagnosed with AR and/or asthma after February 1, 2020, which was set as the beginning of the pandemic.[1]

Exposure variables and covariables

AR was defined as either self-reported AR history from baseline questionnaires or the International Classification of Diseases codes (ICD-10 codes: J30.1, J30.2, J30.3, J30.4; or ICD-9 codes: 460, 477). Asthma was defined as either self-reported asthma history from baseline questionnaires or ICD codes (ICD-10 codes: J45; or ICD-9 codes: 493).

Medication data of UKB participants were available from a verbal interview by a trained nurse on prescription medications including type and number of medications. The long-term medications were defined as regular medications taken weekly and monthly, as opposed to the short-term medications. We summarized different types of medications such as antihistamine, glucocorticoids, corticosteroid nasal sprays (CNS), and β2 adrenoceptor agonists according to their coding in Table E1 (available in this article's Online Repository at www.jaci-inpractice.org).

Covariables included gender, age, Townsend deprivation index, education, body mass index (BMI), ethnic background, smoking status, alcohol drinking status, current employment status, and pre-existing comorbidities.[1,17] Age was defined as baseline age plus the duration of interval before inclusion. Pre-existing comorbidities considered in this study included cancer diagnosed by doctor (self-report in questionnaires), fracture resulting from simple fall (self-report in questionnaires), diabetes mellitus (ICD-10 codes: E10, E11, E12, E13, E14), chronic diseases of the circulatory system (ICD-10 codes: I05-I09, I10-I15, I20-I25, I26-I28, I60-I69), chronic lower respiratory diseases (ICD-10 codes: J40, J41, J42, J43, J44, J47; or ICD-9 codes: 490, 491, 492, 496, 494), diseases of esophagus, stomach, and duodenum (ICD-10 codes: K20, K21, K25, K26, K27, K28, K29, K30; or ICD-9 codes: 530, 531, 532, 533, 534, 535, 5368), renal failure (ICD-10 codes: N17, N18, N19; or ICD-9 codes: 584, 585), dementia (ICD-10 codes: F00, F01, F02, F03, G30; or ICD-9 codes: 2901), liver disease (K72 hepatic failure, not elsewhere classified, K74, 5712, 5715, 5716 fibrosis and cirrhosis of liver), arthritis (ICD-10 codes: M00, M01, M02, M03, M05, M06, M07, M08, M09, M10, M11, M12, M13, M14), and certain immune disorders (ICD-10 codes: D80, D81, D82, D83, D84, D86, D89). However, because of the limited number of

TABLE I. Clinical and demographic characteristics of all study subjects (n = 70,557)

	COVID-19 infection				COVID-19 hospitalization				COVID-19 mortality			
Covariate	Total (n = 70,557) (%)	No (n = 54,867) (%)	Yes (n = 15,690) (%)	*P* value	Total (n = 15,690) (%)	No (n = 10,775) (%)	Yes (n = 4915) (%)	*P* value	Total (n = 15,690) (%)	No (n = 15,054) (%)	Yes (n = 636) (%)	*P* value
Group												
AR	3201 (5)	2656 (5)	545 (3)	**<.001**	545 (3)	419 (4)	126 (3)	**<.001**	545 (3)	531 (4)	14 (2)	**.0011**
Asthma	8624 (12)	6801 (12)	1823 (12)		1823 (12)	1042 (10)	781 (16)		1823 (12)	1720 (11)	103 (16)	
Both	1407 (2)	1151 (2)	256 (2)		256 (2)	177 (2)	79 (2)		256 (2)	247 (2)	9 (1)	
Control	57,325 (81)	44,259 (81)	13,066 (83)		13,066 (83)	9137 (85)	3929 (80)		13,066 (83)	12,556 (83)	510 (80)	
Sex												
Female	37,725 (53)	29,441 (54)	8284 (53)	.058	8284 (53)	5953 (55)	2331 (47)	**<.001**	8284 (53)	8072 (54)	212 (33)	**<.001**
Male	32,832 (47)	25,426 (46)	7406 (47)		7406 (47)	4822 (45)	2584 (53)		7406 (47)	6982 (46)	424 (67)	
Age												
Mean (SD)	67.8 (8.3)	68.7 (8)	64.4 (8.6)	**<.001**	64.4 (8.6)	62.8 (8)	68 (8.8)	**<.001**	64.4 (8.6)	64 (8.5)	74 (5.6)	**<.001**
Median (Min, Max)	69.3 (49.5, 85.2)	70.5 (49.5, 85.2)	63.5 (49.5, 82.9)	**<.001**	63.5 (49.5, 82.9)	61.5 (49.5, 82.6)	69.9 (49.7, 82.9)	**<.001**	63.5 (49.5, 82.9)	62.9 (49.5, 82.7)	75.7 (52.9, 82.9)	**<.001**
Ethnic												
Non-White	4583 (7)	2947 (5)	1636 (10)	**<.001**	1636 (10)	1123 (10)	513 (11)	**.95**	1636 (10)	1582 (11)	54 (9)	.12
White	65,576 (93)	51,617 (95)	13,959 (90)		13,959 (90)	9598 (90)	4361 (89)		13,959 (90)	13,382 (89)	577 (91)	
Missing	398	303	95		95	54	41		95	90	5	
BMI												
Normal/Under	20,185 (29)	16,120 (30)	4065 (26)	**<.001**	4065 (26)	3098 (29)	967 (20)	**<.001**	4065 (26)	3962 (27)	103 (17)	**<.001**
Obese	19,923 (28)	15,031 (28)	4892 (31)		4892 (31)	2994 (28)	1898 (39)		4892 (31)	4616 (31)	276 (44)	
Overweight	29,933 (43)	23,340 (43)	6593 (42)		6593 (42)	4612 (43)	1981 (41)		6593 (42)	6350 (43)	243 (39)	
Missing	516	376	140		140	71	69		140	126	14	
Employment												
Employed	40,585 (58)	29,976 (55)	10,609 (68)	**<.001**	10,609 (68)	8092 (76)	2517 (52)	**<.001**	10,609 (68)	10,426 (70)	183 (29)	**<.001**
Other	6238 (9)	4673 (9)	1565 (10)		1565 (10)	973 (9)	592 (12)		1565 (10)	1493 (10)	72 (11)	
Retired	23,265 (33)	19,865 (36)	3400 (22)		3400 (22)	1633 (15)	1767 (36)		3400 (22)	3021 (20)	379 (60)	
Missing	469	353	116		116	77	39		116	114	2	
Education												
Mean (SD)	14.6 (5.2)	14.6 (5.2)	14.4 (5.2)	**<.001**	14.4 (5.2)	14.8 (5)	13.7 (5.4)	**<.001**	14.4 (5.2)	14.5 (5.1)	12.6 (5.4)	**<.001**
Median (Min, Max)	15 (7, 20)	15 (7, 20)	15 (7, 20)		15 (7, 20)	15 (7, 20)	15 (7, 20)		15 (7, 20)	15 (7, 20)	10 (7, 20)	
Missing	1583	1212	371		371	227	144		371	346	25	
Townsend deprivation index												
High	15,441 (22)	11,249 (21)	4192 (27)	**<.001**	4192 (27)	2674 (25)	1518 (31)	**<.001**	4192 (27)	3984 (26)	208 (33)	**.0021**
Low	13,320 (19)	10,893 (20)	2427 (15)		2427 (15)	1749 (16)	678 (14)		2427 (15)	2340 (16)	87 (14)	
Median	41,705 (59)	32,654 (60)	9051 (58)		9051 (58)	6336 (59)	2715 (55)		9051 (58)	8711 (58)	340 (54)	
Missing	91	71	20		20	16	4		20	19	1	

Smoking status												
Current	7601 (11)	5816 (11)	1785 (11)	**<.001**	1785 (11)	1156 (11)	629 (13)	**<.001**	1785 (11)	1693 (11)	92 (15)	**<.001**
Never	36,525 (52)	28,225 (52)	8300 (53)		8300 (53)	6017 (56)	2283 (47)		8300 (53)	8072 (54)	228 (36)	
Previous	25,924 (37)	20,423 (37)	5501 (35)		5501 (35)	3544 (33)	1957 (40)		5501 (35)	5193 (35)	308 (49)	
Missing	507	403	104		104	58	46		104	96	8	
Smoking (pack-year)												
Mean (SD)	11(16.4)	11.2 (16.6)	10.5 (16)	**.0042**	10.5 (16)	8.9 (13.8)	14 (19.5)	**<.001**	10.5 (16)	10.1 (15.5)	20.2 (23.5)	**<.001**
Missing	504	402	102		102	58	44		102	94	8	
Drinking status												
Current	63,947 (91)	49,925 (91)	14,022 (90)	**<.001**	14,022 (90)	9777 (91)	4245 (87)	**<.001**	14,022 (90)	13,479 (90)	543 (86)	**<.001**
Never	3494 (5)	2525 (5)	969 (6)		969 (6)	614 (6)	355 (7)		969 (6)	926 (6)	43 (7)	
Previous	2827 (4)	2191 (4)	636 (4)		636 (4)	348 (3)	288 (6)		636 (4)	591 (4)	45 (7)	
Missing	289	226	63		63	36	27		63	58	5	

AR, Allergic rhinitis; *BMI*, body mass index; *COVID-19*, corona virus disease 2019; *SD*, standard deviation.
Bold indicates statistical significance, $P < .05$.
Data involving pre-existing comorbidities are presented in Table E1, available in this article's Online Repository at www.jaci-inpractice.org.

TABLE II. Univariable and multivariable analysis for the infection rate, hospitalization rate, and mortality of COVID-19 in participants with allergic rhinitis (AR) and/or asthma

	Univariable analysis			Multivariable analysis		
Outcome	**Number**	**RR (95% CI)**	***P* value**	**Number**	**RR (95% CI)**	***P* value**
COVID-19 infection						
Controls	57,325	Reference	–	54,685	Reference	–
AR	3201	0.75 (0.69-0.81)	**<.001**	3101	0.78 (0.71-0.85)	**<.001**
Asthma	8624	0.93 (0.88-0.97)	**.003**	8121	0.96 (0.91-1.01)	.109
Both	1407	0.80 (0.71-0.9)	**<.001**	1357	0.81 (0.72-0.92)	**.001**
COVID-19 hospitalization						
Controls	13,066	Reference	–	12,424	Reference	–
AR	545	0.77 (0.64-0.92)	**.004**	534	0.95 (0.79-1.13)	.548
Asthma	1823	1.42 (1.32-1.54)	**<.001**	1701	1.1 (1.01-1.19)	**.032**
Both	256	1.03 (0.82-1.28)	.82	246	1.06 (0.84-1.33)	.636
COVID-19 mortality						
Controls	13,066	Reference	–	12,424	Reference	–
AR	545	0.66 (0.39-1.12)	.12	534	1.17 (0.67-2.04)	.58
Asthma	1823	1.45 (1.17-1.79)	**.001**	1701	0.9 (0.72-1.14)	.401
Both	256	0.90 (0.47-1.74)	.76	246	1.23 (0.61-2.48)	.567

AR, Allergic rhinitis; *BMI*, body mass index; *CI*, confidence interval; *COVID-19*, corona virus disease 2019; *RR*, relative risk.
P values refer to comparison between each category and the reference category.
Bold indicates statistical significance, $P < .05$.
Adjusted for age, gender, Townsend deprivation index, education, BMI, ethnic background, smoking status (smoking experience and pack-year) and drinking status, and pre-existing comorbidities (eg, diabetes, circulatory diseases, fracture, lower respiratory disease, upper gastrointestinal diseases, renal diseases, dementia, arthritis, and certain immune disorders).

patients who had liver diseases (n = 609, less than 1%), we excluded liver disease when doing the adjustment.

Outcomes

The definition of COVID-19 infection referred to at least 1 positive testing result of SARS-CoV-2. When exploring the severity and mortality of COVID-19, we focused on the participants who had confirmed COVID-19. SARS-CoV-2-positive patients who progressed to hospitalization were considered as "severe COVID-19."[10] To identify patients died of COVID-19, we used mortality data provided by UKB using the ICD10 identifier of U07.1 (underlying COVID-19 cause of death).

Statistics analyses

Continuous variables were presented as mean and standard deviation, and categorical variables were presented as frequencies and percentages. Student's *t*-test was used for continuous variable comparisons, and the χ^2 test for categorical variable comparisons in order to assess the differences among groups. Generalized linear models (robust Poisson model) were generated to evaluate the correlation of AR and/or asthma with COVID-19 outcomes (including prevalence, hospitalization rate, and mortality), shown as relative risks (RRs) and 95% confidence intervals (CIs). Smoking status consisted of 2 variables: smoking experience, categorized as current, former, and never smoker; and pack-year, defined as the product of the average number of cigarette packs (regular size, 20 cigarettes) smoked per day and the total number of years smoked. According to the variable distribution, observation value, and association of smoking participants,[18] multiple imputation using chained equations that provided multiple predictions for each missing value had been conducted to impute the missing data of smoking pack-year (n = 11,391).

Four models were constructed according to the adjustments of factors: (1) Model* was a univariate model without adjustment; (2) Model** adjusted gender and age additionally; (3) Model*** was further adjusted for potential confounders, including Townsend deprivation index, education, current employment status, BMI, ethnic background, smoking, and drinking status; and (4) Model**** added pre-existing comorbidities mentioned above as adjustments based on Model***. These 4 models were analyzed simultaneously for the AR group, asthma group, and AR and asthma group, respectively, and the reference was the healthy control group for all relevant analyses.

Medication analyses were conducted for participants who had either AR or asthma, and participants who had AR or asthma but never used those medicines served as the controls in corresponding analysis.

For subgroup analyses, Model**** was constructed for participants stratified by gender (female or male), age (<65 or ≥65 years old), BMI (≤30 or >30), ethnic background (White or non-White), and smoking (never, previous, or current). Pre-existing dementia was reported to be associated with dramatically increasing risk of COVID-19 hospitalization and death (OR = 7.30)[1] due to the APOE e4 genotype;[19] hence, sensitivity analysis was conducted for participants without dementia to assess the robustness of our results.

In order to conduct a more in-depth analysis for asthma, participants with asthma were further divided into allergic asthma and nonallergic asthma groups, and Model**** was applied for the subanalysis. Allergic asthma was defined as asthma with any allergic disease (hay fever, allergy rhinitis, or eczema, defined as ICD-10 codes: L20 and J30.1-J30.4 or self-report in questionnaires),[10] and nonallergic asthma referred to asthma without any allergic disease. The reference was the healthy control group without asthma or allergic diseases. In another subanalysis, we explored the differences in the outcomes of COVID-19 between asthma patients with/without COPD (COPD was defined as the following ICD-10 codes: J43, J44 or self-report in questionnaires) and participants without asthma or COPD (reference group).

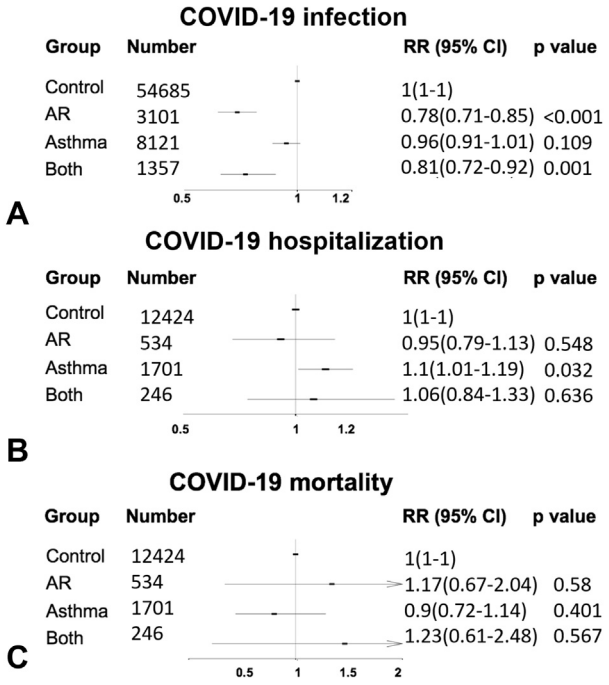

FIGURE 1. Association between the infection rate, hospitalized rate, and mortality of COVID-19 and allergic rhinitis/asthma. (**A**) COVID-19 infection, (**B**) COVID-19 hospitalization, and (**C**) COVID-19 mortality. Adjusted for sex, age, Townsend deprivation index, education, current employment status, body mass index, ethnic background, smoking status (pack-year) and drinking status, and pre-existing comorbidities (eg, diabetes, circulatory diseases, fracture, lower respiratory disease, upper gastrointestinal diseases, renal diseases, dementia, arthritis, and certain immune disorders). The *x*-axis indicates a log-scale. *AR*, Allergic rhinitis; *CI*, confidence interval; *COVID-19*, corona virus disease 2019; *RR*, relative risk.

All analyses were performed by R 3.6.3 (R Development Core Team, Vienna, Austria), and $P < .05$ was considered for statistical significance.

RESULTS

Patient characteristics

As shown in Table I and Table E2 (available in this article's Online Repository at www.jaci-inpractice.org), there were 70,557 participants tested SARS-CoV-2, and 15,690 of them had at least 1 SARS-CoV-2 positive test. Among them, 4915 patients were hospitalized due to COVID-19 and 636 patients died of COVID-19. For analysis, we classified all participants into 4 groups of AR only (n = 3201), asthma only (n = 8624), AR and asthma (n = 1407), and control (neither AR nor asthma, n = 57,325). The mean age of patients with COVID-19 was 64.4 years, versus 68.7 years for those with non-COVID-19. Similarly, hospitalized patients with COVID-19 (mean age: 68 years vs 62.8 years of nonhospitalized patients) were more likely to occur in the older participants than the younger. The same trend was also observed in COVID-19-related death (mean age: 74 years vs 64 years of non-death patients).

The effect of AR and asthma on the infection of COVID-19

As shown in Table II and Figure 1, AR represented a protective effect against COVID-19 infection (RR: 0.75, 95% CI: 0.69-0.81, $P < .001$), and this benefit was consistently observed (RR: 0.78, 95% CI: 0.71-0.85, $P < .001$) after adjustment for gender, age, Townsend deprivation index, education, current employment status, BMI, ethnic background, smoking status and alcohol drinking status, and pre-existing comorbidities by Model****. The protective effect of AR on COVID-19 infection was similar if patients had comorbid asthma (RR: 0.81, 95% CI: 0.73-0.92, $P = .001$). However, the protective effect of asthma alone against the COVID-19 infection was not significant after adjustment (RR: 0.96, 95% CI: 0.91-1.01, $P = .109$). Table E3 (available in this article's Online Repository at www.jaci-inpractice.org) reports the association of AR and/or asthma with COVID-19 infection, hospitalization, and mortality, after adjustment for different covariates.

The effect of AR and asthma on the severity and mortality of COVID-19

As shown in Table II, among those participants with positive SARS-CoV-2 test, AR did not significantly affect the hospitalization rate of COVID-19 after covariate adjustments (RR: 0.95, 95% CI: 0.79-1.13, $P = .548$). On the contrary, asthma was a risk factor for the COVID-19 hospitalization (RR: 1.1, 95% CI: 1.01-1.19, $P = .032$). Neither AR nor asthma had a significant effect on COVID-19 mortality after covariate adjustments for Townsend deprivation index, education, employment, BMI, ethnic background, smoking status, drinking status, and pre-existing comorbidities.

The effects of long-term medications for AR and/or asthma on infection, hospitalization, and mortality of COVID-19

We summarized 4 main long-term medication types that patients commonly used for control symptoms of AR or asthma, including β2 adrenoceptor agonists, antihistamine, systemic glucocorticoids, and corticosteroid nasal sprays (CNS). As shown in Table III and Figure 2, because of the limited sample size (Table E4, available in this article's Online Repository at www.jaci-inpractice.org), none of these medications showed a significant impact on infection, severity, and mortality of COVID-19 among patients with AR and/or asthma.

We further conducted subgroup analyses for the most commonly used types of CNS (beclomethasone and fluticasone propionate), short-acting β2 adrenoceptor agonists and long-acting β2 adrenoceptor agonists, shown in Table E5 (available in this article's Online Repository at www.jaci-inpractice.org). However, because of the limited number of patients with COVID-19 taking certain medicines chronically, none of these were associated with the infection, hospitalization, or mortality of COVID-19 after adjustments for other covariates ($P > .05$).

Subgroup analyses for different clinical factors potentially affecting the infection and severity of COVID-19

As shown in Table E6 (available in this article's Online Repository at www.jaci-inpractice.org), we evaluated the effects of different covariates on the infection, severity, and mortality of COVID-19. Our results revealed that pre-existing comorbidities

TABLE III. The infection rate, hospitalization rate, and mortality of COVID-19 among participants who used long-term medications (antihistamine, glucocorticoids, corticosteroid nasal sprays, β2 adrenoceptor agonists) to control allergic rhinitis (AR) or asthma

		COVID-19 infection (n = 2540/13,232)			COVID-19 hospitalization (n = 945/2624)			COVID-19 mortality (n = 122/2624)		
Medication	Variable	Number	RR (95% CI)	*P* value	Number	RR (95% CI)	*P* value	Number	RR (95% CI)	*P* value
Antihistamine	No	11,732	Reference	.656	2309	Reference	.302	2309	Reference	.891
	Yes	847	1.04 (0.89-1.21)		172	1.14(0.89-1.45)		172	0.95 (0.44-2.05)	
Systemic glucocorticoids	No	10,904	Reference	.922	2180	Reference	.685	2180	Reference	.726
	Yes	1675	0.99 (0.88-1.12)		301	0.96 (0.79-1.16)		301	0.91 (0.55-1.52)	
Corticosteroid nasal sprays	No	11,823	Reference	.649	2348	Reference	.328	2348	Reference	.23
	Yes	756	0.96 (0.81-1.14)		133	0.85 (0.62-1.18)		133	0.42 (0.1-1.72)	
β2 adrenoceptor agonists	No	11,689	Reference	.104	2294	Reference	.736	2294	Reference	.321
	Yes	890	1.13 (0.97-1.32)		187	0.96 (0.77-1.21)		187	1.31 (0.77-2.23)	

BMI, Body mass index; *CI*, Confidence interval; *COVID-19*, corona virus disease 2019; *RR*, relative risk.
Adjusted for sex, age, Townsend deprivation index, education, BMI, ethnic background, smoking status (smoking experience and pack-year), drinking status, and pre-existing comorbidities (eg, diabetes, circulatory diseases, fracture, lower respiratory disease, upper gastrointestinal diseases, renal diseases, dementia, arthritis, and certain immune disorders). Note that β2 adrenoceptor agonists were only prescribed for asthma, not AR.

(such as dementia and circulatory diseases) were important variables that affect the infection and severity of COVID-19 (Model****).

We further carried out multivariable subgroup analyses for the factors of gender, age, BMI, ethnics, and smoking status to explore their individual effects on the infection and severity of COVID-19 (Table E7, available in this article's Online Repository at www.jaci-inpractice.org). With respect to COVID-19 infection and hospitalization, it was worth noting that when stratified participants by ages, asthma demonstrated a potential protective effect against COVID-19 infection in younger participants (aged <65 years, RR: 0.93, 95% CI: 0.86-1, $P = .044$), but this effect on the elderly participants was not significant (aged ≥65 years, RR: 1.02, 95% CI: 0.95-1.1, $P = .59$). Compared with those who never smoked or previous smokers, current smokers with AR and asthma had a higher risk of COVID-19-related hospitalization (RR: 1.98, 95% CI: 1-3.9, $P = .049$).

Subanalyses for patients with asthma

We further compared the differences in COVID-19 infection/outcomes between patients with allergic and nonallergic asthma (Table E8, available in this article's Online Repository at www.jaci-inpractice.org) and between asthma patients with and without COPD (Table E9, available in this article's Online Repository at www.jaci-inpractice.org), respectively. No significant difference between allergic and nonallergic asthma was observed in our results. In line with the above results, both of them reduced the infection risk of COVID-19, whereas neither of them presented a significant association with the COVID-19 hospitalization and mortality. Asthma patients without COPD had a slightly protective effect against COVID-19 infection, but such patients had an increased hospitalization risk of COVID-19.

Sensitivity analysis

Some studies have shown that dementia had a striking association with COVID-19-related hospitalizations and deaths.[1] We therefore performed sensitivity analyses by excluding participants with pre-existing dementia (n = 1876) to evaluate the robustness of our results (Table E10, available in this article's Online Repository at www.jaci-inpractice.org). We observed consistent results that participants with AR (with/without asthma) had lower risk of COVID-19 infection; however, asthma patients with positive SARS-CoV-2 had higher risk of progression to hospitalized COVID-19.

DISCUSSION

After evaluating 70,557 participants in UKB, our results showed that AR was a major protective factor from infecting COVID-19 after covariate adjustments. Asthma also showed a weak association with lower COVID-19 infection risk although it did not reach a statistical significance. It is noteworthy that this trend of asthma on COVID-19 infection was driven primarily in younger participants (aged <65 years), but not in the elderly participants (aged ≥65 years). Nonetheless, having a diagnosis of asthma was associated with a greater chance of COVID-19 hospitalization across all ages, even after covariate adjustments, whereas AR had no impact on COVID-19 hospitalizations. Although it is hard to make firm conclusions due to the limited number of deaths related to COVID-19, neither AR nor asthma was associated with COVID-19 mortality. None of the long-term medications for AR and/or asthma had some effects on the infection, hospitalization, and mortality of COVID-19 after covariate adjustments.

We consider the reason why patients with AR (of all ages) or asthma (among younger participants) were associated with a lower positive rate of SARS-CoV-2 test results. Angiotensin-converting enzyme 2 (ACE2) is the receptor for the attachment and entry of SARS-CoV-2 into the host cells.[20] It has been reported that allergen provocation of respiratory tract would induce allergic airway inflammation, which resulted in a decrease of ACE2 expression, indicating that allergic inflammation may be of great relevance to reduce the risk of COVID-19 infection.[11,21,22] In addition, allergen-specific T cells may recruit a

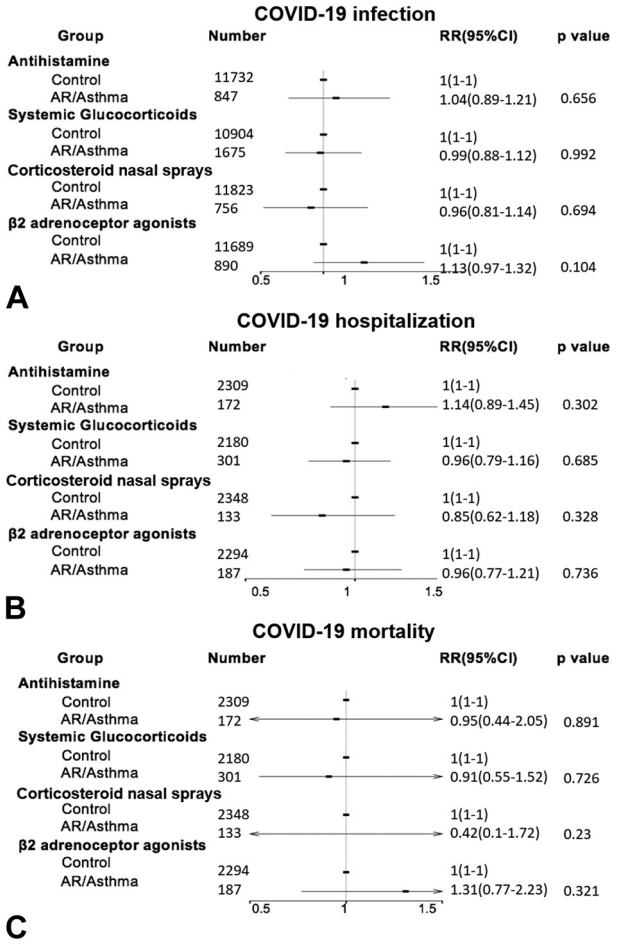

FIGURE 2. Association between long-term control of AR/asthma medications (antihistamine, systemic glucocorticoids, corticosteroid nasal sprays, and β2 adrenoceptor agonists) and the clinical outcomes of COVID-19 in patients with AR/asthma. (**A**) COVID-19 infection, (**B**) COVID-19 hospitalization, and (**C**) COVID-19 mortality. Adjusted for sex, age, Townsend deprivation index, education, body mass index, ethnic background, current employment status, smoking status (pack-year), drinking status, and pre-existing comorbidities (eg, diabetes, circulatory diseases, fracture, lower respiratory disease, upper gastrointestinal diseases, renal diseases, dementia, arthritis, and certain immune disorders). The *x*-axis indicates a log-scale. *AR*, Allergic rhinitis; *AR/Asthma*, either asthma or AR group; *CI*, confidence interval; *COVID-19*, corona virus disease 2019; *RR*, relative risk.

faster and more efficient memory-type response to deal with heterologous SARS-CoV-2 epitopes, which may provide significant advantages for patients with allergic diseases.[23,24] However, this protective effect of asthma on COVID-19 infection was mainly observed in patients who were younger than 65 years in our study. The exact reason is unclear, but we speculated that it might attribute to the decline in lung function and immunity with age,[25] which could lead to poorer prognoses.[26,27]

It is interesting that AR and asthma exhibited distinct effects on COVID-19 hospitalization in our study, of which asthma was a risk factor, whereas the influence of AR was not statistically notable. One potential reason is that SARS-CoV-2 impacts the lung parenchyma, so the additional impact of lower airway disease with asthma (and not with AR) could lead to a synergistically worsened clinical condition (ie, rapid deterioration);[28] further, patients with asthma may have more pulmonary comorbidities that affect the disease outcomes. By contrast, AR (upper airways) is a disease more confined to the nose. Consistent with the findings here, some studies have also proposed that if SARS-CoV-2 succeeded to establish clinical manifestations in patients with asthma, the risk of disease progression is higher.[23] The possible reasons given in these studies are as follows: (1) respiratory viruses provoke the local inflammatory cascades processed by T-lymphocyte trafficking and induce the disruption of the bronchial defense system activated by resident monocytes;[29] (2) respiratory viruses can change the composition of the airway microbiota and promote the growth of pathogens that may contribute to asthma exacerbations;[30] and (3) decreased antiviral function of eosinophils during respiratory viral infections in asthmatic patients may have a potential impact on virus-induced asthma exacerbations.[31]

Bloom et al[32] analyzed the data from the Clinical Characterisation Protocol UK study and revealed that compared with patients without asthma, asthma patients with COVID-19 were more likely to receive critical care during hospitalization. Several independent studies have observed a potential association between asthma phenotypes and COVID-19-related outcomes. According to the results of Zhu et al,[10] nonallergic asthma was significantly associated with severe COVID-19, whereas allergic asthma had no statistically significant association with severe COVID-19. They also reported that this significant association persisted regardless of whether patients with asthma had COPD or not.[10] However, we did not observe such differences between AR and non-AR. Although our research data came from the same UKB database, the confounders we adjusted for and the populations we included were different. In our current study, we excluded participants who did not have SARS-CoV-2 testing results, whereas these participants were considered as SARS-CoV-2 negative in their study.

Another English cohort study (QResearch database) reported that COVID-19 patients with COPD or asthma had an increased risk of hospitalization and death.[33] However, our results did not observe such trends, mainly due to the different population cohort we studied. Another Chinese study indicated that COPD and asthma were both important risk factors for poor clinical outcomes (such as needing invasive ventilation, admission to the intensive care unit, or death within 30 days after hospitalization) in patients with COVID-19.[34] In contrast, our results showed statistically significant relationships only between the hospitalization rate of COVID-19 and asthma comorbidity.

The effect of glucocorticoid on the risk of susceptibility, severity, and mortality of COVID-19 was controversial. Recent studies reported that glucocorticoid such as ciclesonide might decrease the risk of susceptibility of COVID-19.[35-37] However, our results did not observe that long-term use of antihistamine, systemic glucocorticoids, or glucocorticoid nasal sprays was beneficial to the COVID-19 infection or prognosis. Similarly, Aveyard et al[33] reported that the use of glucocorticoids was not associated with the severity of COVID-19. Schultze et al[38] also reported that long-term use of glucocorticoids would not reduce COVID-19-related mortality in patients with asthma or COPD.

Although the advent of our study provided new insights into the association between allergic diseases and the prevalence and outcomes of COVID-19, a few limitations still existed. First, the UKB may have a healthy volunteer selection bias in participant subgroups who were older, female, or lived in less socioeconomically deprived areas.[39] Second, the sample size for assessing COVID-19-related mortality in patients with AR and/or asthma who had taken long-term medications was very small (126 of 2624), limiting our study power to detect differences related to medication use. Third, comorbidity data of participants were obtained from the baseline interviews and hospitalization information, but the current status of diseases remained unknown; the impact on our association is unknown, as some patients could have already taken off medications once remission has been achieved, whereas others had flare ups of their disease during the pandemic period. Fourthly, we have to use an imperfect surrogate for severity of COVID-19, namely COVID-19 hospitalizations, knowing that some patients with severe diseases may have been assumed to have COVID-19 infection and not tested, whereas some hospitalizations may have been misclassified because of other major disorders rather than COVID-19. Finally, our analyses did not take into account changes in participant behavior. It is thus still possible that participants with AR or younger asthmatic patients were either more careful about their own COVID-19 exposures or more afraid to present with COVID-19-like symptoms and therefore were more likely to wear masks or adhere to social distancing.

In summary, AR (in all ages) is associated with lower rates of COVID-19 infection, but not with the severity and mortality of COVID-19. A similar protective effect in patients with asthma, whether allergic asthma or nonallergic asthma, is observed only in those aged less than 65 years, but not in the elderlies (aged $\geq$65 years). In asthmatic patients with confirmed COVID-19, there is a higher risk of hospitalization than healthy controls.

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