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IS ASTHMA ASSOCIATED WITH COVID-19 INFECTION? A UK BIOBANK ANALYSIS

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Author contributions: All authors involved in conception, analysis and/or interpretation of the findings. CL and AD wrote the initial draft to which all authors contributed**.**

Take home message

Reduced risk of SARS-CoV-2 test positive was associated with early onset asthma in males, non-smokers, overweight/obese and non-black participants. Lack of phenotyping and unappreciated interactions may contribute to inconsistent findings for asthma and COVID-19

ABSTRACT

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

Methods: We used UK Biobank data from all participants tested for SARS-CoV-2 (n= 107,412 (17,979 test positive)). Baseline questions at baseline defined ever asthma and asthma medications. Baseline Forced Expiratory Volume in the first second (FEV_1) was categorized into quartiles. Logistic regression modelled relationships between asthma, and asthma categories (age at onset, medications, FEV_1 quartiles), and risk of SARS-CoV-2 positive test. We investigated modification by sex, ethnic group, smoking, and BMI.

Results: There was a reduced risk of a positive test associated with with early-onset asthma (<13 years), (OR **0.91(95% CI 0.84, 0.99)**. This was found for early-onset asthmatics in males (OR 0·87 [95% CI: 0·78,0·98]), non-smokers (0·87 [0·78, 0·98]), overweight/obese (0.85 [0.77,0.93]), and non-Black participants (0·90 [0·82, 0.98]). There was increased risk amongst early onset asthmatics in the highest compared to lowest quartile of lung function (1.44 [1.05, 1.72])

Conclusion: Amongst males, non-smokers, 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. Early-onset asthmatics 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 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 adult asthmatics are particularly susceptible to SARS-CoV-2 infection and/or have a worse prognosis if infected than individuals without asthma. Given that asthma affects more than 339 million people worldwide(1), these are important questions for people with asthma, their families, and health care providers.

Early studies in China reported an unexpectedly low prevalence of asthma in hospital admitted 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 practicing stricter preventive/protective measures to avoid exposure to SARS-CoV-2, especially those with severe asthma, which is correlated with Forced Expiratory Volume in one second (FEV_1)(9). Furthermore, severe asthmatics are more likely to be on asthma treatment, especially inhaled (ICS) or oral corticosteroids (OCS), which may be protective for SARS-CoV-2 infection(10-12). Therefore, asthma medication and FEV_1 need to be considered in the analysis. Lastly, the TH_2 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, FEV_1 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[1] (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 (less than 13 years of age) or late onset (greater than or equal to 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 categorize 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).

FEV_1 derived from spirometry was divided into quartiles of FEV_1 z-scores. Spirometry testers were healthcare technicians or nurses certified to conduct the assessments and all spirometry measures were performed in accordance with ATS/ERS guidelines(15), using a

Vitalograph Pneumotrac 6800. 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 01/04/2020 to 23/06/2021(including specimen data until 14/06/2021).

Other factors (Confounders and effect modifiers)

Confounders. We considered baseline information collected on age, sex, highest level of education, average household income, smoking, Body Mass Index (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, Fig 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 categorized 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 (OR) and corresponding 95% confidence intervals (CI). 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 FEV_1 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 (Table S2), we continued with the fully adjusted model. These models were applied to the entire sample and further analyses of FEV_1 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. Due 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).

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 are presented in Table 1. (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: people being tested had: more asthma ever (14% vs 13%), less early onset asthma (36% vs 37%), more use of steroid medications(39% vs 38%) and antihistamines (11% vs 10%), better baseline lung function, (z-scores: FEV_1 0.41 versus(vs) 0.37; FVC 0.21 vs 0.18; FEV_1/FVC 0.35 vs 0.34), slightly lower levels of the SES 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 age of 64.7 years (SD 8.6) for SARS-CoV-2 test positive participants was lower than for those with a negative test (69.0 (SD 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 *vs.* those without ever asthma (3% reduction in odds, 95% CI: 0·92, 1·02) (Table 2). On phenotyping into early and late onset-asthmatics, 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-asthmatics. 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 2a), there was an increased risk for early-onset asthmatics 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 early-onset asthmatics treated with steroids but confidence intervals crossed 1 (18% increase, 95% CI 0.98, 1.42).

The cohort tested for SARS-CoV-2 whilst in hospital (Origin=1), were more likely to test positive if they had ever had asthma (OR 1.10; 0.99,1.23), and if they were using steroids (OR 1.32; 1.14,1.54), while these associations were not seen for non-hospital samples. (supplementary material, 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 material, Table S4)

Sex, smoking, ethnicity, and BMI by asthma-onset phenotypes (Table 3)

The association between early-onset asthma and a SARS-CoV-2 positive test differed by sex (Table 3). 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. Non-smokers with early-onset asthma, had 13% reduced odds of a positive test compared with non-asthmatic non-smokers (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 to 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 SARSCoV-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 asthmatics 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 *vs.* those without asthma. This association was limited to men, non-smokers, overweight/obese and participants of non-Black ethnicity. Paradoxically, we also found that early-onset asthmatics in the highest quartile of lung function were at greater risk compared to those in the lowest quartile.

Previous studies

Atkins *et al* 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(6). 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 14,988). 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 hospitalization (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 10,926 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 health care earlier for potential COVID-19 symptoms, so there may be reduced positive test results in this group. However, the sample tested is very large (107,000) and the prevalence of asthma in the tested cohort was very similar 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, 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 characterized by specific immune responses. Atopic asthma is characterized by a TH2 response and increased levels of Il4, IL5, IL9 and IL13 cytokines. Conversely, non-atopic asthma is characterized by an increased TH1 response with increased levels of IF gamma and IL2, IL 12, IL17 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 (angiotensin-converting enzyme 2) receptor, and using TMPRSS2 (transmembrane protease serine 2)(20). Analysis of the URECA cohort found that increasing atopy was associated with 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 adult asthmatics 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. Due to an apparent dose response relationship between increased ICS and reduced prevalence of cell surface ACE2 receptors(26), there has been a call for RCTs(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 co-morbidities. 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, 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, early-onset asthmatics 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: males, non-smokers, 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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Tables

Table 1 (UK). Demographic characteristics amongst all UK Biobank individuals who attended an assessment centre and amongst UK Biobank individuals with SARS-CoV-2 test data.

	All UK Biobank	**UK Biobank with** SARS-CoV-2 **test data**		
	Whole sample N = 502,505	*Whole sample[2] N = 107,412*	Positive n = 17,979 (17%)	Negative n = 89,433 (83%)
Age at recruitment*, mean [SD]	*56·53 [8·10]*	*56·70 [8·25]*	53·52 [8·58]	57·33 [8·03]
Mean age at SARS-CoV-2 test* [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				
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)				
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[2]				

FEV1 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}
FEV1/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				
Less than 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%
Greater than 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%
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}
Mean BMI*	*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 300m*	*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 number of participants (%), mean [standard deviation], or median {interquartile range; p25 – p75}

[1] 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 300m

*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.

[2] z-score means represent the mean standard deviation of lung function parameters compared with values for age, sex and race matched individuals

Table 2. Adjusted association between asthma and SARS-CoV-2 positive test.

	Percentage of positive tests (n/N)	OR (95%CI) for a positive test	p
Ever asthma			
No	16.6% (15347/91977)	Ref	
Yes	16.9 % (2539/14988)	0.97(0.92,1.02)	0.28
Asthma onset			
No asthma	16.6% (15347/91977)	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.

Table 2a. The associations between asthma age of onset phenotypes and SARS-CoV-2 positive test by treatment and lung function.

	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
	Early onset		**Late onset**	
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 FEV1 (lowest quartile)	12.4% (70/562)	Ref	18.3% (190/1035)	Ref
Q2 of FEV1	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 FEV1	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 FEV1	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

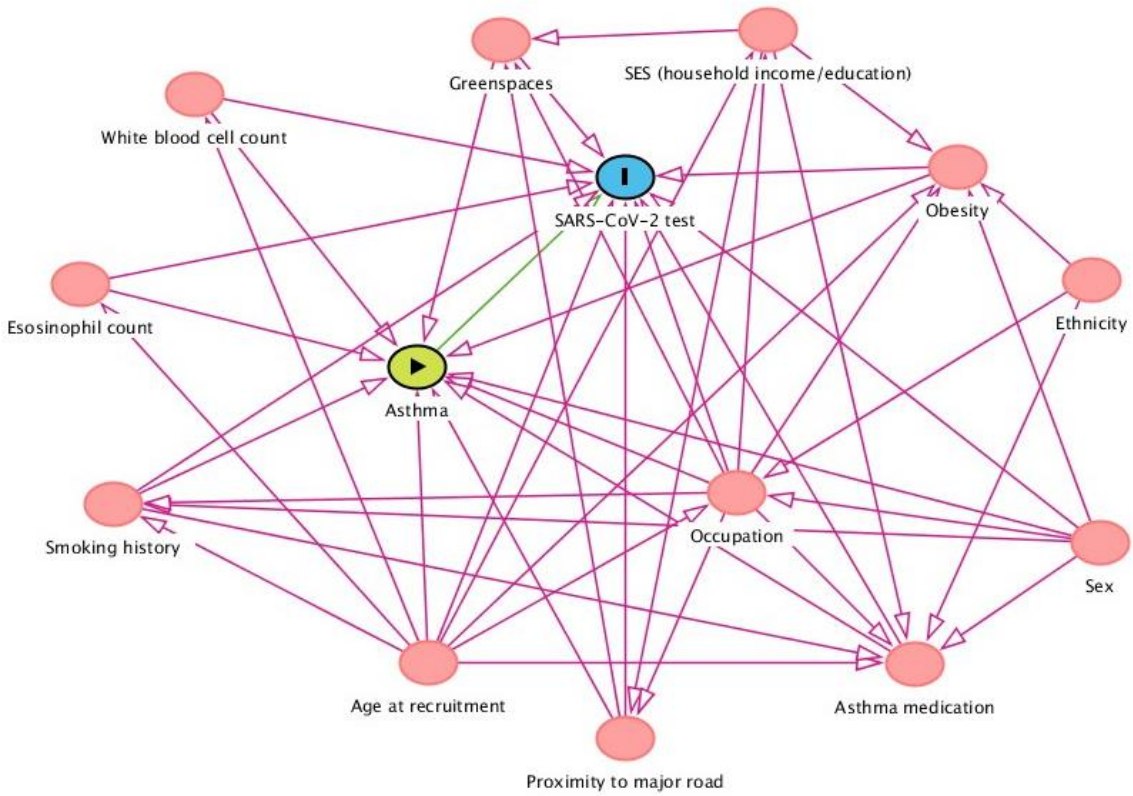
Table 3. The associations between asthma onset phenotypes and SARS-CoV-2 positive test stratified by sex, baseline smoking, obesity and ethnicity (NEW).

	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

Figure 1



The directed acyclic graph (DAG) for the study. 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 circle) and the outcome (SARS-CoV-2 test – blue circle).

IS ASTHMA PROTECTIVE FOR COVID-19? A UK BIOBANK ANALYSIS

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Author contributions: All authors involved in conception, analysis and/or interpretation of the findings. CL and AD wrote the initial draft to which all authors contributed**.**

Take home message

In UK Biobank we found reduced risk of SARS-CoV-2 test positive in people with early onset asthma; specifically amongst males, non-smokers, overweight/obese and non-black participants. Lack of asthma phenotyping and unappreciated interactions by levels of other factors may be contributing to the lack of consistent findings for asthma and COVID-19.

Supplementary Tables

Table S1 (UK). Demographic characteristics amongst all UK Biobank individuals who attended a assessment centre and amongst UK Biobank individuals with SARS-CoV-2 test data. (all numbers)

	All UK Biobank	**UK Biobank with** SARS-CoV-2 **test data**		
	Whole sample N = 502,505	*Whole sample[1] N = 107,412*	Positive n = 17,979 (17%)	Negative n = 89,433 (83%)
Age at recruitment*	*56·53 [8·10]*	*56·70 [8·25]*	53·52 [8·58]	57·33 [8·03]
Mean age at SARS-CoV-2 test*	··	*68·23 [8·23]*	64·69 [8·58]	69·00 [7·94]
Sex*				
Female	*273,382 (54%)*	*58,059 (54%)*	9,507 (53%)	48,552 (54%)
Male	*229,122 (46%)*	*49,353 (46%)*	8,472 (47%)	40,881 (46%)
Ethnicity*				
White	*472,695 (94%)*	*100,596 (94%)*	16,100 (89%)	84,496 (94%)
Mixed	*2,958 (1%)*	*661 (1%)*	136 (1%)	525 (1%)
Asian	*11,456 (2%)*	*2,610 (2%)*	832 (5%)	1,778 (2%)
Black	*8,061 (2%)*	*1,897 (2%)*	526 (3%)	1,371 (2%)
Other ethnic background	*6,436 (1%)*	*1,441 (1%)*	344 (2%)	1,097 (1%)
Ever Asthma				
Yes	*63,306 (13%)*	*14,988 (14%)*	2,539 (14%)	12,449 (14%)
No	*437,153 (87%)*	*91,977 (86%)*	15,347 (85%)	76,630 (86%)
Asthma age of onset (if asthma yes)*	*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)	*23,337 (37%)*	*5,469 (36%)*	887 (35%)	4,582 (37%)
Late onset (>=13 years)	*39,969 (63%)*	*9,519 (64%)*	1,652 (65%)	7,867 (63%)

COPD diagnosis				
Yes	*1,768 (<1%)*	*472 (<1%)*	59 (<1%)	413 (<1%)
No	*119,508 (24%)*	*24,791 (23%)*	3,284 (18%)	21,507 (24%)
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				
Yes	*118,822 (24%)*	*25,761 (24%)*	4,244 (24%)	21,517 (24%)
No	*381,591 (76%)*	*81,194 (76%)*	13,640 (76%)	67,554 (76%)
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)				
No asthma/COPD medications	*29,748 (47%)*	*6,841 (46%)*	1,163 (46%)	5,678 (46%)
Only non-steroidal medications	*9,750 (15%)*	*2,221 (15%)*	373 (15%)	1,848 (15%)
Steroid medications	*23,808 (38%)*	*5,926 (39%)*	1,003 (39%)	4,923 (39%)
Hay fever medication (if hay fever yes)				
No hay fever medication	*98,138 (83%)*	*21,006 (81%)*	3,492 (82%)	17,514 (81%)
Medication; no antihistamines	*8,543 (7%)*	*1,944 (8%)*	312 (7%)	1,632 (8%)
Antihistamines	*12,057 (10%)*	*2,789 (11%)*	438 (10%)	2,351 (11%)
Lung function				
FEV1 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}
FEV1/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				
Less than 18,000	*95,018 (19%)*	*21,117 (20%)*	3,623 (20%)	17,494 (20%)
18,000 to 30,999	*107,955 (21%)*	*22,740 (21%)*	3,637 (20%)	19,103 (21%)
31,000 to 51,999	*112,197 (22%)*	*23,698 (22%)*	4,236 (24%)	19,462 (22%)
52,000 to 100,000	*89,332 (18%)*	*18,496 (17%)*	3,108 (17%)	15,388 (17%)
Greater than 100,000	*24,642 (5%)*	*5,504 (5%)*	789 (4%)	4,715 (5%)
Education*				
None of the following	*4,448 (1%)*	*1,013 (1%)*	150 (1%)	863 (1%)
College or University degree	*162,715 (32%)*	*32,872 (31%)*	4,519 (25%)	28,353 (32%)
A levels/AS levels or equivalent	*54,986 (11%)*	*11,213 (10%)*	1,774 (10%)	9,439 (11%)
O levels/GCSEs or equivalent	*104,598 (21%)*	*22,538 (21%)*	4,028 (22%)	18,510 (21%)

CSEs or equivalent	*26,703 (5%)*	*5,909 (5%)*	1,589 (9%)	4,320 (5%)
NVQ or HND or HNC or equivalent	*33,021 (7%)*	*7,502 (7%)*	1,397 (8%)	6,105 (7%)
Other professional qualifications	*25,971 (5%)*	*5,744 (5%)*	860 (5%)	4,884 (5%)
Smoking history*				
Never	*273,552 (54%)*	*56,029 (52%)*	9,504 (53%)	46,525 (52%)
Past	*173,056 (34%)*	*39,026 (36%)*	6,286 (35%)	32,740 (37%)
Current	*52,978 (10%)*	*11,637 (11%)*	2,074 (12%)	9,563 (11%)
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}
Mean BMI*	*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	*35,351 (7%)*	*7,687 (7%)*	1,333 (7%)	6,354 (7%)
No	*459,773 (91%)*	*98,243 (91%)*	16,441 (91%)	81,802 (91%)
Greenspace percentage, buffer 300m*	*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 number of participants (%), mean [standard deviation], or median {interquartile range; p25 – p75}

[1] 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 300m

*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.

Table S2. Adjusted association between asthma and SARS-CoV-2 positive test (limited adjustment model).

	Number of positive tests/n *(%)*	OR (95%CI) for a positive test
Ever asthma		
No	15347/91977(16.6%)	Ref
Yes	2539/14988(16.9%)	0.95 (0.91, 1.00), p=0.07
Asthma onset		
No asthma	15347/91977(16.6%)	Ref
Early onset (<13 years)	887/5469(16.2%)	**0.88 (0.82, 0.95),p=0.002**
Late onset (>=13 years)	1652/9519(17.3%)	0.99 (0.94, 1.05),p=0.9

Adjusted for age at recruitment, sex, smoking history, BMI.

Table S3. Adjusted association between asthma and SARS-CoV-2 positive test stratified by origin (hospital inpatient versus other settings).

(available for England only)

	Origin=0		**Origin=1**		**Whole sample (England)**	
	Number of positive test/N	OR (95%CI) for a positive test	Number of positive test/N	OR (95%CI) for a positive test	Number of positive test/N	OR (95%CI) for a positive test
Ever asthma						
No	11580/40135(28.8%)	Ref	2918/41852(6.9%)	Ref	14498/81987(17.6%)	Ref
Yes	1848/6204(29.7%)	0.99(0.93,1.06),p=0.92	575/7155(8.0%)	1.10(0.99,1.23),p=0.06	2423/13359(18.1%)	0.97(0.92,1.02),p=0.27
Asthma onset						
No asthma	11580/40135(28.8%)	Ref	2918/41852(6.9%)	Ref	14498/81987(17.6%)	Ref
Early onset (<13 years)	644/2306(27.9%)	0.93(0.84,1.03),p=0.21	206/2596(7.9%)	1.06(0.89,1.26),p=0.48	850/4902(17.3%)	**0.90(0.83,0.98),p=0.03**
Late onset (>=13 years)	1204/3898(30.8%)	1.03(0.95,1.11),p=0.42	369/4559(8.0%)	1.13(0.99,1.29),p=0.06	1573/8457(18.6%)	1.00(0.94,1.07),p=80
Asthma-treatment groups						
No asthma	11580/40135(28.8%)	Ref	2918/41852(6.9%)	Ref	14498/81987(17.6%)	Ref
Asthma + no treatment	893/3097(28.8%)	0.93(0.85,1.02),p=0.16	210/3029(6.9%)	0.93(0.83,1.17),p=0.93	1103/6126(18.0%)	0.94(0.87,1.02),p=0.15
Asthma + medications (not steroids)	279/879(31.7%)	1.03(0.88,1.21),p=0.63	79/1096(7.2%)	0.84(0.63,1.11),p=0.22	358/1975(18.1%)	0.90(0.79,1.02),p=0.12

Asthma + steroids	676/2228(30.3%)	1.06(0.96,1.18),p=0.22	286/3030(9.4%)	**1.32(1.14,1.54),p=0.001**	962/5258(18.3%)	1.02(0.94,1.11),p=0.48
Asthma and FEV_1 categories						
No asthma	11580/40135(28.8%)	Ref	2918/41852(6.9%)	Ref	14498/81987(17.6%)	Ref
Asthma + Q1 FEV1 (lowest quartile)	199/737(27%)	0.89(0.75,1.06),p=0.21	48/673(7.1%)	1.21(0.85,1.70),p=0.27	247/1410(17.5%)	0.97(0.84,1.13),p=0.78
Asthma + Q2 of FEV1	254/875(29.0%)	0.96(0.82,1.13),p=0.68	54/948(5.7%)	0.86(0.62,1.20),p=0.39	308/1823(16.9%)	0.90(0.79,1.03),p=0.15
Asthma + Q3 of FEV1	317/1140(27.8%)	0.98(0.85,1.13),p=0.79	86/1197(7.1%)	1.09(0.84,1.41),p=0.48	403/2337(17.2%)	0.97(0.86,1.09),p=0.61
Asthma + Q4 of FEV1	603/1968(30.6%)	1.02(0.92,1.14),p=0.63	183/2354(7.7%)	1.09(0.91,1.31),p=0.30	786/4322(18.1%)	0.99(0.91,1.08),p=0.95

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

Table S4. Adjusted association of steroid use and baseline lung function with SARS-CoV-2 positive test amongst participants with asthma.

	Number of positive tests/n *(%)*	OR (95%CI) for a positive test
Asthma treatment		
No	1163/6841(17.0%)	Ref
Treated with non-steroid	373/2221(16.7%)	0.96(0.83,1.11),p=0.60
Treated with steroids	1003/5926(16.9%)	1.09(0.98,1.22),p=0.08
Quartiles of baseline FEV1		
Q1 of FEV1 (lowest quartile)	260/1597(16.2%)	Ref
Q2 of FEV1	323/2047(15.7%)	0.93(0.76,1.14),p=0.53
Q3 of FEV1	425/2629(16.1%)	1.00(0.83,1.21),p=0.94
Q4 of FEV1	826/4813(17.1%)	1.04(0.88,1.24),p=0.59

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