

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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active. receiving systemic corticosteroids in Table E4. Further subgroup analysis according to the use of inhaled corticosteroids similar to the ones in Figure 2 is warranted to clarify this issue, and additional evaluation about a dose-response relationship is needed.

Second, the severity of asthma is another confounding factor affecting the outcome of COVID-19. One study using Swedish National Airway Register showed that patients with uncontrolled asthma and high disease burden, including increased asthma medication intensity, would be associated with an increased risk of severe COVID-19.⁶ Similar findings were demonstrated in another national incident cohort study in Scotland.³

In conclusion, although Ren et al's study provided useful information, further analysis according to the use of corticosteroid and the severity of asthma is needed.

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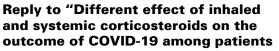
No funding was received for this work.

- Conflicts of interest: The authors declare that they have no relevant conflicts of interest. Received for publication June 11, 2022; Revised June 15, 2022; accepted for publication June 16, 2022.
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https://doi.org/10.1016/j.jaip.2022.06.051



To the Editor:

with asthma"

We sincerely appreciate the interest of Hsu and Lai¹ in our recent publication in *The Journal of Allergy and Clinical Immunology: In Practice* titled "Impact of allergic rhinitis and asthma

on COVID-19 infection, hospitalization, and mortality."² For the 2 main concerns raised in their correspondence, our clarifications are as follows.

In terms of the first concern regarding whether the effect of systemic and inhaled corticosteroids on COVID-19 could differ, in fact, we had initially analyzed the association between inhaled corticosteroids and the infection, severity, and mortality of COVID-19 among patients with allergic rhinitis and/or asthma, and the results were not significant (Table I and Figures 1-3). Because inhaled corticosteroids actually included oral inhaled corticosteroids and intranasal corticosteroids, we separated them in the subgroup analysis. Because the number of oral inhaled corticosteroid patients (n = 251) was significantly smaller than that in the nasal spray group (n = 12,579), we ultimately presented the results of corticosteroid nasal sprays instead of the inhaled corticosteroids. In addition, regarding the doseresponse relationship, no detailed data on dose or duration information were collected in the UK Biobank, so no further analysis of these medications could be performed.

Second, Hsu and Lai also highlighted the potential role of asthma severity in confounding or modifying the association between asthma and the outcome of COVID-19, as other studies^{3,4} have shown that patients with uncontrolled asthma had an increased risk of severe COVID-19 compared with those without asthma or with well-controlled asthma. We also agree that the confounding effects of asthma severity cannot be ignored, but, unfortunately, there are no relevant data on asthma severity in the UK Biobank, thus limiting the analysis of the impact of asthma severity on COVID-19 infection, hospitalization, and mortality in this study.

In conclusion, we concur that further research with more comprehensive data on medications and the severity of asthma is needed to reduce the confounding effects and better elucidate the relationship between asthma and COVID-19.

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- This work was supported by West China Hospital, Sichuan University (grant numbers 2019HXFH003, ZYJC21027, and 2019HXBH079); Sichuan University (grant numbers GSALK2020021 and 2020SCU12049); the Science and Technology Department of Sichuan Province (grant number 2022YFS0066); the Health Department of Sichuan Province (grant number 20PJ030); China Postdoctoral Science Foundation (grant number 2020M673250); and National Natural Youth Science Foundation of China (grant number 82002868).

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

UK Biobank ethical approval was from the North West Multi-centre Research Ethics Committee. The current analysis was approved under the UKB application (Applicant Number: 69718).

Received for publication June 30, 2022; accepted for publication July 7, 2022.

Corresponding author: Yu Zhao, MD, PhD, Department of Oto-Rhino-Laryngology, West China Hospital, Sichuan University, No. 37 Guoxue Lane, Wuhou District, Chengdu City, Sichuan Province 610041, China. E-mail: yutzhao@VIP.163.com. **TABLE I.** The infection rate, hospitalization rate, and mortality of COVID-19 among participants who used long-term medications (antihistamine, glucocorticoids, inhaled corticosteroids, and β_2 -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)	
Inhaled corticosteroids	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)	
β ₂ -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)	

Adjusted for sex, age, Townsend deprivation index, education, body mass index, ethnic background, smoking status (smoking experience and pack-year), drinking status, and preexisting comorbidities (eg, diabetes, circulatory diseases, fracture, lower respiratory disease, upper gastrointestinal diseases, renal diseases, and dementia). Note that β_{2} adrenoceptor agonists were only prescribed for asthma, not AR.

CI, Confidence interval; RR, relative risk.

	Risk Ratio		
Antihistamine			
Asthma		1.02(0.85-1.21)	0.867
Allergic Rhinitis		1.04(0.81-1.32)	0.766
AR and Asthma		0.96(0.65-1.42)	0.846
AR or Asthma		1.02(0.87-1.19)	0.822
Glucocorticoids			
Asthma		0.95(0.83-1.08)	0.408
Allergic Rhinitis		1.03(0.82-1.3)	0.787
AR and Asthma		0.92(0.65-1.28)	0.613
AR or Asthma		0.99(0.88-1.12)	0.888
Inhaled corticosteroids			
Asthma		0.9(0.75-1.07)	0.231
Allergic Rhinitis		1.01(0.77-1.32)	0.951
AR and Asthma		0.79(0.52-1.21)	0.280
AR or Asthma		0.96(0.82-1.13)	0.624
β2 adrenoceptor agonists			
Asthma		1.07(0.95-1.21)	0.249
Allergic Rhinitis		1.23(0.89-1.71)	0.212
AR and Asthma		1.14(0.8-1.63)	0.465
AR or Asthma		1.13(1-1.27)	0.044
	0.5 1 1.5 2		

FIGURE 1. Association between long-term control of allergic rhinitis (AR)/asthma medications (antihistamine, systemic glucocorticoids, inhaled corticosteroids, and β_2 -adrenoceptor agonists) and the infection of COVID-19 in patients with AR/asthma. 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. **Risk Ratio**

Antihistamine			
Asthma		1.18 (0.9-1.53)	0.225
Allergic Rhinitis	· · ·	1.18 (0.75-1.85)	0.469
AR and Asthma		1.22 (0.6-2.49)	0.581
AR or Asthma	_ _	1.16 (0.91-1.47)	0.225
Glucocorticoids			
Asthma	_ _	1.01 (0.83-1.22)	0.947
Allergic Rhinitis		0.91 (0.58-1.43)	0.685
AR and Asthma		1.11 (0.58-2.09)	0.759
AR or Asthma	_ _	0.99 (0.82-1.19)	0.882
Inhaled corticosteroids			
Asthma		0.91 (0.68-1.22)	0.535
Allergic Rhinitis		1.08 (0.64-1.82)	0.764
AR and Asthma	· · · · · · · · · · · · · · · · · · ·	1.52 (0.75-3.08)	0.250
AR or Asthma		0.9 (0.68-1.18)	0.443
β2 adrenoceptor agonists			
Asthma	_ - _	1.02 (0.86-1.22)	0.791
Allergic Rhinitis		0.93 (0.52-1.67)	0.812
AR and Asthma		1.08 (0.57-2.04)	0.825
AR or Asthma		1.04 (0.87-1.24)	0.661
	0.5 1 1.5 2		

FIGURE 2. Association between long-term control of allergic rhinitis (AR)/asthma medications (antihistamine, systemic glucocorticoids, inhaled corticosteroids, and β_2 -adrenoceptor agonists) and the hospitalization of COVID-19 in patients with AR/asthma. 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.

Risk Ratio

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AR and Asthma $1(1-1)$ 0.997 AR or Asthma $0.9(0.42-1.94)$ 0.792 Glucocorticoids $1(0.6-1.66)$ 0.987 Allergic Rhinitis $0.56(0.11-2.96)$ 0.493 AR and Asthma $0.11(0.01-1.96)$ 0.133 AR or Asthma $0.96(0.59-1.58)$ 0.879 Inhaled corticosteroids $0.86(0.37-1.98)$ 0.726 Allergic Rhinitis $1(1-1)$ 0.992 AR and Asthma $1(1-1)$ 0.992 AR and Asthma $1(1-1)$ 0.992 AR and Asthma $0.76(0.33-1.74)$ 0.514 $\beta 2$ adrenoceptor agonists $1.43(1.06-1.93)$ 0.021 Allergic Rhinitis $1.43(1.06-1.93)$ 0.021 Allergic Rhinitis $1.26(0.44-3.57)$ 0.666 AR and Asthma $1.11(0.34-3.66)$ 0.867 AR or Asthma $1.37(1.02-1.84)$ 0.037	Asthma	←■	0.58(0.21-1.57)	0.282
AR or Asthma $0.9(0.42-1.94)$ 0.792 Glucocorticoids $1(0.6-1.66)$ 0.987 Allergic Rhinitis $0.56(0.11-2.96)$ 0.493 AR and Asthma $0.56(0.11-2.96)$ 0.493 AR and Asthma $0.96(0.59-1.58)$ 0.879 Inhaled corticosteroids $0.986(0.37-1.98)$ 0.726 Allergic Rhinitis $1(1-1)$ 0.992 AR and Asthma $0.86(0.37-1.98)$ 0.726 Allergic Rhinitis $1(1-1)$ 0.992 AR and Asthma $0.76(0.33-1.74)$ 0.514 $\beta 2$ adrenoceptor agonists $1.43(1.06-1.93)$ 0.021 Allergic Rhinitis $1.26(0.44-3.57)$ 0.666 AR and Asthma $1.11(0.34-3.66)$ 0.867 AR or Asthma $1.37(1.02-1.84)$ 0.037	Allergic Rhinitis	← ■ →	1.45(0.34-6.1)	0.614
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Asthma 1(0.6-1.66) 0.987 Allergic Rhinitis 0.56(0.11-2.96) 0.493 AR and Asthma 0.11(0.01-1.96) 0.133 AR or Asthma 0.96(0.59-1.58) 0.879 Inhaled corticosteroids 1(1-1) 0.992 Asthma 1(1-1) 0.992 AR and Asthma 1(1-1) 0.992 AR and Asthma 0.76(0.33-1.74) 0.514 β2 adrenoceptor agonists 1.43(1.06-1.93) 0.021 Allergic Rhinitis 1.26(0.44-3.57) 0.666 AR and Asthma 1.11(0.34-3.66) 0.867 AR or Asthma 1.37(1.02-1.84) 0.037	AR or Asthma	← ■	0.9(0.42-1.94)	0.792
Allergic Rhinitis • • • • • • • • • • • • • • • • • • •	Glucocorticoids			
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AR or Asthma 0.96(0.59-1.58) 0.879 Inhaled corticosteroids 0.86(0.37-1.98) 0.726 Allergic Rhinitis 1(1-1) 0.992 AR and Asthma 1(1-1) 0.998 AR or Asthma 0.76(0.33-1.74) 0.514 β2 adrenoceptor agonists 1.43(1.06-1.93) 0.021 Allergic Rhinitis 1.26(0.44-3.57) 0.666 AR and Asthma 1.11(0.34-3.66) 0.867 AR or Asthma 1.37(1.02-1.84) 0.037	Allergic Rhinitis	<∎>	0.56(0.11-2.96)	0.493
Inhaled corticosteroids 0.86(0.37-1.98) 0.726 Allergic Rhinitis 1(1-1) 0.992 AR and Asthma 1(1-1) 0.998 AR or Asthma 0.76(0.33-1.74) 0.514 β2 adrenoceptor agonists 1.43(1.06-1.93) 0.021 Allergic Rhinitis 1.26(0.44-3.57) 0.666 AR and Asthma 1.11(0.34-3.66) 0.867 AR or Asthma 1.37(1.02-1.84) 0.037	AR and Asthma	<	0.11(0.01-1.96)	0.133
Asthma 0.86(0.37-1.98) 0.726 Allergic Rhinitis 1(1-1) 0.992 AR and Asthma 1(1-1) 0.998 AR or Asthma 0.76(0.33-1.74) 0.514 β2 adrenoceptor agonists 1.43(1.06-1.93) 0.021 Allergic Rhinitis 1.26(0.44-3.57) 0.666 AR and Asthma 1.11(0.34-3.66) 0.867 AR or Asthma 1.37(1.02-1.84) 0.037	AR or Asthma		0.96(0.59-1.58)	0.879
Allergic Rhinitis 1(1-1) 0.992 AR and Asthma 1(1-1) 0.998 AR or Asthma 0.76(0.33-1.74) 0.514 β2 adrenoceptor agonists 1.43(1.06-1.93) 0.021 Allergic Rhinitis 1.26(0.44-3.57) 0.666 AR and Asthma 1.11(0.34-3.66) 0.867 AR or Asthma 1.37(1.02-1.84) 0.037	Inhaled corticosteroids			
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β2 adrenoceptor agonists 1.43(1.06-1.93) 0.021 Asthma 1.26(0.44-3.57) 0.666 AR and Asthma 1.11(0.34-3.66) 0.867 AR or Asthma 1.37(1.02-1.84) 0.037	AR and Asthma	-	1(1-1)	0.998
Asthma 1.43(1.06-1.93) 0.021 Allergic Rhinitis 1.26(0.44-3.57) 0.666 AR and Asthma 1.11(0.34-3.66) 0.867 AR or Asthma 1.37(1.02-1.84) 0.037	AR or Asthma	← ∎	0.76(0.33-1.74)	0.514
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AR and Asthma Image: 1.11(0.34-3.66) 0.867 AR or Asthma Image: 1.37(1.02-1.84) 0.037	Asthma		1.43(1.06-1.93)	0.021
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0.5 1 1.5 2	AR or Asthma		1.37(1.02-1.84)	0.037
		0.5 1 1.5 2		
death		death		

FIGURE 3. Association between long-term control of allergic rhinitis (AR)/asthma medications (antihistamine, systemic glucocorticoids, inhaled corticosteroids, and β_2 -adrenoceptor agonists) and the mortality of COVID-19 in patients with AR/asthma. 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.

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https://doi.org/10.1016/j.jaip.2022.07.024