DOI:
10.1111/cea.14445

Document Version
Publisher's PDF, also known as Version of record

Received: 18 September 2023 | Revised: 15 December 2023 | Accepted: 19 December 2023

DOI: 10.1111/cea.14445

RESEARCH LETTER

WILEY

Protective effects of allergic diseases in COVID-19 outcomes: A retrospective cohort study in UK Biobank in the general population and in patients with cancer

To the Editor,

SARS-CoV-2 (COVID-19) infection can lead to acute respiratory distress syndrome (ARDS) in severe cases. Preliminary evidence during the COVID-19 pandemic suggested that respiratory diseases could be associated with poorer outcomes.[1,2] Th2 conditions, namely lower Th1/Th2 ratios and eosinophilia in allergic diseases, including allergic asthma, could mount an impaired immune response in COVID-19. Asthma was initially considered a predisposing factor to infection and disease severity due to impaired immune responses in patients;[3] UK and American cohorts highlighted asthma as a risk factor of contracting COVID-19.[4] However, later data suggested lower prevalence of asthma in COVID-19 populations.[5] A subsequent international meta-analysis reported no definitive link between COVID-19 risk and asthma.[1] Regarding COVID-19 severity, a UK study presented asthma as a risk factor for increased COVID-19-associated morbidity,[6] while others reported no, or negative associations, between asthma and COVID-19-related morbidity and mortality.[7] These disparities may have arisen through poor distinction between non-type 2 (non-allergic) versus type 2 (allergic) asthmatics. Moreover, immunocompromised groups, including oncological patients, could present higher prevalence of COVID-19 morbidity and mortality than the general population;[8] allergy on the other hand may dysregulate immunity. Therefore, it is relevant to understand the role of allergic disease in COVID-19, particularly in cancer patients.

Here, we explored associations between allergy and asthma (categorized as 'clinically diagnosed' or 'not clinically diagnosed' based on an algorithm developed to capture the information available in UK BIOBANK (https://osf.io/dfskp/files/osfstorage/657c3ec5513a74079faed217)) and COVID-19 infection (positive first PCR COVID-19 test result) and COVID-19 hospitalization (positive PCR COVID-19 result obtained in hospital following a positive PCR test prior to presenting at hospital), in the general and cancer patient populations. We conducted multivariate logistic regression analyses adjusted for age, gender, smoking status, socio-economical parameters and non-allergic disease, guided by a directed acyclic graph, using data from the UK Biobank cohort and from England, Scotland and Wales provided by Public Health England (PHE), Public Health Scotland (PHS) and Secured Anonymised Information Linkage (SAIL) (July 2020–July 2022). The general population comprised 104,550 individuals; of whom 17,339 tested positive for COVID-19, with 2409 individuals of this group having a following positive COVID-19 result in hospital. The cancer cohort comprised 14,791 patients, of whom 2023 had a COVID-19 infection and 340 of these had a subsequent COVID-19-positive test in hospital. Study population characteristics were in line with those previously reported for COVID-19 infection in relation to several parameters including age, gender, ethnic background and socio-economic status.

In the general population, allergy diagnosis conferred an 8.3% reduced risk of COVID-19 infection (OR allergy (95%CI): 0.917 (0.884–0.951)). Associations exploring asthma and COVID-19 infection were inconsistent. Allergy and asthma demonstrated strong protective associations from COVID-19 hospitalization (OR allergy (95%CI): 0.845 (0.769–0.928) (OR asthma (95%CI): 0.873 (0.766–0.995)). In the cancer population, a non-significant protective association was observed for allergy in COVID-19 infection (OR (95%CI): 0.968 (0.871–1.076)) and hospitalization (OR (95%CI): 0.803 (0.619–1.041)) (Table 1).

Different mechanisms may contribute to the negative association between allergic status and COVID-19 infection and outcomes. ACE2 (angiotensin-converting enzyme-2) is implicated in COVID-19 infection pathology. Lower ACE2 levels in allergy, potentially offer reduced viral entry in allergic states and in allergy treatment, may confer protection against COVID-19. The protective effects of allergic disease against COVID-19 may also relate to allergic immune states. IgE as key contributor to allergy, can activate airway smooth muscles to produce cytokines, chemokines, tumour necrosis factor (TNFα) and interleukins (IL-13, IL-4 and IL-5) and promote eosinophil infiltration. Multiple studies report links between low blood eosinophil counts and percentages with COVID-19 morbidity. Allergy may drive eosinophil accretion in the blood and airways through degranulation and release of toxic molecules. Additionally, COVID-19 triggers biological and inflammatory consequences that bear some similarities to type I hypersensitivity. Therefore, patients with allergic diseases may already be receiving treatments addressing the same mechanism considered important in SARS-CoV-2 pathological

		CI (95%)			CI (95%)	
	Univariate OR	Low	High	Multivariate OR	Low	High
COVID-19 infection						
Total population						
Allergy	0.968	0.934	1.004	0.917	0.884	0.951
Asthma	1.025	0.974	1.077	0.999	0.949	1.052
Cancer population						
Allergy	1.034	0.932	1.147	0.968	0.871	1.076
Asthma	1.041	0.899	1.205	1.005	0.866	1.167
Haematological cancers						
Allergy	1.075	0.934	1.236	1.084	0.996	1.322
Asthma	1.075	0.934	1.236	0.999	0.949	1.051
Solid cancers						
Allergy	0.895	0.483	1.657	0.968	0.535	1.798
Asthma	0.896	0.484	1.659	0.968	0.521	1.799
COVID-19 hospitalization						
Total population						
Allergy	0.870	0.793	0.954	0.845	0.769	0.928
Asthma	0.866	0.762	0.985	0.873	0.766	0.995
Cancer population						
Allergy	0.816	0.632	1.053	0.803	0.619	1.041
Asthma	1.033	0.745	1.433	1.055	0.757	1.471
Haematological cancers						
Allergy	1.031	0.432	2.213	1.071	0.472	2.433
Asthma	1.029	0.431	2.206	1.027	0.737	1.431
Solid cancers						
Allergy	0.978	0.638	1.667	0.958	0.590	1.554
Asthma	0.975	0.637	1.666	0.955	0.619	1.550

TABLE 1 Univariate and multivariate logistic regression (multivariate regression adjusted for sex, age, ethnic background, smoking status, blood eosinophil percentage and illness/disability outside of cancer, allergy and asthma) for allergy and asthma and COVID-19 infection and hospitalization for the total population and cancer patient population.

Note: The Forests plot presenting the results of the associations can be accessed via Open Science Framework online repository (https://osf.io/dfskp/files/osfstorage/657adc82ded50405f7d28ca9; https://osf.io/dfskp/files/osfstorage/657adc7dda3ee0053c94552e; https://osf.io/dfskp/files/osfstorage/657adc80da3ee00540945658; https://osf.io/dfskp/files/osfstorage/657adc7cda3ee00541945674).

pathways, and thus, may be partly protected from severe COVID-19-related immune reactions. These mechanisms are consistent with our findings of allergic status showing a protective association from COVID-19 infection and related hospitalization.

While we found no significant association between asthma and COVID-19 diagnosis, a protective effect from COVID-19 hospitalization was present. This may be a consequence of the smaller cohort size and the lack of differentiation between asthma endotypes in this group. Allergic asthma, being IgE-mediated and eosinophilic, and associated with lower ACE2 expression, may be a protective factor in the context of COVID-19. However, non-allergic asthma may be driven by different inflammatory and biological pathways and higher ACE2 levels. Higher ACE2 levels are reported in COPD, diabetes and smoking, known factors predisposing to more severe COVID-19 outcomes.[9]

A limitation of this study is the lack of specific allergy test and lung function information that will facilitate disentanglement of non-allergic asthma alone from the protective effects of allergy. A larger and stratified asthmatic cohort will be required to ascertain whether allergic, but not non-allergic, asthma may be protective against COVID-19 infection and severity.[9] The lack of statistical significance in the cancer patient subtype analysis, could be due to the smaller cohort size. Further subtypes of cancers should be explored with special attention to more immunogenic cancers, such as melanoma. A wider evaluation for particularly at-risk patient groups may be beneficial.

In summary, contrary to original assumptions that allergic diseases may constitute risk factors for COVID-19, we report significant protective effects of allergy from COVID-19 infection, and of both allergy and asthma from COVID-19-related hospitalization, in the general population. These findings may reflect altered immune mechanisms in allergic disease that might moderate COVID-19-associated hyperinflammatory effects and their negative clinical

outcomes. Furthermore, allergic or asthmatic status contributes no additional risk for either COVID-19 infection or hospitalization in cancer patients.

SUMMARY

Associations between allergies and asthma with COVID-19 risk in general and cancer populations are unclear.

Allergy conferred reduced risk of COVID-19 infection and hospitalization in general but not cancer populations.

AUTHOR CONTRIBUTIONS

A.SO. and S.N.K. designed the study and conducted all experiments. A.SO., H.J.B., J.C., D.H.J. and M.V.H. edited and commented on this article. This article was written by A.SO. and S.N.K.

ACKNOWLEDGEMENTS

The authors acknowledge support by Cancer Research UK (C30122/A11527; C30122/A15774); the Guy's and St Thomas' Foundation Trust Charity Melanoma Special Fund (SPF573); Cancer Research UK King's Health Partners Centre at King's College London (C604/A25135); and Breast Cancer Now (147; KCL-BCN-Q3). The research was supported by the National Institute for Health and Care Research Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and King's College London and the NIHR Clinical Research Facility (NIHR Biomedical Research Centre at Guy's and St Thomas' NHS Foundation Trust and King's College London, IS-BRC-1215-20006). The authors are solely responsible for the study design, data collection, analysis, decision to publish, and preparation of the article. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, or the Department of Health and Social Care. Moreover, we thank all the patients and families that have contributed to this study and to Raphaelle Boulas for the contribution to the data analysis. This research has been conducted using the UK Biobank Resource under Application Number 63317.

CONFLICT OF INTEREST STATEMENT

S.N.K. is founder of Epsilogen Ltd. H.J.B. is presently employed and J.C. formerly employed, through a fund from Epsilogen Ltd. S.N.K., D.H.J. and H.J.B. hold patents on antibody technologies. The remaining authors declare no competing interests.

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REFERENCES

1. Terry PD, Heidel RE, Dhand R. Asthma in adult patients with COVID-19. Prevalence and risk of severe disease. *Am J Respir Crit Care Med*. 2021;203(7):893-905.
2. Warner JO, Warner JA, Munblit D. Hypotheses to explain the associations between asthma and the consequences of COVID-19 infection. *Clin Exp Allergy*. 2022;52(1):7-9.
3. James KM, Peebles RS Jr, Hartert TV. Response to infections in patients with asthma and atopic disease: an epiphenomenon or reflection of host susceptibility? *J Allergy Clin Immunol*. 2012;130(2):343-351.
4. Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature*. 2020;584(7821):430-436.
5. Avdeev S, Moiseev S, Brovko M, et al. Low prevalence of bronchial asthma and chronic obstructive lung disease among intensive care unit patients with COVID-19. *Allergy*. 2020;75(10):2703-2704.
6. Zhu Z, Hasegawa K, Ma B, Fujiogi M, Camargo CA, Liang L. Association of asthma and its genetic predisposition with the risk of severe COVID-19. *J Allergy Clin Immunol*. 2020;146(2):327-329.
7. Docherty AB, Harrison EM, Green CA, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO clinical characterisation protocol: prospective observational cohort study. *BMJ*. 2020;369.
8. Di Felice G, Visci G, Teglia F, Angelini M, Boffetta P. Effect of cancer on outcome of COVID-19 patients: a systematic review and meta-analysis of studies of unvaccinated patients. *eLife*. 2022;11:e74634.
9. Branco AC, Sato MN, Alberca RW. The possible dual role of the ACE2 receptor in asthma and coronavirus (SARS-CoV2) infection. *Front Cell Infect Microbiol*. 2020;10:550571.