Effect modification by age of the association between obstructive lung diseases, smoking, and COVID-19 severity

Peter P Moschovis, Mengdi Lu, Douglas Hayden, Lael M Yonker, Jesiel Lombay, Elsie Taveras, Alexy Arauz Boudreau, Virginia A Triant, Andrea S Foulkes, Ingrid Bassett, Patricia L Hibberd, T Bernard Kinane

ABSTRACT

Introduction Obstructive lung diseases (asthma and chronic obstructive pulmonary disease (COPD)) and smoking are associated with greater risk of respiratory infections and hospitalisations, but conflicting data exist regarding their association with severity of COVID-19, and few studies have evaluated whether these associations differ by age.

Objectives To examine the associations between asthma, COPD and smoking on the severity of COVID-19 among a cohort of hospitalised patients, and to test for effect modification by age.

Methods We performed a retrospective analysis of electronic health record data of patients admitted to Massachusetts General Hospital, assigning the maximal WHO Clinical Progression Scale score for each patient during the first 28 days following hospital admission. Using ordered logistic regression, we measured the association between maximal severity score and asthma, COPD and smoking and their interaction with age.

Measurements and main results Among 1391 patients hospitalised with COVID-19, we found an increased risk of severe disease among patients with COPD and prior smoking, independent of age. We also found evidence of effect modification by age with asthma and current smoking; in particular, asthma was associated with decreased COVID-19 severity among older adults, and current smoking was associated with decreased severity among younger patients.

Conclusions This cohort study identifies age as a modifying factor for the association between asthma and smoking on severity of COVID-19. Our findings highlight the complexities of determining risk factors for COVID-19 severity, and suggest that the effect of risk factors may vary across the age spectrum.

INTRODUCTION

The majority of severe COVID-19 and COVID-19-related deaths occur among those with comorbidities, including those with chronic respiratory disease. The United States Center for Disease Control and Prevention currently classifies chronic obstructive pulmonary disease (COPD, moderate-to-severe asthma and current and former smoking as associated with increased risk of severe COVID-19 complications. Though the majority of deaths due to COVID-19 occur among older adults, chronic respiratory diseases may increase the risk of severe outcomes even among younger patients. In the spring 2020 surge, chronic respiratory diseases were present in 20.9% of people under age 65 who died of COVID-19 in the USA through 18 May 2020, and a large study in the UK found that 20.9% of patients aged 16–49 and 44.4% of those aged 50–69 hospitalised with COVID-19 were diagnosed with asthma. By contrast, in a large cohort of hospitalised patients with COVID-19 in China, only 2.8% of patients had chronic respiratory disease. Since viruses (including non-SARS coronaviruses) are associated with both asthma and COPD exacerbations, patients with either obstructive lung disease would be expected to have a higher rate of severe outcomes due to COVID-19. Despite initial reports of
low prevalence of asthma among patients hospitalised with COVID-19 in China. Investigators have reported prolonged intubation course among asthmatics, increased risk of death among asthmatics with recent oral corticosteroid use, and worse clinical outcomes, especially among those with non-allergic asthma. Multiple studies have also reported increased risk of death among patients with COPD, with an even greater risk among men.

Smoking increases the risk of acquiring respiratory infections by impairing macrophage and cytokine responses and upregulating pathogen receptors. It is the primary risk factor for developing COPD, and contributes to development and exacerbations of asthma. Smoking is also associated with upregulation of the ACE-2 receptor in airways, raising concerns early in the pandemic regarding increased entry of SARS-CoV-2 into host cells.

An initial report from patients in Wuhan in December/January 2019 noted that patients with a history of smoking had significantly increased odds of disease progression, but subsequent meta-analyses have reported lower-than-expected prevalence of smoking among hospitalised patients with COVID-19.

To better understand the relative contributions of obstructive lung disease and smoking on the severity of COVID-19 across the age spectrum, we analysed data from the first 1391 patients admitted to Massachusetts General Hospital (MGH) with COVID-19. We hypothesised that obstructive lung diseases and smoking would be associated with severe COVID-19 disease, and that these associations would be greater among older patients.

## METHODS

### Study design and data sources

We performed a retrospective analysis of electronic health record data of patients admitted to MGH between 11 March and 3 June 2020. Demographic, hospitalisation, laboratory and body mass index (BMI) data were extracted from the MGH Enterprise Data Warehouse using structured query language procedures. Clinical data, including medical history, treatments in the hospital and outcomes were manually abstracted by trained chart reviewers and entered into a Redcap (Research Electronic Data Capture) database hosted on a MassGeneral Brigham server.

### Population

We included all patients in the MGH COVID-19 Registry, a cohort of children and adults with positive SARS-CoV-2 PCR testing who were inpatients during the study period and had 28-day outcome data available at the time of the analysis. The inclusion criteria for the cohort were (1) any positive SARS-CoV-2 PCR test, infection flag that indicates COVID-19 infection, or ICD-10 diagnosis of U07.1, and (2) at least one hospitalisation at MGH with an admission date within 45 days after criterion (1). Patients who did not satisfy these criteria were excluded.

### Variable definitions

Demographic data and medical history (including prior diagnoses of asthma and COPD) were obtained from the health record. BMI was calculated from height and weight measured within ±14 days of hospitalisation. We used results of laboratory testing closest to the time of admission to the hospital.

The primary outcome used for this analysis is the WHO Clinical Progression Scale (WHO CPS), which was developed to measure the full range of disease severity and progression in COVID-19 disease. While the scale as created ranges from 0 (uninfected) to 10 (dead), our analysis focuses on severity of illness among hospitalised patients and therefore only includes WHO CPS scores 4 and higher (moderate and severe disease, see table 1). We calculated the maximal WHO CPS for each patient during the first 28 days following hospital admission using the highest oxygen flow rate, fraction of inspired oxygen (FiO₂), or mode of ventilatory support; and the presence of haemodialysis, vasopressor or extracorporeal membrane oxygenation (ECMO) use reported in the registry. Because concurrent arterial partial pressure of oxygen (PaO₂), arterial oxyhaemoglobin saturation (SpO₂) and FiO₂ were recorded, we used the lowest of these as the value to enter into the analysis. The WHO CPS scores are calculated based on disease severity, with each increasing score representing a step up in disease severity (table 1). The WHO CPS is a validated tool for summarising clinical severity and progression among COVID-19 patients.

### Table 1: WHO CPS among hospitalised patients

| Patient state | Descriptor Description | Score |
|---------------|------------------------|-------|
| Hospitalised: moderate disease | Hospitalised; no oxygen therapy | 4 |
| | Hospitalised; oxygen by mask or nasal prongs | 5 |
| Hospitalised: severe disease | Hospitalised; oxygen by non-invasive ventilation or high flow | 6 |
| | Intubation and mechanical ventilation with pO₂/FiO₂≥150 or SpO₂/FiO₂≥200 | 7 |
| | Mechanical ventilation with pO₂/FiO₂<150 (SpO₂/FiO₂<200) or vasopressors | 8 |
| | Mechanical ventilation, with pO₂/FiO₂<150 (SpO₂/FiO₂<200) and vasopressors, dialysis or extracorporeal membrane oxygenation | 9 |
| Dead | Dead | 10 |

Adapted from Marshall et al. 
FiO₂, fraction of inspired oxygen; pO₂, partial pressure of oxygen; SpO₂, arterial oxyhaemoglobin saturation; WHO CPS, WHO Clinical Progression Scale.
### Table 2  Demographic and clinical characteristics by WHO Clinical Progression Score

|                      | Total | 4   | 5   | 6   | 7   | 8   | 9   | 10  | P value |
|----------------------|-------|-----|-----|-----|-----|-----|-----|-----|---------|
| **Age (years)**      |       |     |     |     |     |     |     |     | <0.001  |
| (N=1391)             | 59.0  | 52.8| 59.0| 62.3| 50.2| 57.7| 56.9| 75.5|         |
|                      | (18.7)| (20.3)| (18.0)| (17.2)| (17.8)| (16.9)| (13.2)| (13.2)|         |
| **Sex**              |       |     |     |     |     |     |     |     | 0.0015  |
| Male                 | 795   | 196 | 297 | 11  | 7   | 53  | 116 | 115 |         |
| (100%)               | (25%) |     | (37%)| (1%)| (1%)| (7%)| (15%)| (14%)|         |
| Female               | 596   | 166 | 256 | 6   | 4   | 43  | 64  | 57  | (10%)   |
| (100%)               | (28%) |     | (43%)| (1%)| (1%)| (7%)| (11%)| (10%)|         |
| **Race/ethnicity**   |       |     |     |     |     |     |     |     | 0.0458  |
| White                | 550   | 137 | 220 | 5   | 3   | 30  | 49  | 106 |         |
| (100%)               | (25%) |     | (40%)| (1%)| (1%)| (5%)| (9%) | (19%)|         |
| Black/African American| 149  | 52  | 48  | 3   | 3   | 2   | 18  | 16  |         |
| (100%)               | (35%) |     | (32%)| (2%)| (2%)| (6%)| (12%)| (11%)|         |
| Hispanic             | 492   | 132 | 205 | 9   | 5   | 37  | 79  | 25  |         |
| (100%)               | (27%) |     | (42%)| (2%)| (1%)| (8%)| (16%)| (5%) |         |
| Other                | 84    | 23  | 30  | 0   | 0   | 0   | 13  | 8   |         |
| (100%)               | (27%) |     | (36%)| (0%)| (0%)| (0%)| (15%)| (10%)|         |
| **BMI (kg/m²)**      |       |     |     |     |     |     |     |     | 0.0003  |
| (N=1391)             | 30.1  | 28.6| 30.7| 28.7| 26.9| 30.4| 32.3| 29.5|         |
|                      | (7.0) | (6.2)| (6.9)| (5.3)| (7.0)| (6.8)| (7.2)| (8.0)|         |
| **BMI category (kg/m²)**|   |     |     |     |     |     |     |     | 0.0594  |
| <25                  | 274   | 90  | 94  | 4   | 3   | 17  | 22  | 44  |         |
| (100%)               | (33%) |     | (34%)| (1%)| (1%)| (6%)| (8%) | (16%)|         |
| 25.0–29.9            | 411   | 118 | 171 | 5   | 4   | 27  | 40  | 46  |         |
| (100%)               | (29%) |     | (42%)| (1%)| (1%)| (7%)| (10%)| (11%)|         |
| 30.0–34.9            | 302   | 67  | 126 | 3   | 0   | 24  | 49  | 33  |         |
| (100%)               | (22%) |     | (42%)| (1%)| (0%)| (8%)| (16%)| (11%)|         |
| 35.0–39.9            | 147   | 30  | 71  | 2   | 0   | 8   | 24  | 12  |         |
| (100%)               | (20%) |     | (48%)| (1%)| (0%)| (5%)| (16%)| (8%) |         |
| >40                  | 114   | 20  | 51  | 0   | 1   | 9   | 20  | 13  |         |
| (100%)               | (18%) |     | (45%)| (0%)| (1%)| (8%)| (18%)| (11%)|         |
| **Smoking history**  |       |     |     |     |     |     |     |     | <0.001  |
| Never                | 777   | 226 | 315 | 9   | 6   | 54  | 103 | 64  |         |
| (100%)               | (29%) |     | (41%)| (1%)| (1%)| (7%)| (13%)| (8%) |         |
| Yes—past             | 404   | 73  | 166 | 8   | 2   | 25  | 48  | 82  |         |
| (100%)               | (18%) |     | (41%)| (2%)| (0%)| (6%)| (12%)| (20%)|         |
| Yes—current          | 102   | 44  | 34  | 0   | 2   | 6   | 7   | 9   |         |
| (100%)               | (43%) |     | (33%)| (0%)| (2%)| (6%)| (7%) | (9%) |         |
| Unknown              | 108   | 19  | 38  | 0   | 1   | 11  | 22  | 17  |         |
| (100%)               | (18%) |     | (35%)| (0%)| (1%)| (10%)| (20%)| (16%)|         |
| **Asthma**           |       |     |     |     |     |     |     |     | 0.0329  |
| No                   | 1209  | 314 | 462 | 15  | 9   | 89  | 162 | 158 |         |
| (100%)               | (26%) |     | (38%)| (1%)| (1%)| (7%)| (13%)| (13%)|         |
| Yes                  | 182   | 48  | 91  | 2   | 2   | 7   | 18  | 14  |         |
| (100%)               | (26%) |     | (50%)| (1%)| (1%)| (4%)| (10%)| (8%) |         |
| **COPD**             |       |     |     |     |     |     |     |     | 0.0006  |
| No                   | 1248  | 346 | 477 | 17  | 10  | 90  | 173 | 135 |         |
| (100%)               | (28%) |     | (38%)| (1%)| (1%)| (7%)| (14%)| (11%)|         |
| Yes                  | 143   | 16  | 76  | 0   | 1   | 6   | 7   | 5   |         |
| (100%)               | (11%) |     | (53%)| (0%)| (1%)| (4%)| (10%)| (8%) |         |
| **Bronchodilator use**|     |     |     |     |     |     |     |     | 0.2180  |
| No                   | 1169  | 312 | 459 | 14  | 6   | 82  | 165 | 131 |         |
| (100%)               | (27%) |     | (39%)| (1%)| (1%)| (7%)| (14%)| (11%)|         |
| Yes                  | 222   | 50  | 94  | 3   | 5   | 14  | 15  | 41  |         |
| (100%)               | (23%) |     | (42%)| (2%)| (2%)| (6%)| (7%) | (18%)|         |
| **Inhaled corticosteroid use**| |     |     |     |     |     |     |     | 0.7889  |
| No                   | 1239  | 327 | 485 | 17  | 10  | 84  | 165 | 151 |         |
| (100%)               | (26%) |     | (39%)| (1%)| (1%)| (7%)| (13%)| (12%)|         |
| Yes                  | 152   | 35  | 68  | 0   | 1   | 12  | 15  | 21  |         |
| (100%)               | (23%) |     | (45%)| (0%)| (1%)| (8%)| (10%)| (14%)|         |

Continued
| Montelukast use | Total | 4 | 5 | 6 | 7 | 8 | 9 | 10 | P value |
|-----------------|-------|---|---|---|---|---|---|----|---------|
|                 | N=1391| n=362 | n=553 | n=17 | n=11 | n=96 | n=180 | n=172 |         |
| No              | 1372 (100%) | 356 (26%) | 545 (40%) | 17 (1%) | 11 (1%) | 96 (7%) | 179 (13%) | 168 (12%) | 0.6712 |
| Yes             | 19 (100%) | 6 (32%) | 8 (42%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (5%) | 4 (21%) |         |
| Any cardiac/metabolic disorder | <0.001 |
| No              | 334 (100%) | 132 (40%) | 127 (38%) | 0 (0%) | 6 (2%) | 20 (6%) | 38 (11%) | 11 (3%) |         |
| Yes             | 1057 (100%) | 230 (22%) | 426 (40%) | 17 (2%) | 5 (0%) | 76 (7%) | 142 (13%) | 161 (15%) |         |
| Coronary artery disease/myocardial infarction | 0.0008 |
| No              | 1180 (100%) | 322 (27%) | 463 (39%) | 15 (1%) | 9 (1%) | 87 (7%) | 166 (14%) | 118 (10%) |         |
| Yes             | 211 (100%) | 40 (19%) | 90 (43%) | 2 (1%) | 2 (1%) | 9 (4%) | 14 (7%) | 54 (26%) |         |
| Heart failure   | <0.001 |
| No              | 1227 (100%) | 333 (27%) | 491 (40%) | 11 (1%) | 11 (1%) | 86 (7%) | 170 (14%) | 125 (10%) |         |
| Yes             | 164 (100%) | 29 (18%) | 62 (38%) | 6 (4%) | 0 (0%) | 10 (6%) | 10 (6%) | 47 (29%) |         |
| Hypertension    | <0.001 |
| No              | 694 (100%) | 231 (33%) | 262 (38%) | 6 (1%) | 7 (1%) | 48 (7%) | 92 (13%) | 48 (7%) |         |
| Yes             | 697 (100%) | 131 (19%) | 291 (42%) | 11 (2%) | 4 (1%) | 48 (7%) | 88 (13%) | 124 (18%) |         |
| Diabetes        | <0.001 |
| No              | 941 (100%) | 280 (30%) | 377 (40%) | 15 (2%) | 7 (1%) | 53 (6%) | 113 (12%) | 96 (10%) |         |
| Yes             | 450 (100%) | 82 (18%) | 176 (39%) | 2 (0%) | 4 (1%) | 43 (10%) | 67 (15%) | 76 (17%) |         |
| Kidney disease  | <0.001 |
| No              | 1132 (100%) | 313 (28%) | 455 (40%) | 15 (1%) | 10 (1%) | 79 (7%) | 155 (14%) | 105 (9%) |         |
| Yes             | 233 (100%) | 47 (20%) | 89 (38%) | 2 (1%) | 0 (0%) | 15 (6%) | 23 (10%) | 57 (24%) |         |

Values indicate count (proportion) and mean (SD) as appropriate.
P values calculated using the Wald χ² test in an ordered logistic regression model with a single predictor variable.
BMI, body mass index; COPD, chronic obstructive pulmonary disease.
(SpO₂) and FiO₂ data were not consistently available in the registry, we approximated the minimum SpO₂/FiO₂ ratio by using the maximal reported FiO₂ and assuming an SpO₂ of 90% based on the target SpO₂ in the hospital’s standard mechanical ventilation order set and usual target for oxygen supplementation.

**Statistical/analytic methods**

After calculating descriptive statistics for major variables of interest, we measured the unadjusted association between potential predictors of disease severity (including the CDC underlying conditions on which data were available) and the WHO CPS using ordered logistic regression. We then constructed a multivariable model that included the variables of interest as well as demographic variables and cardiometabolic comorbidities. We also tested for effect modification creating two-way interaction terms between age and asthma, age and COPD and age and smoking. We estimated predicted probabilities of each WHO CPS level across age, at the mean level of each covariate, using the Stata `margins` and `marginsplot` commands. Standard errors and 95% CI were calculated using the delta method. Finally, we compared biomarkers of disease severity and host response between patients with and without asthma, between patients with and without COPD and among patients with varying exposures to smoking, using Wilcoxon rank-sum and Kruskal-Wallis tests as appropriate. All analyses were performed in Stata V.16.1 (StataCorp, College Station, Texas, USA).

**Human subjects approval**

The MGH COVID-19 registry was reviewed and approved by the MassGeneral Brigham Human Research Committee (#2020P000829). The present analysis was reviewed and determined to be exempt.

**Patient and public involvement**

Patients were not directly involved in the design of this data analysis, though the question of how obstructive lung diseases and smoking affect COVID-19 outcomes was raised by many of our patients and their families.

---

**Figure 1** Distribution of WHO clinical progression scale.

**Figure 2** Predicted probability of WHO CPS score levels by age and asthma. ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; HD, hemodialysis; VP, vasopressors; WHO CPS, WHO Clinical Progression Scale.
RESULTS
We analysed data from 1391 patients who were hospitalised with COVID-19 and had complete 28-day outcome data. Baseline characteristics of the study population are summarised in the first column of table 2. Patients ranged in age from newborn to 99 years (mean age: 59 years), were predominantly men (57%), and were primarily white or Hispanic. The majority (78%) of patients were overweight or obese and 76% had a cardiac or metabolic disorder. Among all admitted patients, 22% (301/1391) had a prior diagnosis of obstructive lung disease: asthma (158/1391), COPD (119/1391) or both (24/1391). The majority of patients were either never (55.9%) or previous smokers (29.0%); 102 (7%)/1391 reported currently smoking. Six (0.4%) patients reported current use of electronic nicotine delivery systems. Inhaled corticosteroid use was common among both patients with asthma (40.1%) and COPD (43.4%).

Figure 1 demonstrates the distribution of the WHO CPS among the study population. Most patients (74%) required oxygen or other ventilator support during hospitalisation, and 12% died during the 28-day period of data review. The majority (69%) of patients were treated on hospital floors; 31% were admitted an intensive care unit (ICU) during their hospitalisation. On univariate analysis (table 2), we found a strong positive association between WHO CPS score and age, male sex, BMI, previous smoking, COPD, coronary artery disease (CAD), heart failure, hypertension, diabetes and chronic kidney disease. We found a negative unadjusted association between WHO CPS score and Hispanic ethnicity, asthma and current smoking. We did not find any significant association between WHO CPS score and prior use of inhaled bronchodilator medications, inhaled corticosteroids or montelukast.

We then estimated the association between asthma, COPD and smoking status with WHO CPS score in a multivariable model adjusting for relevant demographic and comorbidity covariates and interaction terms by age for the three risk factors of interest (online supplemental table 1). We found that a history of asthma was associated with an increased risk of requiring oxygen among younger patients and a reduced risk of severe disease among older patients (figure 2, \( p_{interaction}=0.006 \)), that no significant effect modification was observed by age with COPD (figure 3, \( p_{interaction}=0.61 \)), and that current smoking was associated with a reduced risk of severe disease among younger patients but not among older patients (figure 4, \( p_{interaction}=0.002 \)). The effect of asthma on WHO CPS ranged from OR 1.51 (95% CI: 0.76 to 2.99) at age 20 to OR 0.44 (95% CI: 0.26 to 0.74) at age 80, and the effect of smoking ranged from OR 0.07 (95% CI: 0.02 to 0.26) at age 20 to OR 0.375 (95% CI: 0.66 to 3.59) at age 80 (see table 3). Other significant covariates in the multivariable model included age (OR: 1.02 (95% CI: 1.01 to 1.03)), female sex (OR: 0.71 (95% CI: 0.55 to
open access

To further characterise the effects of asthma, COPD and smoking on the host response to SARS-CoV-2 infection, we compared laboratory testing at the time of hospital admission between patients with and without asthma, between patients with and without COPD and among patients across categories of smoking history (table 4). We observed an increased absolute lymphocyte count and reduced levels of inflammatory markers (ferritin, CRP, ESR and procalcitonin) among patients with asthma and among patients who reported currently smoking. Patients with COPD also had reduced levels of inflammatory markers but increased markers of cardiovascular stress (troponin, D-dimer and NT-proBNP).

**DISCUSSION**

In this cohort of 1391 hospitalised patients with COVID-19, we found evidence of significant effect modification of the association between asthma, smoking and COVID-19 severity by age. In particular, we found that asthma was

---

**Table 3** OR for WHO CPS score for asthma, COPD and smoking across levels of age

| Age (years) | Asthma OR (P value) | COPD OR (P value) | Smoking OR (P value) |
|------------|----------------------|-------------------|----------------------|
| 20         | 1.51 (0.76 to 2.99)  (0.232) | 3.40 (0.59 to 19.66) (0.170) | 0.07 (0.02 to 0.26) (0.001) |
| 30         | 1.23 (0.72 to 2.11)  (0.444) | 2.87 (0.68 to 12.22) (0.153) | 0.12 (0.05 to 0.33) (0.001) |
| 40         | 1.00 (0.66 to 1.51)  (0.982) | 2.42 (0.77 to 7.65)  (0.131) | 0.20 (0.10 to 0.42) (0.001) |
| 50         | 0.81 (0.58 to 1.13)  (0.231) | 2.04 (0.86 to 4.84)  (0.104) | 0.34 (0.20 to 0.58) (0.001) |
| 60         | 0.66 (0.48 to 0.92)  (0.004) | 1.72 (0.94 to 3.15)  (0.077) | 0.56 (0.34 to 0.93) (0.024) |
| 70         | 0.54 (0.37 to 0.80)  (0.013) | 1.45 (0.95 to 2.23)  (0.088) | 0.93 (0.50 to 1.74) (0.817) |
| 80         | 0.44 (0.26 to 0.74)  (0.002) | 1.23 (0.78 to 1.92)  (0.375) | 1.54 (0.66 to 3.59) (0.321) |

OR and 95% CIs calculated from ordered logistic regression model adjusting for age, sex, race, asthma, age × asthma, COPD, age × COPD, smoking, age × smoking, body mass index, coronary artery disease, heart failure, hypertension, diabetes and chronic kidney disease. COPD, chronic obstructive pulmonary disease; WHO CPS, WHO Clinical Progression Scale.
Table 4  Laboratory test values at the time of admission

|                          | Total     | Yes   | No     | P value | Yes—current | Yes—past | Never | Unknown | P value |
|--------------------------|-----------|-------|--------|---------|-------------|----------|-------|---------|---------|
|                          | N=1391    | n=182 | n=1209 |         | n=143       | n=1248   |       |         |         |
| White blood cell count  | 6.78      | 6.96  | 6.76   | 0.94    | 6.34        | 6.82     | 0.057 | 6.81    | (5.21 to 9.05) |
|                          | (5.11 to 9.23) | (4.95 to 9.04) | (5.13 to 9.23) |         | (4.84 to 8.38) | (5.15 to 9.24) |       | (5.11 to 9.14) |         |
| Absolute lymphocyte     | 0.98      | 1.06  | 0.96   | 0.022   | 0.82        | 1.00     | 0.001 | 1.10    | (0.75 to 1.87) |
| count (K/μL)            | (0.67 to 1.41) | (0.74 to 1.54) | (0.66 to 1.39) |         | (0.53 to 1.32) | (0.89 to 1.42) |       | (0.60 to 1.28) |         |
| Haemoglobin (g/dL)      | 13.3      | 13.3  | 13.3   | 0.92    | 12.6        | 13.4     | <0.001| 12.9    | (11.5 to 14.3) |
|                          | (12.0 to 14.5) | (12.1 to 14.6) | (12.0 to 14.5) |         | (10.8 to 13.9) | (12.1 to 14.6) |       | (11.5 to 14.7) |         |
| Platelets (K/μL)        | 203       | 201   | 203    | 0.81    | 189         | 207      | 0.034 | 208     | (154 to 268) |
|                          | (156 to 264) | (156 to 257) | (156 to 264) |         | (153 to 236) | (157 to 265) |       | (148 to 265) |         |
| Lactate (mmol/L)        | 1.5       | 1.4   | 1.5    | 0.080   | 1.4         | 1.5      | 0.007 | 1.6     | (1.1 to 2.7) |
|                          | (1.1 to 2.1) | (1.0 to 2.0) | (1.2 to 2.1) |         | (1.0 to 1.7) | (1.2 to 2.1) |       | (1.2 to 2.0) |         |
| Anion gap (mmol/L)      | 15        | 15    | 15     | 0.039   | 15          | 15       | 0.002 | 14      | (13 to 17) |
|                          | (14 to 17) | (14 to 16) | (14 to 17) |         | (13 to 17) | (14 to 17) |       | (14 to 21) |         |
| BUN (mg/dL)             | 14        | 12    | 15     | <0.001  | 21          | 14       | <0.001| 15      | (11 to 22) |
|                          | (10 to 22) | (9 to 17) | (10 to 23) |         | (16 to 33) | (9 to 21) |       | (13 to 30) |         |
| Creatinine (mg/          | 0.95      | 0.86  | 0.97   | <0.001  | 1.13        | 0.93     | <0.001| 0.98    | (0.79 to 1.28) |
| dL)                     | (0.78 to 1.28) | (0.72 to 1.05) | (0.79 to 1.30) |         | (0.90 to 1.65) | (0.77 to 1.22) |       | (0.86 to 1.56) |         |
| Glucose (mg/             | 124       | 118   | 125    | 0.23    | 117         | 126      | 0.013 | 115     | (99 to 145) |
| dL)                     | (106 to 161) | (103 to 165) | (106 to 161) |         | (103 to 149) | (106 to 162) |       | (107 to 163) |         |
| Haemoglobin A1C (%)      | 6.5       | 6.8   | 6.5    | 0.71    | 6.9         | 6.5      | 0.42  | 6.8     | (6.0 to 8.4) |
|                          | (6.0 to 8.4) | (5.8 to 8.4) | (6.0 to 8.4) |         | (6.2 to 9.0) | (6.0 to 8.4) |       | (6.0 to 8.4) |         |
| LDH (U/L)               | 314       | 305   | 315    | 0.24    | 288         | 318      | <0.001| 262     | (212 to 361) |
|                          | (242 to 419) | (231 to 393) | (243 to 422) |         | (214 to 370) | (245 to 427) |       | (240 to 399) |         |
| Ferritin (μg/L)         | 512       | 408   | 546    | <0.001  | 296         | 540      | <0.001| 330     | (240 to 399) |
|                          | (242 to 1027) | (189 to 719) | (256 to 1058) |         | (150 to 793) | (260 to 1048) |       | (237 to 1075) |         |
| CRP (mg/L)              | 72.6      | 63.0  | 73.8   | 0.025   | 56.4        | 74.1     | 0.003 | 42.5    | (9.3 to 117.5) |
|                          | (30.8 to 143.4) | (28.1 to 125.0) | (32.4 to 144.3) |         | (20.8 to 113.7) | (32.5 to 145.3) |       | (32.5 to 140.1) |         |
| ESR (mm/hour)           | 39        | 36    | 39     | 0.086   | 37          | 39       | 0.07  | 31      | (13 to 54) |
|                          | (23 to 60) | (21 to 54) | (23 to 61) |         | (22 to 54) | (23 to 60) |       | (25 to 59) |         |
| Procalcitonin (ng/mL)   | 0.15      | 0.13  | 0.15   | <0.001  | 0.17        | 0.14     | 0.46  | 0.11    | (0.06 to 0.31) |
|                          | (0.09 to 0.39) | (0.07 to 0.20) | (0.09 to 0.34) |         | (0.09 to 0.29) | (0.09 to 0.30) |       | (0.10 to 0.35) |         |
| IL-6 (pg/mL)            | 26.6      | 17.6  | 28.6   | 0.008   | 16.9        | 28.6     | 0.19  | 22.3    | (11.6 to 77.2) |
|                          | (12.9 to 57.6) | (6.9 to 42.2) | (14.3 to 63.6) |         | (14.5 to 44) | (12.6 to 60.6) |       | (12.2 to 63.2) |         |
| Modena PR et al. BMJ Open Resp Res 2021;8:e001038. doi:10.1136/bmjresp-2021-001038 Continued on September 14, 2023 by guest. Protected
associated with decreased COVID-19 severity among older patients, and that current smoking was associated with decreased severity among younger patients, and that current smoking was associated with decreased severity among younger patients. We found an increased risk of severe disease among patients with COPD and prior smoking, independent of age. We also noted differences in inflammatory biomarkers between patients with and without asthma and across smoking statuses. We did not find any evidence of association between use of bronchodilators, inhaled corticosteroids or montelukast prior to hospitalisation and COVID-19 severity.

Our findings extend prior studies that have evaluated the relationship between obstructive lung diseases, smoking and COVID-19 outcomes. While other studies have reported associations between both asthma and COPD and severe COVID-19 outcomes, COPD and severe COVID-19 outcomes, COPD and severe COVID-19 outcomes, COPD and severe COVID-19 outcomes. We also noted differences in inflammatory biomarkers between patients with and without asthma and across smoking statuses. We did not find any evidence of association between use of bronchodilators, inhaled corticosteroids or montelukast prior to hospitalisation and COVID-19 severity.

Two recent meta-analyses confirmed the lack of an association between presence of asthma and mortality, but two large studies in Korea and the UK reported that while asthma in general was not a risk factor for disease severity, asthma exacerbation within the past year was associated with an increased risk for death. Two recent meta-analyses confirmed the lack of an association between presence of asthma and mortality, but two large studies in Korea and the UK reported that while asthma in general was not a risk factor for disease severity, asthma exacerbation within the past year was associated with an increased risk for death. Two recent meta-analyses confirmed the lack of an association between presence of asthma and mortality, but two large studies in Korea and the UK reported that while asthma in general was not a risk factor for disease severity, asthma exacerbation within the past year was associated with an increased risk for death. Two recent meta-analyses confirmed the lack of an association between presence of asthma and mortality, but two large studies in Korea and the UK reported that while asthma in general was not a risk factor for disease severity, asthma exacerbation within the past year was associated with an increased risk for death. Two recent meta-analyses confirmed the lack of an association between presence of asthma and mortality, but two large studies in Korea and the UK reported that while asthma in general was not a risk factor for disease severity, asthma exacerbation within the past year was associated with an increased risk for death.

The mechanism of the observed protective effect of asthma is unclear, and may be in part related to increased care seeking or a lower threshold for hospitalisation among patients with asthma. For example, patients with asthma may be more likely to be hospitalised for milder symptoms and therefore have lower WHO CPS scores. The effect of asthma on the severity of COVID-19 disease may also be determined by the severity of the host. Several investigations have postulated that the allergic phenotype may have a protective effect by reducing the risk of viral infection, but may confer a risk of severe disease. The severe asthma phenotype that is associated with worse outcomes in COVID-19 is often associated with more severe disease. The severe asthma phenotype that is associated with more severe disease. The severe asthma phenotype that is associated with more severe disease. The severe asthma phenotype that is associated with more severe disease. The severe asthma phenotype that is associated with more severe disease. The severe asthma phenotype that is associated with more severe disease. The severe asthma phenotype that is associated with more severe disease. The severe asthma phenotype that is associated with more severe disease. The severe asthma phenotype that is associated with more severe disease. The severe asthma phenotype that is associated with more severe disease. The severe asthma phenotype that is associated with more severe disease. The severe asthma phenotype that is associated with more severe disease. The severe asthma phenotype that is associated with more severe disease. The severe asthma phenotype that is associated with more severe disease. The severe asthma phenotype that is associated with more severe disease. The severe asthma phenotype that is associated with more severe disease. The severe asthma phenotype that is associated with more severe disease. The severe asthma phenotype that is associated with more severe disease. The severe asthma phenotype that is associated with more severe disease. The severe asthma phenotype that is associated with more severe disease.
The observed inverse correlation between current smoking status and COVID-19 severity adds to the existing literature regarding the association between current smoking and risk of SARS-CoV-2 infection, disease severity and mortality.58-57 Our findings contrast with observations from other common respiratory pathogens, including Middle East Respiratory Syndrome, in which smoking has been associated with increased risk of both infection and mortality,58 59 influenza, in which history of smoking is associated with increased risk of hospital admission,60 and respiratory syncytial virus, in which maternal smoking is associated with increased risk of acute lower respiratory infection in children.61 Compared with former smokers and never smokers, current smoking is associated with an increased risk of death from pneumococcal pneumonia.62

Postulated mechanisms for a protective effect of current smoking include an inhibitory effect of nicotine on the production of proinflammatory cytokines and increased tolerance of airway or lung injury among current smokers.63-65 The clinical relevance of these hypotheses cannot be fully tested without accounting for potential confounders, including differences in behaviours leading to SARS-CoV-2 exposure, differences in thresholds for seeking testing, and access to healthcare. While we found evidence of age-specific effects of smoking, it is likely that the effects of smoking are also modified by other host factors that we did not examine, including amount of smoking, type of smoking, race/ethnicity and genetics.

Our study does not address several important questions relating to the effects of obstructive lung disease and smoking on COVID-19 outcomes. First, our cohort is limited to inpatients with COVID-19 and is therefore unable to assess the effect of these risk factors on becoming infected with SARS-CoV-2 or developing mild disease. The small number of children included in the sample (n=16), all of whom were non-smokers, also limits our ability to draw conclusions about children. Second, because the WHO CPS focuses on supportive measures provided during hospitalisation, decisions to forgo life-sustaining treatment including mechanical ventilation, vasopressor support or renal replacement therapy may bias the score downward for some severely ill patients.34

Because of institutional infection control practice patterns, few patients were treated with high-flow oxygen or non-invasive ventilation (WHO CPS 6), and most patients with acute respiratory distress syndrome (ARDS) ultimately developed either severe ARDS or required vasopressors (WHO CPS 8 or higher), which limits our ability to draw conclusions regarding WHO CPS scores 6 and 7. Third, our analysis relies on accurate reporting and abstraction of data from the medical record; these data may be incomplete, especially for patients who did not previously receive their care within the MassGeneral Brigham system. Finally, the presence or absence of obstructive lung disease was determined based on diagnoses present during chart review, which is subject to underdiagnosis, overdiagnosis and misdiagnosis.66-67

In addition, we were unable to characterise or stratify by severity of obstructive lung disease or duration and amount of smoking, which may affect the severity of COVID-19. Further studies are required to evaluate these factors and to test for other potential effect modifiers, including asthma phenotype, the nature of inflammatory responses, and the effects of asthma/COPD treatment. In addition, future studies should examine the effects of these risk factors on the long-term sequelae of COVID-19.

Conclusion
In summary, this study identifies age as a modifying factor for the association between asthma and smoking on severity of COVID-19. Our findings highlight the complexities of determining risk factors for COVID-19 severity, and suggest that predicting disease severity based on single risk factors may not be appropriate.

Acknowledgements The authors wish to thank the dedicated manual chart reviewers and data managers for their efforts in creating the MGH COVID-19 Registry.

Contributors Drafting of the manuscript and statistical analysis was done by PPM, who is also guarantor of the study. Conception and design was done by PPM, DH, and TBK. Acquisition of the data was done by VAT, ASf, IB and ML. Critical revision of the manuscript for important intellectual content was performed by ML, DH, LMY, JL, ET, AAB, VAT, ASF, IB, PLH and TBK.

Funding The authors report the following funding sources: The National Institutes of Health: K23ES030399-03 (PPM), R57AI058736-1651 (IVB), 5K08HL143183 (LY); Weissman Family MGH Research Scholar (IB); the Cystic Fibrosis Foundation (YONKER1800 to LMY); and R01HL132786 and R01AG062393 (VAT). This work was conducted with support from Harvard Catalyst, the Harvard Clinical and Translational Science Center (National Center for Advancing Translational Sciences, National Institutes of Health Award UL 1TR002541) and financial contributions from Harvard University and its affiliated academic healthcare centers. The center is solely the responsibility of the authors and does not necessarily represent the official views of Harvard Catalyst, Harvard University and its affiliated academic healthcare centers, or the National Institutes of Health.

Competing interests Dr Moschovis is a member of an adjudication committee for Pfizer.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data requests will be reviewed by the MGH COVID Registry.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

ORCID iD
Peter P Moschovis http://orcid.org/0000-0002-9664-5959

REFERENCES
1 Stokes EK, Zambrano LD, Anderson KN, et al. Coronavirus Disease 2019 Case Surveillance - United States, January 22-May 30, 2020. MMWR Morb Mortal Wkly Rep 2020;69:759–65.
2 Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFE. Nature 2020;584:430–6.
3 Centers for Disease Control and Prevention. Certain medical conditions and risk for severe COVID-19 illness, 2021. Available: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html [Accessed 3 May 2021].

4 Centers for Disease Control and Prevention. Science brief: evidence used to update the list of underlying medical conditions that increase a person’s risk of severe illness from COVID-19, 2021. Available: https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/underlying-evidence-table.html [Accessed 3 May 2021].

5 Wortham JM, Lee JT, Althomsons S, et al. Characteristics of Persons Who Died with COVID-19 - United States, February 12-May 18, 2020. MMWR Morb Mortal Wkly Rep 2020;69:923–9.
6 Bloom CI, Drake TM, Docherty AB, et al. Risk of adverse outcomes in patients with underlying respiratory conditions admitted to hospital with COVID-19: a national, multicentre prospective cohort study using the ISARIC who clinical characterisation protocol UK. Lancet Respir Med 2021;9:699–711.
7 Guan W-J, Liang W-H, Shi Y, et al. Chronic respiratory diseases and the outcomes of COVID-19: a worldwide retrospective cohort study of 39,420 cases. J Allergy Clin Immunol 2020;146:545–55.
8 Zheng X-Y, Xu Y-J, Guan W-J, et al. Regional, age and respiratory-secretion-specific prevalence of viral respiratory diseases associated with asthma exacerbation: a literature review. Arch Viral 2018;163:845–53.
9 Bafadhel M, McKenna S, Terry S, et al. Acute exacerbations of chronic obstructive pulmonary disease: identification of biologic clusters and their biomarkers. Am J Respir Crit Care Med 2011;184:662–71.
10 Zhang J-J, Dong X, Cao Y-Y, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy 2020;75:1730–41.
11 Mahdavina M, Foster KJ, Jauregui E, et al. Asthma prolongs intubation in COVID-19. J Allergy Clin Immunol Pract 2020;8:3388–91.
12 Yang JM, Koh HY, Moon SY, et al. Allergic disorders and susceptibility to and severity of COVID-19: A nationwide cohort study. J Allergy Clin Immunol 2020;146:790–8.
13 Rabbani G, Shariful Islam SM, Rahman MA, et al. Pre-existing COPD is associated with an increased risk of mortality and severity in COVID-19: a rapid systematic review and meta-analysis. Expert Rev Respir Med 2021;15:705–16.
14 Nuorti JP, Butler JC, Farley MM, et al. Cigarette smoking and invasive pneumococcal disease. active bacterial core surveillance team. N Engl J Med 2000;342:681–9.
15 Ancavi L, Benowitz NL. Cigarette smoking and infection. Arch Intern Med 2004;164:2206–16.
16 Bozinovski S, Vlahos R, Zhang Y, et al. Carbonylation caused by cigarette smoke extract is associated with defective macrophage immunity. Am J Respir Cell Mol Biol 2011;45:229–36.
17 Feldman C, Anderson R. Cigarette smoking and mechanisms of susceptibility to infections of the respiratory tract and other organ systems. J Infect 2013;67:169–84.
18 Gaschler GJ, Zavitz CGJ, Bauer CMT, et al. Cigarette smoke exposure attenuates cytokine production by mouse alveolar macrophages. Am J Respir Cell Mol Biol 2008;38:219–26.
19 Hocking WG, Golde DW. The pulmonary-alveolar macrophage (first of two parts). N Engl J Med 1979;301:580–7.
20 Philipp JC, Aronoff DM, Curtis JL, et al. Cigarette smoke exposure impairs pulmonary bacterial clearance and alveolar macrophage complement-mediated phagocytosis of Streptococcus pneumoniae. Infect Immun 2010;78:1214–20.
21 Buist AS, Vollmer WM, McBurnie MA. Worldwide burden of COPD in high- and low-income countries. Part I. The burden of obstructive lung disease (BOLD) initiative. Int J Tuberc Lung Dis 2008;12:703–8.
22 Coogan PF, Castro-Webb N, Yu J, et al. Active and passive smoking and the incidence of asthma in the black women’s health study. Am J Respir Crit Care Med 2015;191:168–76.
23 Gilliland FD, Islam T, Berhane K, et al. Regular smoking and asthma incidence in adolescents. Am J Respir Crit Care Med 2006;174:1094–100.
24 Strachan DP, Butland BK, Anderson HR. Incidence and prognosis of asthma and wheezing illness from early childhood to age 33 in a national British cohort. BMJ 1996;312:1195–9.
25 Leung JM, Yang CX, Tam A, et al. ACE-2 expression in the small airway epithelia of smokers and COPD patients: implications for COVID-19. Eur Respir J 2020;55:2000688. doi:10.1183/13993003.00688-2020
26 Cai G, Bosse Y, Xiao F, et al. Tobacco smoking increases the lung gene expression of ACE2, the receptor of SARS-CoV-2. Am J Respir Crit Care Med 2020;201:1557–9.
27 Brake SJ, Barnsley K, Lu W, et al. Smoking upregulates angiotensin-converting enzyme-2 (ACE2) receptor: a potential adhesion site for novel coronavirus SARS-CoV-2 (Covid-19). J Clin Med 2020;9:841. doi:10.3390/jcm9030841
28 Sehab Sharif-Akari N, Sehab Sharif-Akari F, Alabed M, et al. Airways expression of SARS-CoV-2 receptor, ACE2, and TMPRSS2 is lower in smokers than in non-smokers and increases with smoking and COPD. Mol Ther Methods Clin Dev 2020;18:1–6.
29 Liu W, Tao Z-W, Wang L, et al. Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. Chin Med J 2020;133:1032–8.
30 Gonzalez-Rubio J, Navarro-Lopez G, Lopez-Najera E, et al. A systematic review and meta-analysis of hospitalised current smokers and COVID-19. Int J Environ Res Public Health 2020;17:7394. doi:10.3390/ijerph17023794
31 Farsalinos K, Barbouni A, Niaura R. Systematic review of the prevalence of current smoking among hospitalised COVID-19 patients in China: could nicotine be a therapeutic option? Emerg Med Int 2020;15:845–52.
32 Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap) – a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42:377–81.
33 Bassett IV, Triant VA, Banda BA, et al. Massachusetts general hospital COVID-19 registry reveals two distinct populations of hospitalized patients by race and ethnicity. PLoS One 2020;15:e0244270.
34 The WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection. A minimal common outcome measure set for COVID-19 clinical research. Lancet Infect Dis 2020;20:e192–7.
35 Rice TW, Wheeler AP, Bernard GR, et al. Comparison of the SpO2/FIO2 ratio and the PaO2/FIO2 ratio in patients with acute lung injury or ARDS. Chest 2007;132:410–7.
36 StataCorp. Stata 16 base reference manual. College Station, TX: Stata Press, 2019.
37 Williams R. Using the margins command to estimate and interpret adjusted predictions and marginal effects. Stata J 2012;12:308–31. doi:10.1177/1536867X1201200209
38 Robinson LB, Fu X, Bassett IV, et al. COVID-19 severity in hospitalized patients with asthma: a matched cohort study. J Clin Immunol 2021;9:497–500. doi:10.1016/j.jci.2020.10.021
39 Wang Y, Chen J, Chen W, et al. Does asthma increase the mortality of patients with COVID-19?: a systematic review and meta-analysis. Int Arch Allergy Immunol 2021;182:76–82.
40 Reyes FM, Hache-Marliere M, Karamanis D, et al. Assessment of the association of COPD and asthma with in-hospital mortality in patients with COVID-19: A systematic review, meta-analysis, and meta-regression analysis. J Clin Med 2021;10:2087. doi:10.3390/jcm10120209
41 Lee SC, Son KJ, Han CH, et al. Impact of comorbid asthma on severity of coronavirus disease (COVID-19). Sci Rep 2020;10:21805.
42 Liu S, Zhi Y, Ying S. COVID-19 and asthma: reflection during the pandemic. Clin Rev Allergy Immunol 2020;59:78–88.
43 Gonzales-van Horn SR, Farrar JD. Interferon at the crossroads of allergy and viral infections. J Leukoc Biol 2015;98:185–94.
44 Carli G, Cecchi L, Stebbing J. Is asthma protective against COVID-19? Allergy 2020. doi:10.1111/all.14471
45 Du H, Dong X, Zhang J-J, et al. Clinical characteristics of 182 pediatric COVID-19 patients with different severities and allergic status. Allergy 2021;76:510–32.
46 Wenzel SE. Asthma phenotypes: the evolution from clinical to pleiotropic aspects of obesity produce distinct asthma phenotypes. Am J Respir Cell Mol Biol 2016;54:601–8.
47 Dixon AE, Poynter ME. Mechanisms of asthma in obesity: pleiotropic aspects of obesity produce distinct asthma phenotypes. Am J Respir Cell Mol Biol 2012;18:716–25.
48 Bates JHT, Poynter ME, Frodella CM, et al. Pathophysiology to phenotype in the asthma of obesity. Ann Am Thorac Soc 2017;14:3895–40.
Open access

51 Popkin BM, Du S, Green WD, et al. Individuals with obesity and COVID-19: a global perspective on the epidemiology and biological relationships. *Obes Rev* 2020;21:e13128.
52 Simonnet A, Chetboun M, Poissy J, et al. High prevalence of obesity in severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation. *Obesity* 2020;28:1195–9.
53 Simons D, Shahab L, Brown J, et al. The association of smoking status with SARS-CoV-2 infection, hospitalization and mortality from COVID-19: a living rapid evidence review with Bayesian meta-analyses (version 7). *Addiction* 2021;116:1319–68.
54 Alqahtani JS, Oyelade T, Aldhahir AM, et al. Prevalence, severity and mortality associated with COPD and smoking in patients with COVID-19: a rapid systematic review and meta-analysis. *PLoS One* 2020;15:e0233147.
55 Patanavanich R, Glantz SA. Smoking is associated with worse outcomes of COVID-19 particularly among younger adults: a systematic review and meta-analysis. *BMC Public Health* 2021;21:1554.
56 Sanchez-Ramirez DC, Mackey D. Underlying respiratory diseases, specifically COPD, and smoking are associated with severe COVID-19 outcomes: a systematic review and meta-analysis. *Respir Med* 2020;171:106096.
57 Taylor EH, Marson EJ, Elhadi M, et al. Factors associated with mortality in patients with COVID-19 admitted to intensive care: a systematic review and meta-analysis. *Anaesthesia* 2021;76:1224–32.
58 Alraddadi BM, Watson JT, Almarashi A, et al. Risk factors for primary middle East respiratory syndrome coronavirus illness in humans, Saudi Arabia, 2014. *Emerg Infect Dis* 2016;22:49–55.
59 Park J-E, Jung S, Kim A, et al. MERS transmission and risk factors: a systematic review. *BMC Public Health* 2018;18:574.
60 Han L, Ran J, Mak Y-W, et al. Smoking and influenza-associated morbidity and mortality: a systematic review and meta-analysis. *Epidemiology* 2019;30:405–17.
61 Shi T, Balsells E, Wastnedge E, et al. Risk factors for respiratory syncytial virus associated with acute lower respiratory infection in children under five years: systematic review and meta-analysis. *J Glob Health* 2015;5:020416.
62 Bello S, Menéndez R, Antoni T, et al. Tobacco smoking increases the risk for death from pneumococcal pneumonia. *Chest* 2014;146:1029–37.
63 Wenzl T. Smoking and COVID-19: a review of studies suggesting a protective effect of smoking against COVID-19. Luxembourg: Publications Office of the European Union, 2020.
64 Mabley J, Gor don S, Pacher P. Nicotine exerts an anti-inflammatory effect in a murine model of acute lung injury. *Inflammation* 2011;34:231–7.
65 Ulloa L. The vagus nerve and the nicotinic anti-inflammatory pathway. *Nat Rev Drug Discov* 2005;4:673–84.
66 Kavanagh J, Jackson DJ, Kent BD. Over- and under-diagnosis in asthma. *Breathe* 2019;15:e20–7.