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Original Research

Multiple manifestations of uncontrolled asthma increase the risk of severe COVID-19

Stina Selberg [a,*], Johanna Karlsson Sundbaum [b], Jon R. Konradsen [c], Helena Backman [d], Linnea Hedman [d], Anne Lindberg [a], Caroline Stridsman [a]

[a] Department of Public Health and Clinical Medicine, Division of Medicine/the OLIN-unit, Umeå University, Umeå, Sweden
[b] Department of Health, Education and Technology, Luleå University of Technology, Luleå, Sweden
[c] Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden
[d] Department of Public Health and Clinical Medicine, Section of Sustainable Health/The OLIN-unit, Umeå University, Umeå, Sweden

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ABSTRACT

Objective: Asthma control is of importance when assessing the risk of severe outcomes of COVID-19. The aim of this study was to explore associations of clinical characteristics and the effect of multiple manifestations of uncontrolled asthma with severe COVID-19.

Methods: In 2014–2020, adult patients with uncontrolled asthma, defined as Asthma Control Test (ACT) ≤19 were identified in the Swedish National Airway Register (SNAR) (n = 24533). The SNAR database, including clinical data, was linked with national registers to identify patients with severe COVID-19 (n = 221). The effect of multiple manifestations of uncontrolled asthma was based on: 1) ACT ≤15, 2) frequent exacerbations and 3) previous asthma inpatient/secondary care and evaluated stepwise. Poisson regression analyses were conducted with severe COVID-19 as the dependent variable.

Results: In this cohort with uncontrolled asthma, obesity was the strongest independent risk factor for severe COVID-19 in both sexes, but even greater in men. Multiple manifestations of uncontrolled asthma were more common among those with severe COVID-19 vs. without: one, 45.7 vs. 42.3%, two, 18.1 vs. 9.1% and three, 5.0 vs. 2.1%. The risk ratio (RR) of severe COVID-19 increased with an increasing number of manifestations of uncontrolled asthma: one, RR 1.49 (95% CI 1.09–2.02), two, RR 2.42 (95% CI 1.64–3.57) and three, RR 2.96 (95% CI 1.57–5.60), when adjusted for sex, age, and BMI.

Conclusions: It is important to consider the effect of multiple manifestations of uncontrolled asthma and obesity when assessing patients with COVID-19, as this increases the risk of severe outcomes substantially.

1. Introduction

During the coronavirus disease 2019 (COVID-19) pandemic, several underlying medical conditions particularly obesity, diabetes and cardiovascular disease were frequently associated with COVID-19 severity [1–3]. Initially, patients with asthma were also presumed to have a higher risk of severe outcomes, as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) results in respiratory manifestations [4]. However, there have been conflicting results on whether asthma is a risk factor for severe COVID-19, which is likely dependent on the complex interplay in asthma between numerous factors involved, such as asthma control and severity, phenotype, medication and other comorbidities [5–8]. In recent times, it has become evident that mainly patients with a more severe and uncontrolled asthma had an increased risk for COVID-19 related hospitalization and death [3,9–13].

Achieving asthma control, is an important and in most cases realistic treatment goal [13–15]. Nevertheless, uncontrolled asthma occurs in all treatment steps, although more common in severe asthma and it affects 20–60% of the patients [14,16,17]. The prevalence of severe asthma is about 4–6% [18,19]. The concepts of severe and uncontrolled asthma can be difficult to differentiate as the definition of asthma severity is based on the level of treatment needed to obtain asthma control [20]. Manifestations of uncontrolled asthma generally include poor symptom control and risk of adverse outcomes, such as exacerbations, sometimes low lung function is also included in the concept [13,14]. To asses asthma control there are several instruments that can be used in the

* Corresponding author. The OLIN studies, Robertsviksgatan 9, SE- 972 41, Luleå, Sweden.
E-mail address: stina.selberg@norrbotten.se (S. Selberg).

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clinic as well as in research, such as the Asthma Control Test (ACT), among others [13,21,22]. When using these instruments, uncontrolled asthma have been shown to associate with female sex, older age, smoking, non-allergic asthma, obesity, depression, and low socioeconomic status [14,16,23–26].

A previous study from the Swedish National Airway Register (SNAR) found that uncontrolled asthma, assessed with ACT, was a strong predictor of severe COVID-19 [11]. Nevertheless, it is still not known which dimensions of uncontrolled asthma that is associated with severe COVID-19. Thus, the aim of this study was to explore associations of clinical characteristics and the effect of multiple manifestations of uncontrolled asthma with severe COVID-19. Our hypothesis is that different manifestations of uncontrolled asthma such as very poorly controlled asthma, exacerbations and low lung function are associated with severe COVID-19, either separately or combined.

2. Materials and methods

2.1. Study design

This is a retrospective cohort study with data from the Swedish National Airway Register (SNAR) which is a national quality register that includes patients in primary and secondary care with a physician-diagnosed asthma (International Classification of Diseases, version 10; ICD-10 J45) or chronic obstructive pulmonary disease (COPD) (ICD-10 J44) [27]. In order to obtain information on severe COVID-19 and other variables of interest, the SNAR database has been linked with registers from the National Board of Health and Welfare including the National Patient Register (NPR), National Cause of Death Register (NCDR) and National Prescribed Drug Register (NPDR), and also with Statistics Sweden's (SCB) registers [28,29]. The study complies with the Declaration of Helsinki and was approved by the Swedish Ethical Review Authority (2020–02777).

2.2. Participants

Patients ≥18 years with an asthma diagnosis (excluding concomitant COPD diagnosis) who had responded to ACT were identified in SNAR between January 2, 2014 and February 29, 2020 (n = 65751). Among these, 37% (n = 24533) had uncontrolled asthma defined as an ACT score of ≤19 [30] and they constituted the study sample.

2.3. Data collection

Included registers, variables and different time-frames of data collection are visualized in Fig. 1. Clinical data were obtained from SNAR between January 2, 2014 and no later than February 29, 2020 i.e. before the COVID-19 pandemic was declared by the World Health Organization (WHO) on March 11th, 2020 [31]. When participants had data from several registrations, we used the last observation carried forward (LOCF) method in order to get the most recent and complete data. Variables analyzed from SNAR were sex, age, Body Mass Index (BMI), smoking habits, ACT scores and lung function. BMI was categorized as normal weight (BMI <25.0) overweight (BMI 25.0–29.9) and obesity (BMI≥30.0) [32]. Smoking habits were divided into two categories; ever smoker (i.e. current smoker and ex-smoker) and non-smoker. Asthma control was further categorized into very poorly controlled, ACT ≤15 [13]. Lung function was assessed through Forced Expiratory Volume in 1 s as percent of predicted value (FEV_1%), and a Swedish reference value was used [33,34]. If post-bronchodilator values were missing, pre-values were used and FEV_1% of predicted was categorized as FEV_1<80% [14,20].

Data on COVID-19 was obtained through mandatory national registries; NPR and NCDR up until December 31, 2020, i.e. before the widespread availability of the COVID-19 vaccines [35]. The diagnoses were based on the ICD-10 codes U07.1 (COVID-19 confirmed by laboratory testing) and U07.2 (COVID-19 clinically or epidemiologically diagnosed, but laboratory testing is inconclusive or not available). A majority of cases, 99% were confirmed by laboratory testing. The definition of severe COVID-19 was hospitalization (identified as primary discharge diagnosis in NPR) and/or death due to COVID-19 (registered as an underlying cause of death in NCDR).

Comorbidities, allergy and asthma medication were classified through dispensed medication in the NPDR using Anatomical Therapeutic Chemical (ATC)-codes between January 1, 2019 and February 29, 2020 (Table 1). Comorbidities were classified into cardiovascular disease, depression and diabetes. Inhaled asthma medications included in the analyses were; short-acting β2-agonists (SABA), short-acting muscarinic antagonists (SAMA), inhaled corticosteroids (ICS), long-acting β2-agonists (LABA), and long-acting muscarinic antagonists (LAMA). A 4-months dispensed coverage of single or combination medication were then used when categorizing inhaled asthma medication into the following groups: no inhalation treatment, only SABA or

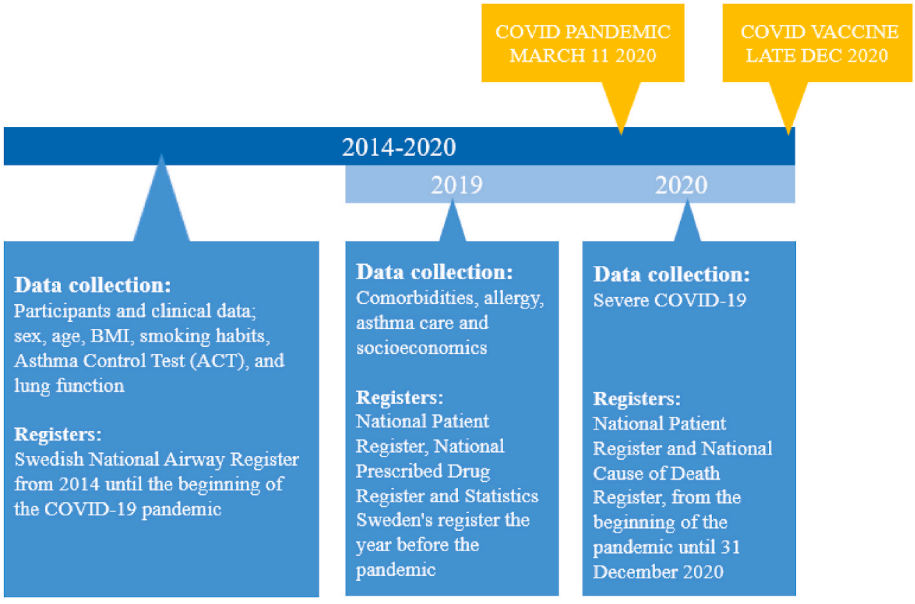


Fig. 1. Flow-chart illustrating year of data collection, variables and registers.

Table 1
Comorbidities, allergy and asthma medication were defined and classified through dispensed medication in the National Prescribed Drug Register (NPDR) and Anatomical Therapeutic Chemical (ATC)-codes between January 1, 2019 and February 29, 2020.

	ATC-code
Medication for comorbidities	
Cardiovascular disease	C01–03, C08, C09
Depression	N06
Diabetes	A10A, A10B
Medication for allergy	R06AE07, R06AX
Inhaled medication	
Short-acting β-agonists (SABA)	R03AC02-03
Short-acting muscarinic antagonists (SAMA)	R03BB01
Long-acting β-agonists (LABA)	R03AC12,13,18,19
Long-acting muscarinic antagonists (LAMA)	R03BB04-07
Inhaled corticosteroids (ICS)	R03BA
ICS/LABA combinations	R03AK
ICS/LABA/LAMA combinations	R03AL08,09,11,12
Other asthma medication	
Leukotriene antagonists (LTRA)	R03DC03
Medication for exacerbations	
Oral corticosteroids (OCS)	H02AB01,02,06

SAMA, only ICS, ICS/LABA and ICS/LABA/LAMA. Dispensed moderate to high dose of inhaled ICS (with or without LABA) were categorized according to the definition in Global Initiative for Asthma (GINA) [13], indicating a more severe asthma. Other asthma medications included in the analyses were leukotriene antagonists (LTRA). Frequent asthma exacerbations were defined as ≥2 oral corticosteroids (OCS) dispensed in 2019. Previous inpatient/secondary care due to asthma were identified from the NPR, defined as patients who had ≥1 inpatient or secondary care visit the year before the pandemic (2019) with a primary ICD-10 code J45 (asthma) or J46 (status asthmaticus).

Multiple manifestations of uncontrolled asthma were studied as one to three of: 1) ACT ≤15; 2) frequent exacerbations; and 3) previous asthma inpatient/secondary care.

Data on level of education was used as a proxy for socioeconomic status and retrieved from SCB registers [28,29] and classified into primary school (≤9 years), secondary school [10–12 years) and tertiary education (>12 years).

2.4. Statistical analysis

All statistical analyses were conducted using IBM SPSS Statistics (Version 27). To asses differences between patients with and without severe COVID-19 independent-sample t-tests and chi-square tests were used. P-values <0.05 were considered statistically significant. Unadjusted Poisson regression analyses were conducted with severe COVID-19 as the dependent variable to estimate risk ratio (RR) and 95% confidence intervals (CI). Thereafter, adjusted Poisson regression models were constructed with severe COVID-19 as the dependent variable, and the statistical significant variables from the unadjusted analyses as independent variables. To increase statistical power in the adjusted models, missing values were handled as a separate category (BMI and FEV_1% of predicted).

3. Results

3.1. Demographic and clinical characteristics

In this cohort of patients with uncontrolled asthma (n = 24533), 1% (n = 221) had severe COVID-19 (Fig. 2). Of these were n = 186 identified as hospitalized due to COVID-19, n = 35 died due to COVID-19 whereof n = 28 at the hospital and n = 7 outside hospital.

Among all participants with uncontrolled asthma women were in the majority (66%), but there was a higher proportion of men in the group with severe COVID-19 than in those without severe COVID-19 (42% vs. 34%, p = 0.012) (Fig. 2). Older age, higher BMI, and dispensed medications for cardiovascular disease, depression, diabetes and allergy were also associated with severe COVID-19. Ever smoking was not associated with severe COVID-19 (Table 2).

A lower ACT score, lower lung function (FEV_1% of predicted) and a moderate/high dose of ICS and LTRA were associated with severe COVID-19, whereas having no dispensed inhaled asthma medication was more common among patients without severe COVID-19. Frequent exacerbations and previous asthma inpatient/secondary care were more common among those with severe COVID-19 (Table 3).

3.2. Clinical characteristics associated with severe COVID-19 in uncontrolled asthma

Adjusted analysis showed that, male sex, older age, overweight, obesity, diabetes and allergy were risk factors for severe COVID-19 among patients with uncontrolled asthma (Fig. 3). When stratified for sex, the analyses revealed that older age, overweight, obesity and allergy were still significant independent risk factors of severe COVID-19 in both sexes. Obesity was the strongest risk factor, but even greater among

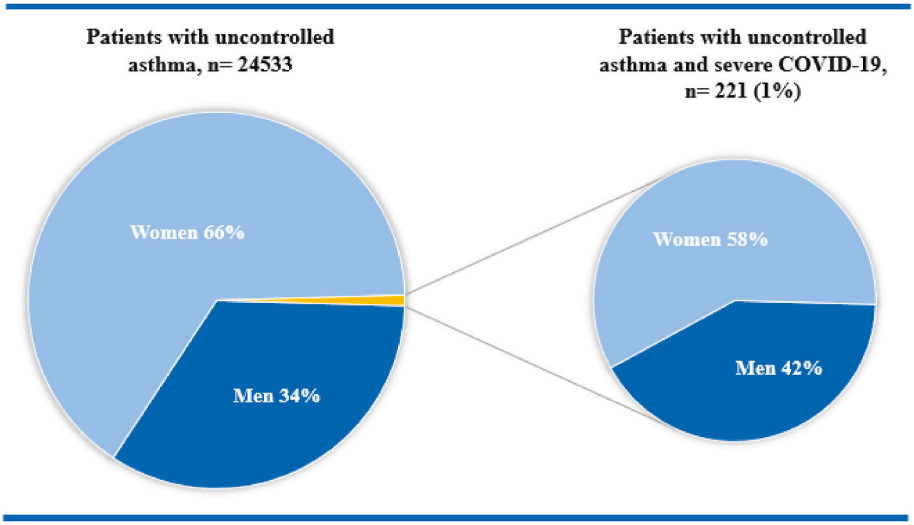


Fig. 2. The prevalence (%) of severe COVID-19 between men and women by chi-square test, p < 0.012 among patients n = 24533 with uncontrolled asthma (ACT≤19) from the Swedish National Airway Register.

Table 2
Clinical characteristics of patients in the Swedish Nation Airway Register (SNAR) uncontrolled asthma cohort, with and without severe COVID-19, by sex and all.

	Severe COVID-19			Without severe COVID-19			
		n = 221			n = 24312		
	Men	Women	All	Men	Women	All	p-value 1
Age (years), mean (sd)	61.8 (15.4)	64.3 (15.4)	63.3 (15.4)	49.1 (18.7)	51.1 (19.2)	50.4 (19.0)	**<0.001**
Level of education							
Primary	20 (21.7)	29 (22.5)	49 (22.2)	2028 (24.8)	3282 (20.8)	5310 (22.1)	
Secondary	51 (55.4)	48 (37.2)	99 (44.8)	3913 (47.9)	6736 (42.6)	10649 (44.4)	
Tertiary	21 (22.8)	52 (40.3)	73 (33.0)	2223 (27.2)	5794 (36.6)	8017 (33.4)	0.991
Body Mass Index (BMI)							
BMI, mean (sd)	31.3 (5.6)	34.1 (25.9)	32.9 (20.1)	28.5 (14.0)	28.6 (14.3)	28.6 (14.2)	**<0.001**
Normal BMI <25	7 (7.8)	18 (14.3)	25 (11.6)	2359 (29.8)	5460 (35.5)	7819 (33.6)	
Overweight, BMI 25–29.9	35 (38.9)	40 (31.7)	75 (34.7)	3111 (39.3)	4701 (30.6)	7812 (33.6)	
Obesity, BMI ≥30	48 (53.3)	68 (54.0)	116 (53.7)	2452 (31.0)	5199 (33.8)	7651 (32.9)	**<0.001**
Smoking habits							
Ever smoker	39 (43.3)	34 (27.2)	73 (34.0)	3023 (38.2)	5391 (35.2)	8414 (36.2)	0.267
Comorbidities							
Cardiovascular disease	58 (63.0)	71 (55.0)	129 (58.4)	2610 (31.5)	5155 (32.2)	7765 (31.9)	**<0.001**
Depression	17 (18.5)	46 (35.7)	63 (28.5)	1239 (14.9)	4054 (25.3)	5293 (21.8)	**0.010**
Diabetes	19 (20.7)	31 (24.0)	50 (22.6)	752 (9.1)	1228 (7.7)	1980 (8.1)	**<0.001**
Allergy	43 (46.7)	62 (48.1)	105 (47.5)	2642 (31.9)	6202 (38.7)	8844 (36.4)	**<0.001**

Notes: The numbers presented are n (%) unless otherwise specified.). [1] P-value comparing patients with and without severe COVID-19. Bold font indicate $p < 0.05$. Missing data n (%): level of education 336 (1.4), BMI 1035 (4.2), smoking habits 1100 (4.5).

Table 3
Asthma specific characteristics of patients in the Swedish Nation Airway Register (SNAR) uncontrolled asthma cohort, with and without severe COVID-19, by sex and all.

	Severe COVID-19			Without severe COVID-19			
		n = 221			n = 24312		
	Men	Women	All	Men	Women	All	p- value[1]
Asthma Control Test (ACT)							
ACT, mean (sd)	14.1 (3.8)	14.3 (3.5)	14.2 (3.6)	15.5 (3.3)	15.1 (3.4)	15.2 (3.4)	**<0.001**
ACT ≤15	47 (51.1)	73 (56.6)	120 (54.3)	3418 (41.2)	7489 (46.8)	10907 (44.9)	**0.005**
Lung function							
FEV_1%, mean (sd)	74.5 (18.9)	78.5 (18.9)	76.8 (19.9)	83.7 (17.3)	82.9 (15.8)	83.1 (16.3)	**<0.001**
FEV_1 <80%	41 (55.4)	55 (52.9)	96 (53.9)	2581 (37.5)	5155 (38.8)	82 (46.1)	**<0.001**
Asthma medication dispensed in 2019							
No inhaled medication	7 (7.6)	6 (4.7)	13 (5.9)	1066 (12.9)	1944 (12.1)	3010 (12.4)	**0.002**
Only SABA or SAMA	7 (7.6)	6 (4.7)	13 (5.9)	512 (6.2)	995 (6.2)	1507 (6.2)	0.495
Only ICS	7 (7.6)	21 (16.3)	28 (12.7)	1946 (23.5)	3933 (24.6)	5879 (24.2)	**<0.001**
ICS/LABA	54 (58.7)	81 (62.8)	135 (61.1)	4017 (48.4)	7813 (48.8)	11830 (48.7)	**<0.001**
ICS/LABA/LAMA	12 (13.0)	14 (10.9)	26 (11.8)	572 (6.9)	937 (5.9)	1509 (6.2)	**0.001**
Moderate/high dose of ICS[2]	50 (54.3)	59 (45.7)	109 (49.3)	3246 (39.1)	6024 (37.6)	9270 (38.1)	**<0.001**
LTRA	31 (33.7)	39 (30.2)	70 (31.7)	1587 (19.1)	3236 (20.2)	4823 (19.8)	**<0.001**
Frequent exacerbations	32 (34.8)	32 (24.8)	64 (29.0)	964 (11.6)	2329 (14.5)	3293 (13.5)	**<0.001**
Asthma inpatient/secondary care in 2019	14 (15.2)	18 (14.0)	32 (14.5)	711 (8.6)	1315 (8.2)	2026 (8.3)	**<0.001**

Notes: The numbers presented are n (%) unless otherwise specified. [1] P-value comparing patients with and without severe COVID-19. Bold font indicate $p < 0.05$. Forced Expiratory Volyme in 1 s (FEV_1) % of predicted, short-acting beta-agonists (SABA), short-acting muscarinic antagonists (SAMA), ICS=Inhaled corticosteroids (ICS), long-acting beta-agonists (LABA), long-acting muscarinic antagonists (LAMA), leukotriene receptor antagonists (LTRA), [2]with or without LABA. Missing data n (%): FEV_1% of predicted 4169 (17.0).

men (RR 4.09, CI 95% 1.82–9.18). Diabetes was a significant risk factor in women only (Fig. 4).

3.3. Multiple manifestations of uncontrolled asthma associated with severe COVID-19

Frequent exacerbations and previous asthma inpatient/secondary care were risk factors for severe COVID-19, but not ACT ≤15, when adjusted for sex, age and BMI (Fig. 5). When comparing patients with and without severe COVID-19: 45.7 vs. 42.3% had one manifestation of uncontrolled asthma, 18.1 vs. 9.1% had two, and 5.0 vs. 2.1% had all three manifestations (all $p < 0.001$). Adjusted analyses showed that the risk of severe COVID-19 increased with an increasing number of multiple manifestations of uncontrolled asthma: one, RR 1.49 (95% CI 1.09–2.02), two, RR 2.42 (95% CI 1.64–3.57) and three, RR 2.96 (95% CI 1.57–5.60), also adjusted for sex, age, and BMI (Fig. 6). A lower lung function (FEV_1 <80% of predicted) was not a significant risk factor when included in the model and the effect on the RR's was negligible (data not shown).

4. Discussion

In this registered-based study including over 20 000 patients with uncontrolled asthma defined as ACT≤19, several different manifestations of poor asthma control were associated with severe COVID-19. It was clear that an even poorer asthma control (ACT ≤15) as well as frequent exacerbations and previous asthma inpatient/secondary care was associated with severe COVID-19. However, in the adjusted analysis only frequent exacerbations and previous asthma inpatient/secondary care persisted as risk factors of severe COVID-19. There is a effect of multiple manifestations of uncontrolled asthma as it increases the risk of severe COVID-19 up to three times. In addition, already known risk

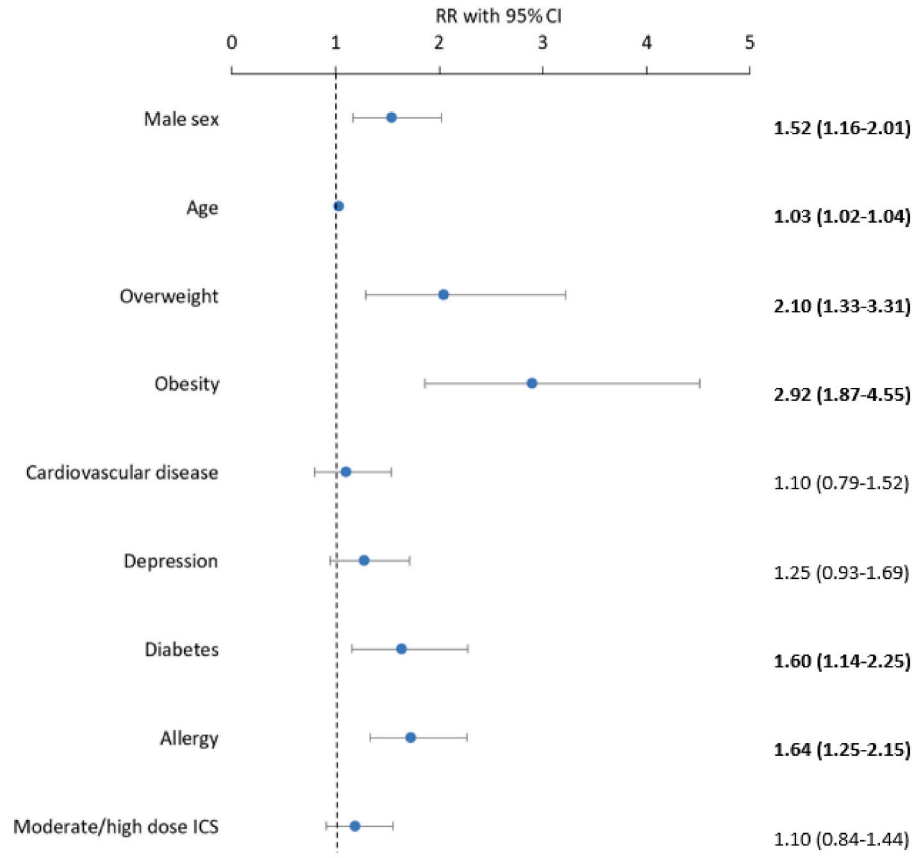


Fig. 3. Risk factor analysis of clinical characteristics for severe COVID-19 among patients with uncontrolled asthma by adjusted Poisson regression, with results presented as risk ratios (RR) with 95% confidence intervals (CI).

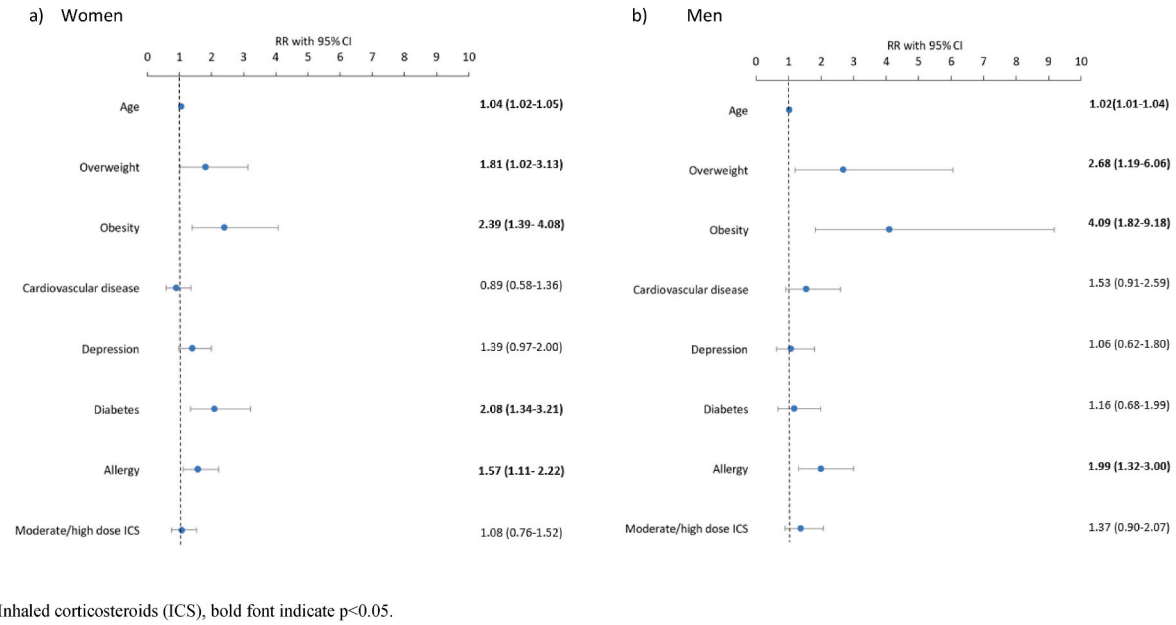
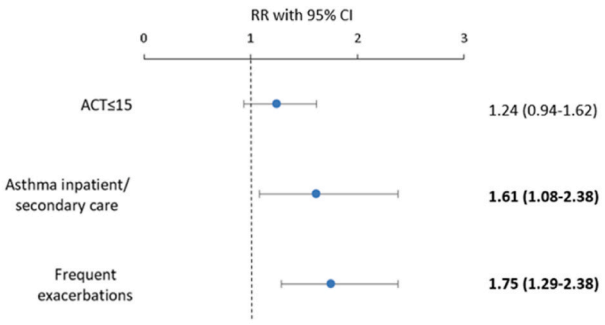


Fig. 4. Risk factor analyses of clinical characteristics for severe COVID-19 stratified by sex among patients with uncontrolled asthma by adjusted Poisson regression models, with results presented as risk ratios (RR) with 95% confidence intervals (CI).

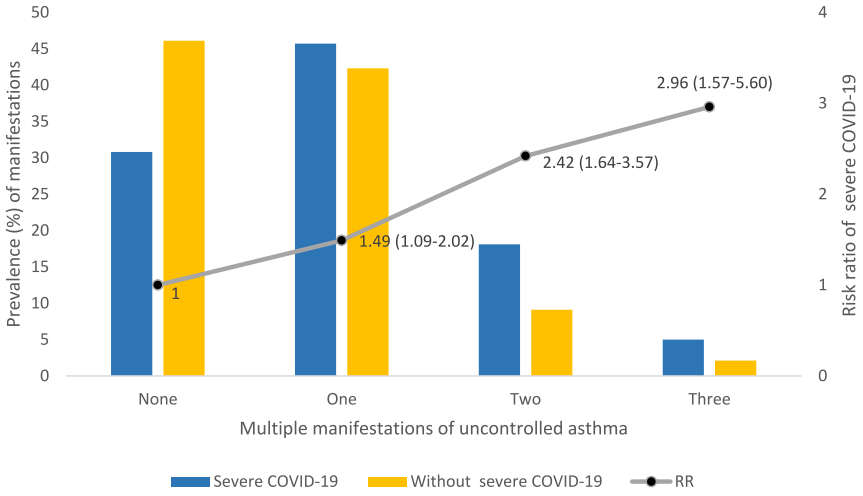
factors sush as older age, male sex, diabetes and obesity were assocatied with severe COVID-19, with obesity being the single most important predictor, especially in men.

The concept of uncontrolled asthma generally includes poor symptom control, and/or frequent exacerbations that require OCS treatment and/or hospitalization [13,14]. Still in studies, uncontrolled asthma is



Asthma Control Test (ACT). The Poisson regression analyses are also adjusted for male sex 1.50 (1.15-1.97), age 1.03 (1.03-1.04), overweight 2.13 (1.35-3.37) and obesity 3.26 (2.11-5.04). Bold font indicate p<0.05.

Fig. 5. Risk factor analysis of different manifestations of uncontrolled asthma for severe COVID-19 among patients with uncontrolled asthma by adjusted Poisson regression, with results presented as risk ratios (RR) with 95% confidence intervals (CI).



Manifestations: Asthma Control Test (ACT) ≤15, frequent exacerbations and previous asthma inpatient/secondary care. Chi- square test assessing differences between patients with and without severe COVID-19, p<0.001.The Poisson regression analyses are also adjusted for male sex 1.51 (1.26-1.98), age 1.03 (1.03-1.04), overweight 2.11 (1.34-3.34) and obesity 3.22 (2.08-4.97). Bold font indicate p<0.05.

Fig. 6. The prevalence of multiple manifestations of uncontrolled asthma and the adjusted risk of severe COVID-19 by Poisson regression risk ratio (RR) (95% confidence intervals (CI)).

defined variously and also interchangeably with severe asthma. These variations make it difficult to compare results between studies. However, our results showed that the effect of multiple manifestations of uncontrolled asthma, even in a population with uncontrolled asthma (here defined as ACT ≤19), significantly increased the risk for severe COVID-19. This highlights the importance of taking different manifestations of uncontrolled asthma into account when assessing patients with asthma and COVID-19. Furthermore, this study has drawn attention to the need for post pandemic research on uncontrolled asthma in relation to outcomes other than severe COVID-19, such as influenza [36].

Frequent exacerbations, ie. ≥2 dispensed OCS, was the manifestation of uncontrolled asthma with the highest risk of severe COVID-19 in our study. The results aligns closely with a previous study from the UK [3], although they defined a recent use of OCS as severe asthma, not uncontrolled as defined in GINA [13]. On the contrary, another study showed no association between asthma exacerbations and severe COVID-19. Instead, they suggested that COVID-19 related hospitalization was associated with severe asthma defined as high-dose ICS according to GINA [37]. In our study, there was an association between severe outcomes in COVID-19 and higher ICS doses, indicating a more severe asthma. However, in the adjusted analysis, higher doses of ICS was not an independent risk factor for severe COVID-19. It is hypothesized that ICS may impart a protective effect against severe COVID-19 by downregulating the angiotensin converting enzyme 2 (ACE2) receptor required for the viral airway infection [37]. Still, previous research are showing conflicting results, both about the risk increasing and the protective effects of ICS in the course of COVID-19 disease [5,12,38], neither of which could be shown in this study.

ERS/ATS international guidelines include FEV_1 <80% predicted in the definition of uncontrolled asthma [14,20]. In our study, patients with severe COVID-19 had a mean value of FEV_1 predicted below 80% while those without severe COVID-19 had higher lung function values. Unfortunately, due to low statistical power, we could not include FEV_1 <80% predicted as an independent manifestation of uncontrolled asthma in the model examining the multiple effect. However, when adjusting the model for FEV_1 <80% predicted, the effect on other manifestations was negligible.

Obesity is a known risk factor in severe COVID-19 [2,3], similarly, poor asthma control is related to obesity [26] suggesting there may be a correlation between these factors. In our study, overweight and obesity were, as expected more prevalent among those with severe COVID-19.

And in addition, obesity was the single most important predictor of severe COVID-19 in both sexes, especially in men. Our result supports that preventive measures against overweight and obesity are of great importance in the care of patients with asthma [26]. In some studies, non-allergic asthma have been shown to be associated with severe COVID-19. This may be due to the protective factor of allergy as it also is linked to a lower expression of the ACE2 receptor [6,8], similar to the ICS hypothesis discussed above [37]. However, in this study, allergy was associated with severe COVID-19. This conflicting result may be due to different definitions of allergy. We defined allergy only on the basis of dispensed antihistamine medication, which may have led to a high specificity especially among patients with a more severe allergy.

4.1. Strengths and limitations

The strength of this study is the large study sample with well-characterized physician-diagnosed patients with asthma. A further strength is the possibility to link data from SNAR to several mandatory national registers with an almost complete coverage rate in order to study severe COVID-19 and other factors of interest. National Cause of Death Register (NCDR) data is of very high quality, but somewhat lower among older individuals with multiple illnesses [39], which in turn are the same patients at higher risk of contracting severe COVID-19. Moreover COVID-19 as a cause of death may have been underreported in the NCDR due to difficulties with registrations at the beginning of the pandemic [40]. This means that we may have underestimated the prevalence of severe COVID-19 in our study.

Although we used ACT, which is a validated and well used instrument to define patients with an uncontrolled asthma, we cannot ignore the risk for selection bias. In healthcare, patients with more symptoms are probably more likely to be asked to respond to the questionnaire. However, in the current study about 60% had a low ICS dose, indicating that patients with both mild and severe asthma are included in the study. Finally, studying the role of asthma in relation to severe COVID-19 is complex. And also that the COVID-19 outcome highly depends on a complicated interaction between the host, virus, and environment [41] of which this study addresses some but not all of the factors.

5. Conclusions

Multiple manifestations of uncontrolled asthma increased the risk of severe COVID-19 up to three times, with frequent exacerbations being the strongest risk factor. This should be taken into account in healthcare when assessing patients with uncontrolled asthma and COVID-19. Moreover, obesity was the single most important risk factor, especially among men with asthma, thus emphasising the need for preventive interventions against obesity. The result of this study is relevant even post pandemic as the coronavirus, SARS-CoV-2 will continue to affect the public health for an unforeseeable period of time. We also see a need for more research on manifestations of uncontrolled asthma in relation to other common infections, such as influenza.

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CRediT authorship contribution statement

Stina Selberg: Conceptualization, Methodology, Formal analysis, Writing – original draft, Visualization, Project administration. **Johanna Karlsson Sundbaum:** Conceptualization, Methodology, Writing – review & editing. **Jon R. Konradsen:** Conceptualization, Methodology, Writing – review & editing. **Helena Backman:** Conceptualization, Methodology, Writing – review & editing. **Linnea Hedman:** Conceptualization, Methodology, Writing – review & editing. **Anne Lindberg:** Conceptualization, Methodology, Writing – review & editing. **Caroline Stridsman:** Conceptualization, Methodology, Resources, Writing – review & editing, Supervision, Funding acquisition.

Declaration of competing interest

Stina Selberg declarations of interest: none.

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