



Is asthma associated with COVID-19 infection? A UK Biobank analysis

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Reduced risk of positive #SARSCoV2 test was associated with early-onset asthma in males, nonsmokers, overweight/obese and non-black participants. Lack of phenotyping and unappreciated interactions may contribute to inconsistent findings for asthma and #COVID19. <https://bit.ly/3yn3Nvi>

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Abstract

Background The relationship between asthma and coronavirus disease 2019 (COVID-19) risk is not clear and may be influenced by level of airway obstruction, asthma medication and known COVID-19 risk factors. We aimed to investigate COVID-19 risk in people with asthma.

Methods We used UK Biobank data from all participants tested for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (n=107 412; 17 979 test positive). Questions at baseline defined ever asthma and asthma medications. Baseline forced expiratory volume in 1 s (FEV₁) was categorised into quartiles. Logistic regression modelled relationships between asthma, and asthma categories (age at onset, medications, FEV₁ quartiles), and risk of SARS-CoV-2 positive test. We investigated modification by sex, ethnic group, smoking and body mass index.

Results There was a reduced risk of a positive test associated with early-onset asthma (<13 years) (OR 0.91, 95% CI 0.84–0.99). This was found for participants with early-onset asthma who were male (OR 0.87, 95% CI 0.78–0.98), nonsmokers (OR 0.87, 95% CI 0.78–0.98), overweight/obese (OR 0.85, 95% CI 0.77–0.93) and non-Black (OR 0.90, 95% CI 0.82–0.98). There was increased risk amongst early-onset individuals with asthma in the highest compared to lowest quartile of lung function (1.44, 1.05–1.72).

Conclusion Amongst male, nonsmoking, overweight/obese and non-Black participants, having early-onset asthma was associated with lower risk of a SARS-CoV-2 positive test. We found no evidence of a protective effect from asthma medication. Individuals with early-onset asthma of normal weight and with better lung function may have lifestyle differences placing them at higher risk. Further research is needed to elucidate the contribution of asthma pathophysiology and different health-related behaviour, across population groups, to the observed risks.

Introduction

As of July 14, 2021, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has infected over 187 million people globally and is responsible for over 4 million deaths (John Hopkins Coronavirus Resource Centre). It is unclear if adults with asthma are particularly susceptible to SARS-CoV-2 infection and/or have a worse prognosis if infected than individuals without asthma. Given that asthma affects >339 million people worldwide [1], these are important questions for people with asthma, their families and healthcare providers.

Early studies in China reported an unexpectedly low prevalence of asthma in hospital admitted coronavirus disease 2019 (COVID-19) patients compared to the general population [2]. Yet, subsequent reports provided conflicting results with some studies finding a reduced asthma prevalence in patients with



COVID-19 [3], and others reporting similar [4, 5] or increased prevalence compared with the local general population [6]. Failure to account for other factors like age, sex, smoking, ethnic group and body mass index (BMI) may contribute to the inconsistent findings [7, 8].

There are several hypotheses to explain the potentially lower risk of COVID-19 in patients with asthma. People with asthma may be practising stricter preventive/protective measures to avoid exposure to SARS-CoV-2, especially those with severe asthma, which is correlated with forced expiratory volume in 1 s (FEV₁) [9]. Furthermore, individuals with severe asthma are more likely to be on asthma treatment, especially inhaled (ICS) or oral corticosteroids, which may be protective for SARS-CoV-2 infection [10–12]. Therefore, asthma medication and FEV₁ need to be considered in the analysis. Lastly, the TH₂ predominant immune response found in patients with asthma may be protective [13].

Addressing the above research gaps may potentially inform decisions around risk and preventive treatment during the pandemic. Therefore, in the UK Biobank cohort tested for SARS-CoV-2, we sought to investigate: 1) the association between asthma and a positive SARS-CoV-2 test; 2) the association between asthma, stratified across age-of-onset phenotypes, FEV₁ categories and asthma treatment categories, and a positive SARS-CoV-2 test; and 3) how the asthma–SARS-CoV-2 relationship may be modified by sex, BMI, ethnic group and smoking.

Methods

Study population: UK Biobank Cohort

Detailed information on the design and methodologies of the UK Biobank Cohort have been described previously (<https://www.ukbiobank.ac.uk/>). Briefly, it recruited 500 000 participants aged 40–69 years living close to one of 22 assessment centres across England, Scotland and Wales, between the years 2007 and 2010. The data on SARS-CoV-2 infection is derived from the entire cohort. At recruitment participants undertook a range of measurements, including questionnaires regarding basic demographic information, lifestyle and disease history, with linkages to electronic medical records and pre-bronchodilator spirometry. Ethnic group and smoking status were self-reported. Participant medical histories were based on self-reported doctor diagnosis, which was verified during the assessment interview.

Ethics approval

The current analysis was approved by the North West MultiCentre Research Biobank ethics committee (UKB application 28502) and by the Human Research Ethics Committee at the University of Melbourne (Approval ID 2057006.2).

Definitions and data collection

Exposures

We identified participants as having “ever asthma” [14] if they reported asthma in a verbal interview at the time of recruitment to UK Biobank or if they answered “asthma” to the touch-screen question “Has a doctor ever told you that you have had any of the following conditions?” at any of the follow-ups. Age of asthma onset was classified into temporal phenotypes of early onset (<13 years of age) or late onset (≥13 years of age).

A three-level, mutually exclusive variable was generated using asthma medication codes collected during the verbal interview at the UK Biobank Assessment Centre, to categorise medication use for asthma into three groups: 1) no medication, 2) medications other than steroids or 3) steroid medications (including inhaled corticosteroids and oral steroids ± other medications).

FEV₁ derived from spirometry was divided into quartiles of FEV₁ z-scores. Spirometry testers were healthcare technicians or nurses certified to conduct the assessments, and all spirometry measures were performed in accordance with American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines [15], using a Vitalograph Pneumotrac 6800 (Vitalograph, Lenexa, KS, USA). The Biobank spirometry protocol has been published elsewhere [16].

Outcome

Our outcome of interest was SARS-CoV-2 test positive compared to test negative. The test used for SARS-CoV-2 detection was a polymerase chain reaction (PCR) test considered the current gold standard worldwide. UK Biobank data was linked to national SARS-CoV-2 laboratory test data through Public Health England (PHE). Data provided included SARS-CoV-2 test results, specimen origin at the time of testing (hospital inpatient *versus* other settings). Data used were for the period April 1, 2020 to June 23, 2021 (including specimen data until June 14, 2021).

TABLE 1 Demographic characteristics amongst all UK Biobank individuals who attended an assessment centre and amongst UK Biobank individuals with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) test data

	All UK Biobank	UK Biobank with SARS-CoV-2 test data		
	Whole sample	Whole sample [#]	Positive	Negative
Subjects n	502 505	107 412	17 979 (17%)	89 433 (83%)
Age at recruitment[¶] (mean±sd)	56.53±8.10	56.70±8.25	53.52±8.58	57.33±8.03
Age at SARS-CoV-2 test[¶] (mean±sd)		68.23±8.23	64.69±8.58	69.00±7.94
Sex[¶]				
Female	54.0	54.0	52.9	54.3
Male	45.6	45.9	47.1	45.7
Ethnicity[¶]				
White	94.1	93.6	89.5	94.5
Mixed	0.6	0.6	0.8	0.6
Asian	2.3	2.4	4.6	2.0
Black	1.6	1.8	2.9	1.5
Other ethnic background	1.3	1.3	1.9	1.2
Ever asthma				
Yes	12.6	13.9	14.1	13.9
No	87.0	85.6	85.4	85.7
Asthma age of onset (if asthma yes)[¶] (mean±sd)	31.16±18.69	31.67±18.81	30.02±17.71	32.02±19.02
Asthma onset (if asthma yes)				
Early-onset (<13 years)	36.9	36.5	34.9	36.8
Late onset (≥13 years)	63.1	63.5	65.1	63.2
COPD diagnosis				
Yes	0.3	0.4	0.3	0.5
No	23.8	23.1	18.3	24.0
COPD age of onset	59.52±9.28	58.82±10.18	58.39±9.64	58.89±10.26
Hay fever or eczema diagnosis (mean±sd)				
Yes	23.6	24.0	23.6	24.1
No	75.9	75.6	75.9	75.5
Hay fever or eczema age of onset[¶]	25.21±16.13	25.68±16.39	24.46±15.14	25.91±16.61
Asthma medication (if asthma yes) (mean±sd)				
No asthma/COPD medications	47.0	45.6	45.8	45.6
Only non-steroidal medications	15.4	14.8	14.7	14.8
Steroid medications	37.6	39.5	39.5	39.5
Hay fever medication (if hay fever yes)				
No hay fever medication	82.6	81.5	82.3	81.4
Medication; no antihistamines	7.2	7.5	7.3	7.6
Antihistamines	10.1	10.8	10.3	10.9
Lung function[†]				
FEV ₁ at baseline, z-score [¶]	0.37 (−0.32–1.08)	0.41 (−0.29–1.12)	0.44 (−0.27–1.16)	0.40 (−0.30–1.11)
FVC at baseline, z-score [¶]	0.18 (−0.48–0.84)	0.21 (−0.46–0.88)	0.24 (−0.44–0.92)	0.21 (−0.46–0.87)
FEV ₁ /FVC at baseline, z-score	0.34 (−0.16–0.90)	0.35 (−0.16–0.90)	0.34 (−0.16–0.92)	0.35 (−0.16–0.90)
Household income GBP				
<18 000	18.9	19.7	20.1	19.6
18 000 to 30 999	21.5	21.2	20.2	21.4
31 000 to 51 999	22.3	22.1	23.6	21.8
52 000 to 100 000	17.8	17.2	17.3	17.2
>100 000	4.9	5.1	4.4	5.3
Education[¶]				
None of the following	0.9	0.9	0.8	1.0
College or University degree	32.4	30.6	25.1	31.7
A levels/AS levels or equivalent	10.9	10.4	9.9	10.5
O levels/GCSEs or equivalent	20.8	21.0	22.4	20.7
CSEs or equivalent	5.3	5.5	8.8	4.8
NVQ or HND or HNC or equivalent	6.6	7.0	7.8	6.8
Other professional qualifications	5.2	5.3	4.8	5.5
Smoking history[¶]				
Never	54.4	52.2	52.9	52.0
Past	34.4	36.3	35.0	36.6
Current	10.5	10.8	11.5	10.7

Continued

TABLE 1 Continued

	All UK Biobank	UK Biobank with SARS-CoV-2 test data		
	Whole sample	Whole sample [#]	Positive	Negative
Smoking pack-years	19.00 (10.00–32.00)	19.88 (10.13–33.00)	20.00 (10.50–33.00)	19.88 (10.00–33.00)
BMI [¶] (mean±SD)	27.43±4.80	27.83±4.96	28.29±5.10	27.74±4.93
White blood cell count [¶]	6.65 (5.63–7.86)	6.70 (5.69–7.90)	6.73 (5.70–7.99)	6.70 (5.69–7.90)
Eosinophil count	0.14 (0.10–0.21)	0.14 (0.10–0.21)	0.14 (0.10–0.22)	0.14 (0.10–0.21)
Close to major road				
Yes	7.0	7.2	7.4	7.1
No	91.5	91.5	91.4	91.5
Greenspace percentage, buffer 300 m [¶]	29.53 (17.22–48.41)	29.53 (17.17–48.21)	27.44 (16.37–44.02)	29.97 (17.35–49.11)

Values are % of participants, mean±SD or median (interquartile range) unless stated otherwise. FEV₁: forced expiratory volume in 1 s; FVC: forced vital capacity; BMI: body mass index. [#]: sample of UK Biobank with SAR-CoV-2 test data differs from whole UK Biobank cohort (p<0.05) in all parameters except greenspace percentage, buffer 300 m. [¶]: all p-values are <0.001, except for FVC at baseline, z-score (p=0.002) and white blood cell count (p=0.008). p-values are comparing positive and negative test result: chi-square for categorical exposures, ANOVA for parametric and Mann-Whitney U-test (Wilcoxon rank sum test) for non-parametric analysis of variance for continuous variables. [†]: z-score means represent the mean standard deviation of lung function parameters compared with values for age-, sex- and race-matched individuals.

Other factors (confounders and effect modifiers)

Confounders

We considered baseline information collected on age, sex, highest level of education, average household income, smoking, BMI, ethnic group, white blood cell count, eosinophil count, proximity to a major road, greenspace percentage, and other allergic and respiratory conditions as confounders (table 1). The minimum set of confounders for adjustment was determined by our knowledge of the field and by using causal modelling theory [17] (Directed Acyclic Graph, figure 1).

Effect modifiers

Baseline smoking status was categorised as “never smoked”, “past smoker” or “current smoker”, derived from participant responses to the question “do you smoke tobacco now?” and subsequently “in the past, how often have you smoked tobacco?”. BMI was categorised according to height and weight measured during the initial assessment centre visit. Ethnic group was defined from a series of sequential branching questions asked during the initial assessment centre visit as part of the touch-screen questionnaire.

Statistical analysis

Causal modelling theory was used to model the relationship between asthma and a SARS-CoV-2 positive result. We used Directed Acyclic Graphs (DAG) in order to explore potential confounders and to determine those to include in final models (figure 1).

Results are presented as adjusted odds ratios and corresponding 95% confidence intervals. Logistic regression analyses were performed to estimate: 1) the association between ever asthma (and age of asthma onset) and a SARS-CoV-2 positive test in the UK Biobank participants for whom test results were available; 2) the association of asthma medication use; and 3) asthma stratified by quartiles of baseline pre-bronchodilator FEV₁ with a SARS-CoV-2 positive test. Adjustments were made for confounders listed above. A further model was performed including a limited number of confounders (age at recruitment, sex, smoking history, BMI) to address the possibility that some of the included confounders may be mediators. As no appreciable difference was demonstrated (supplementary Table S2), we continued with the fully adjusted model. These models were applied to the entire sample and further analyses of FEV₁ quartiles and medication use were limited to participants with asthma (tables from the asthma subsample are included in the supplement). We also performed interaction analyses for sex, smoking, obesity, and ethnic group and a positive test, and stratified results are presented with interaction terms tested using likelihood ratio tests. Owing to low numbers of observations when stratified, self-reported ethnic group was re-categorised as “Black” or “non-Black”, in accordance with current literature indicating “Black” ethnic group as a possible risk factor. Similarly, BMI was classified as “normal weight” or “overweight/obese” and smoking history groups “past and current” were collapsed to one “ever smoked” group. All analyses were performed with Stata 15 (StataCorp, College Station, TX, USA).

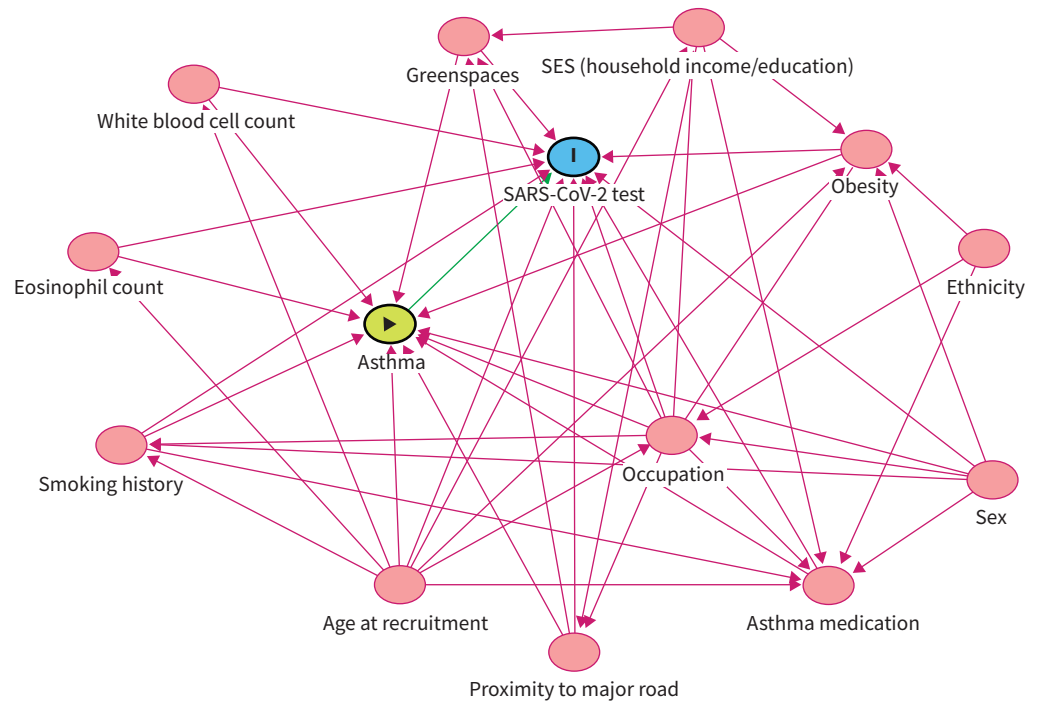


FIGURE 1 Directed Acyclic Graph (DAG) identifying potential confounders for the relationship between asthma and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) positive test. An arrow from a factor to another means possible association. Red circles indicate variables that require adjustment to assess the relationship between exposure (asthma, green) and the outcome (SARS-CoV-2 test, blue).

Results

Study population

The distribution of demographic characteristics for all UK Biobank participants, and those with SARS-CoV-2 test data, stratified by positive and negative test results is presented in table 1 (supplementary Table S2 contains participant numbers). When the tested sample was compared with the entire English UK Biobank (table 1), there were no or only slight differences in the proportions for most demographic/baseline variables that were statistically significant due to the very large sample size. The percentages differed slightly for the following parameters, where people being tested had: more asthma ever (14% versus 13%), less early-onset asthma (36% versus 37%), more use of steroid medications (39% versus 38%) and antihistamines (11% versus 10%), better baseline lung function (z-scores: FEV₁ 0.41 versus 0.37; forced vital capacity (FVC) 0.21 versus 0.18; FEV₁/FVC 0.35 versus 0.34), slightly lower levels of the socioeconomic status indicators (income and education) and more total, ever and current smoking.

A total of 107 412 UK Biobank participants (mean age 68.23 years) had SARS-CoV-2 test data, of which 17 979 (17%) were positive and 89 433 (83%) negative. The mean±SD age of 64.7±8.6 years for SARS-CoV-2 test positive participants was lower than for those with a negative test (69.0±7.9 years) (p<0.001). The whole cohort and the sample used in this analysis was predominately of “white” ethnicity (both 94%); however, other ethnic groups demonstrated a relatively higher proportion of positive test results. The percentage of reported doctor-diagnosed asthma at baseline was the same amongst the positive and negative test groups (14%; p=0.458). Similarly, the percentage of asthma medication used (both steroid and other) did not differ between participants with or without a positive test.

Association between asthma and a SARS-CoV-2 positive test

For all tested participants (n=107 412), the risk of a SARS-CoV-2 positive test was non-significantly lower in those with ever asthma versus those without ever asthma (3% reduction in odds, 95% CI 0.92–1.02) (table 2). On phenotyping into individuals with early and late-onset asthma, there was a reduced risk of a SARS-CoV-2 positive test in the early-onset group (9% reduction in odds, 95% CI 0.84–0.99) but not in the late-onset group compared to non-asthma individuals. We found no association between asthma

treatment groups or different quartiles of lung function in all participants with asthma and risk of test positivity when compared with participants without asthma (table 2). When stratified by onset phenotypes (table 3), there was an increased risk for individuals with early-onset asthma with the highest lung function compared with the lowest quartile (44% increased odds, 95% CI 1.05–1.72). There was also some evidence for an increased risk in individuals with early-onset asthma treated with steroids but confidence intervals crossed 1 (18% increase, 95% CI 0.98–1.42).

The cohort tested for SARS-CoV-2 while in hospital (Origin=1), were more likely to test positive if they had ever had asthma (OR 1.10, 95% CI 0.99–1.23), and if they were using steroids (OR 1.32, 95% CI 1.14–1.54), while these associations were not seen for non-hospital samples (supplementary Table S3).

When the analysis was restricted to those with asthma, again, there was no evidence of associations for asthma treatment or lung function and risk of positive SARS-CoV-2 test (supplementary Table S4).

Sex, smoking, ethnicity and BMI by asthma-onset phenotypes (table 4)

The association between early-onset asthma and a SARS-CoV-2 positive test differed by sex (table 4). Males with early-onset asthma had 14% reduction in the odds of a positive test (95% CI 0.76–0.97) compared to males without asthma. This was not the case for female participants (P_{int} early-onset asthma/sex 0.29).

Associations also differed by smoking status. Nonsmokers with early-onset asthma had 13% reduced odds of a positive test compared with non-asthmatic nonsmokers (95% CI 0.78–0.98) (P_{int} early-onset asthma/smoking 0.45).

Amongst participants who were overweight/obese, those with early-onset asthma had 15% reduced odds of testing positive for SARS-CoV-2 (95% CI 0.77–0.93) (P_{int} early-onset asthma/BMI 0.01).

Amongst participants with self-reported “non-Black” ethnicity, those with early-onset asthma had 10% decreased odds of testing positive to SARS-CoV-2 (95% CI 0.82–0.98) compared to “non-Black” participants without asthma. Conversely, amongst participants with self-reported “Black” ethnicity, those with asthma had 1.5 times increased odds of a positive SARS-CoV-2 test, but 95% confidence intervals included the null value (0.90–2.6) (P_{int} early-onset asthma/ethnicity 0.14).

Sample sizes were too small to stratify by ethnic group for the relationship between treatment in individuals with asthma and SARS-CoV-2 test status.

Discussion

Using UK Biobank data from 107 412 participants who had been tested for SARS-CoV-2, we observed evidence for a lower risk of a SARS-CoV-2 positive test in those with early-onset asthma *versus* those without asthma. This association was limited to males, nonsmokers, overweight/obese and participants of non-Black ethnicity. Paradoxically, we also found that individuals with early-onset asthma in the highest quartile of lung function were at greater risk compared to those in the lowest quartile.

TABLE 2 Adjusted association between asthma and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) positive test

	Percentage of positive tests (n/N)	OR (95% CI) for a positive test	p-value
Ever asthma			
No	16.6 (15 347/91 977)	Ref	
Yes	16.9 (2539/14 988)	0.97 (0.92–1.02)	0.28
Asthma onset			
No asthma	16.6 (15 347/91 977)	Ref	
Early-onset (<13 years)	16.2 (887/5469)	0.91 (0.84–0.99)	0.03
Late onset (≥13 years)	17.3 (1652/9519)	1.00 (0.94–1.07)	0.87

Adjusted for age at recruitment, sex and baseline measures of: education, average household income, smoking history, BMI, ethnicity, white blood cell count, eosinophil count, close to major road and greenspaces buffer. Bold values indicate p-value <0.05.

TABLE 3 The associations between asthma age-of-onset phenotypes and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) positive test by treatment and lung function

	Early onset		Late onset	
	Percentage of positive tests (n/N)	OR (95% CI) for a positive test	Percentage of positive tests (n/N)	OR (95% CI) for a positive test
Asthma treatment				
No	15.8 (491/3114)	Ref	18 (672/3727)	Ref
Treated with non-steroid	17.3 (112/645)	1.05 (0.81–1.36), p=0.67	16.5 (261/1576)	0.90 (0.75–1.08), p=0.26
Treated with steroids	16.6 (284/1710)	1.18 (0.98–1.42), p=0.07	17.1 (719/4216)	1.04 (0.91–1.19), p=0.55
Quartiles of baseline FEV₁				
Q1 of FEV ₁ (lowest quartile)	12.4 (70/562)	Ref	18.3 (190/1035)	Ref
Q2 of FEV ₁	16.7 (120/715)	1.25 (0.88–1.79), p=0.20	15.2 (203/1332)	0.81 (0.64–1.03), p=0.09
Q3 of FEV ₁	14.8 (145/976)	1.22 (0.87–1.72), p=0.23	16.9 (280/1653)	0.92 (0.73–1.15), p=0.48
Q4 of FEV ₁	16.7 (310/1851)	1.44 (1.05–1.72), p=0.02	17.4 (516/2962)	0.90 (0.73–1.15), p=0.36

FEV₁: forced expiratory volume in 1 s.

Previous studies

ATKINS *et al.* [6] studied 507 participants from UK Biobank and found that asthma was not a protective or a risk factor for a SARS-CoV-2 positive test in fully adjusted models. The smaller number of patients with asthma included in that study may have limited power to observe associations as compared to the present study (90 versus 14988). In keeping with our study, they found evidence for interaction by sex, so amongst patients with asthma, females were at greater risk of COVID-19 hospitalisation (but not death) [6]. On the other hand, WILLIAMSON *et al.* [7], using the OpenSAFELY platform, comprising data from the NHS of over 17 million people in England, analysed factors related to 10926 COVID-19 deaths and found evidence of increased risk of death for male sex, older age, severe asthma, ethnicity (Black and South Asian), smoking and obesity (BMI >40). Severe asthma in this study was defined by prescription of oral corticosteroid in the past 12 months. In our analyses, quartiles of lung function served as a proxy for asthma severity, and we found some contrasting evidence that participants with early-onset asthma in the highest quartile of lung function were at greater risk of SARS-CoV-2 positivity than people without asthma.

Interpretation of findings

We believe that our findings are underpinned by a mix of biological and behavioural mechanisms. Several mechanisms may explain our observation that asthma may be protective for COVID-19 in the early-onset asthmatic participants. Firstly, as we have limited our analysis to the sample in the UK Biobank tested for SARS-CoV-2, there may be a degree of collider bias [18] since patients with asthma may have different health-related behaviour and undertake more stringent protective and avoidance measures as well as seeking healthcare earlier for potential COVID-19 symptoms, so there may be reduced positive test results in this group. However, the sample tested is very large (107000) and the prevalence of asthma in the tested cohort was very similar to the entire UK Biobank cohort (14% versus 13%), and the prevalence of positive tests amongst those with asthma was the same (17%) as the entire tested sample.

Secondly, the immunological characteristics of patients with asthma may be protective for SARS-CoV-2 infection. Asthma is characterised by increased populations of both CD4⁺ and CD8⁺ cells and reduced expression of the SARS-CoV-2 receptor, angiotensin-converting enzyme 2 (ACE2) [19]. There is evidence that reduced levels of CD4⁺ and CD8⁺ cells are associated with increased risk of COVID-19 disease and increased severity [13], so greater levels in people with asthma may be protective. Notably, there are two major forms of asthma characterised by specific immune responses. Atopic asthma is characterised by a TH2 response and increased levels of interleukin (IL)-4, IL-5, IL-9 and IL-13 cytokines. Conversely, non-atopic asthma is characterised by an increased TH1 response with increased levels of interferon- γ (IFN- γ) and IL-2, IL-12 and IL-17 cytokines. There is some evidence to suggest that atopic asthma with a TH2 response may be more protective through downregulation of ACE2 cell surface receptors. The SARS-CoV-2 virus is known to enter host cells *via* the ACE2 receptor using transmembrane protease serine 2 (TMPRSS2) [20]. Analysis of the URECA cohort found that increasing atopy was associated with

TABLE 4 The associations between asthma onset phenotypes and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) positive test stratified by sex, baseline smoking, obesity and ethnicity (NEW)

	Percentage of positive tests (n/N)	OR (95% CI) for a positive test	Percentage of positive tests (n/N)	OR (95% CI) for a positive test	p-value for interaction
	Male		Female		Sex
Asthma onset					0.53
No asthma	17.2 (7374/42981)	Ref	16.3 (7973/48996)	Ref	
Early-onset (<13 years)	15.5 (417/2684)	0.86 (0.76–0.97), p=0.01	16.8 (470/2785)	0.94 (0.83–1.06), p=0.33	0.29
Late onset (≥13 years)	18.1 (626/3464)	1.00 (0.91–1.11), p=0.88	16.9 (1023/6055)	0.99 (0.92–1.08), p=0.95	0.75
	Never smoked		Ever smoked		Smoking
Asthma onset					0.71
No asthma	16.9 (8156/48191)	Ref	16.4 (7152/43479)	Ref	
Early-onset (<13 years)	16.5 (495/3003)	0.87 (0.78–0.98), p=0.02	16.0 (399/2497)	0.94 (0.84–1.07), p=0.40	0.45
Late onset (≥13 years)	17.4 (819/4711)	1.00 (0.91–1.09), p=0.86	17.2 (793/4589)	1.00 (0.91–1.09), p=0.97	0.79
	Normal weight		Overweight/Obese		BMI
Asthma onset					0.03
No asthma	14.8 (4202/28226)	Ref	17.4 (11036/63271)	Ref	
Early-onset (<13 years)	16.1 (264/1634)	1.09 (0.94–1.27), p=0.22	16.2 (625/3854)	0.85 (0.77–0.93), p=0.001	0.01
Late onset (≥13 years)	14.4 (330/2280)	0.94 (0.82–1.08), p=0.43	18.2 (1293/7070)	1.02 (0.94–1.09), p=0.59	0.41
	Non-black		Black		Ethnicity
Asthma onset					0.32
No asthma	16.5 (14900/90327)	Ref	27.1 (444/1637)	Ref	
Early-onset (<13 years)	15.9 (859/5389)	0.90 (0.82–0.98), p=0.01	34.6 (27/78)	1.54 (0.90–2.6), p=0.11	0.14
Late onset (≥13 years)	17.1 (1601/9355)	0.99 (0.93–1.06), p=0.89	31.1 (51/164)	1.18 (0.79–1.7), p=0.40	0.67

Adjusted for age at recruitment, sex, and baseline measures of: education, average household income, smoking history, BMI, ethnicity, white blood cell count, eosinophil count, close to major road and greenspaces buffer. Bold values indicate p-value <0.05.

reduced ACE2 expression in nasal epithelium when compared to children with asthma and no atopy [19]. Conversely, non-atopic asthma was not associated with reduced ACE2 expression [19]. Therefore, atopic asthma may be protective through reduced ACE2 expression on cell surfaces limiting viral entry. This hypothesis has received further support from a recent publication finding that amongst hospital inpatients with COVID-19 and asthma, those with an allergic phenotype (history, eosinophils, cytokines) had less severe COVID-19 disease [21]. The prevalence of non-atopic asthma in adults is around 50% and is far more frequent in women [22]. In our analyses, we found evidence that sex differences may be associated with risk amongst people with asthma. Men, who are more likely to have early-onset atopic asthma [23], were protected compared with women. This may be partly explained by the adult atopic/non-atopic asthma phenotypes. This sex difference for COVID-19 risk amongst adults with asthma has now been found in several studies [5, 24, 25].

Thirdly, asthma treatments may be protective for SARS-CoV-2 infection. There is evidence that both steroid [26] and non-steroid medications [10] may modify cellular entry of SARS-CoV-2 through downregulation of cell surface ACE2 expression and interference with the action of TMPRSS2, respectively. In this way, asthma medications may reduce SARS-CoV-2 cellular entry and protect against both SARS-CoV-2 infection and severity. Owing to an apparent dose–response relationship between increased ICS and reduced prevalence of cell surface ACE2 receptors [26], there has been a call for randomised controlled trials [27, 28] and several are underway (NCT04331054, NCT04330586). SCHULTZE *et al.* [29] used the OpenSAFELY platform to investigate the association between ICS use and COVID-19-related death. From 820 000 people with asthma, they found evidence that those taking higher doses of ICS had a higher risk of death than those on medium to low doses. Further modelling suggested that these differences may be due to underlying confounding related to the overall health of the individual and associated comorbidities. They concluded that there was no major protective role from ICS for

COVID-19. In line with this, we also did not observe a protective effect of asthma medication on risk of a positive SARS-CoV-2 test.

Finally, we also found evidence amongst overweight/obese individuals that early-onset asthma may be associated with protection, and better lung function may be associated with increased risk for SARS-CoV-2 infection. These are counterintuitive findings, and we postulate that the mechanism may be from health-related behaviours. People with asthma who are overweight/obese may be less active in the community and more inclined to follow COVID-19 health directives, limiting their exposure to SARS-CoV-2. In contrast, individuals with early-onset asthma with good lung function and likely mild asthma may be more active and less likely to observe all COVID-19 precautionary measures.

Strengths and limitations

Major strengths of this study are its large sample size, that asthma disease status was ascertained prior to the COVID-19 pandemic, along with potential confounders and effect modifiers, and that we had prior objective measurements of lung function that allowed us to classify asthma objectively into proxy severity groups. Potential limitations include that the group is limited to older adults, and that the sample tested, in contrast to the entire UK Biobank cohort, may differ in health-related behaviours that may also be related to asthma and asthma severity. Ascertainment of doctor-diagnosed asthma was from questionnaire, and although this method has been found to have high sensitivity/specificity [30], it may have led to a degree of non-differential misclassification. Given that, associations found may be underestimates of true associations. Furthermore, participants of the UK Biobank are known to be a healthier, more educated group than the general population. Despite this, our findings show considerable overlap with those from the large population-based NHS studies [7, 29].

Conclusions

From UK Biobank data, there is evidence that early-onset asthma is protective for SARS-CoV-2 infection in specific groups: male, nonsmoking, overweight/obese and non-Black participants. Lack of asthma phenotyping in previous research may have led to inconsistent associations. Further research is required to investigate the impact of health-related behaviour in people with asthma and likely mechanisms before a causal association can be implied.

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