Severe outcomes of COVID-19 among patients with COPD and asthma

Erik Soeren Halvard Hansen, Amalie Lykkemark Moeller, Vibeke Backer, Mikkel Porsborg Andersen, Lars Kober, Kristian Kragholm, Christian Torp-Pedersen

This manuscript has recently been accepted for publication in the *ERJ Open Research*. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJOR online.

Severe outcomes of COVID-19 among patients with COPD and asthma

Erik Soeren Halvard Hansen, MD[1]; Amalie Lykkemark Moeller, MSPH[2]; Vibeke Backer, MD DMSci[1]; Mikkel Porsborg Andersen, MScPH PhD[2]; Lars Kober, MD DMSci[3]; Kristian Kragholm, MD PhD[4]; Christian Torp-Pedersen, MD DMSci[2]

1. Centre for Physical Activity Research, Rigshospitalet, University of Copenhagen, Denmark
2. Department of Clinical Research, Nordsjaellands Hospital, Hillerød, Denmark
3. Department of Cardiology, Rigshospitalet, University of Copenhagen, Denmark
4. Unit of Clinical Epidemiology and Biostatistics and Department of Cardiology, Aalborg University Hospital, Denmark

Corresponding author:

Erik Soeren Halvard Hansen

Rigshospitalet 7641

The Centre for Physical Activity Research

Blegdamsvej 9,

DK-2100, Copenhagen, Denmark

(+45) 42160931

E-mail: eriksorenhalvardhansen@gmail.com

E-mails to authors

Amalie Lykkemark Moeller:	amalie.lykkemark.moeller@regionh.dk
Vibeke Backer:	backer@dadlnet.dk
Mikkel Porsborg Andersen:	mikkel.porsborg.andersen@regionh.dk
Lars Kober:	lars.koeber.01@regionh.dk
Kristian Kragholm:	kdks@rn.dk
Christian Torp-Pedersen:	ctp@heart.dk

Keywords

Asthma, COPD, COVID-19, SARS-COV-2, Epidemiology

Take home message

Patients with chronic obstructive pulmonary disease, but not asthma, have slightly increased risk of severe outcomes of COVID-19 compared with patients without obstructive lung disease. However, in age standardized analysis the risk difference disappears.

Abstract

Introduction: Patients with obstructive lung diseases are possibly at risk of developing severe outcomes of COVID-19. Therefore, the aim with this study was to determine the risk of severe outcomes of COVID-19 among patients with asthma and COPD.

Methods: We performed a nationwide cohort study including patients with COVID-19 from February 1 to July 10, 2020. All patients with COVID-19 registered in the Danish registers were included. With ICD-codes and medication history, patients were divided into asthma, COPD or no asthma or COPD. Primary outcome was a combined outcome of severe COVID-19, intensive care or death.

Results: Among 5104 patients with COVID-19 (median age 54.8 years (25-75th% 40.5 to 72.3); women, 53.0%), 354 had asthma and 432 COPD. The standardized absolute risk of the combined endpoint was 21.2% (95% CI 18.8 to 23.6) in patients with COPD; 18.5% (95% CI 14.3 to 22.7) in patients with asthma and 17.2% (95% CI 16.1 to 18.3) in patients with no asthma or COPD. Patients with COPD had slightly increased risk of the combined endpoint compared with patients without asthma or COPD (Risk difference 4.0%; 95% CI 1.3 to 6.6; P=0.003). In age standardized analyses, there were no differences between the disease groups. Low blood eosinophil counts (<0.3 x 10^9 cells/liter) were associated with increased risk of severe outcomes among patients with COPD.

Conclusion: Patients with COPD have slightly increased risk of developing severe outcomes of COVID-19 compared with patients without obstructive lung diseases. However, in age standardized analysis, the risk difference disappears.

Introduction

The coronavirus COVID-19 pandemic is spreading across the globe infecting millions of people. Vulnerable patient groups infected with SARS-COV-2 are at risk of developing acute respiratory failure ultimately leading to death. Worldwide, it is estimated that 10-20% population have asthma or chronic obstructive pulmonary disease (COPD)[1,2] and thus research into the effects of COVID-19 in these patient groups is critical. Persons with asthma and COPD are potentially more susceptible to severe outcomes of COVID-19 as viral infections affecting the upper or lower airways are some of the leading causes of admissions and exacerbations[3,4]. Recent Asian and European studies have found that COPD is associated with severe outcomes of COVID-19[5,6]. However, similar data on patients with asthma are scarce and evidence on risk factors and patient characteristics within asthma and COPD is lacking. In COPD, high levels of Type 2-inflammation (defined as elevated blood eosinophils) is associated with increased risk of exacerbations[7]. However, in COVID-19, Type 2-inflammation has been suggested as potentially being protective against adverse outcomes of COVID-19[8]. As societies on lock-down are beginning to open up and measures of social distancing are loosened it is becoming clear that SARS-COV-2 will persist in the world as a threat to vulnerable patient groups for several years. This underlines the importance of identifying if people with certain diseases are more prone to severe outcomes of COVID-19 than others. Therefore, through the Danish registries, we sought to investigate whether asthma and COPD are risk factors for severe outcomes of COVID-19. Further, we wanted to investigate whether eosinophilic inflammation was associated frequency of severe outcomes of COVID-19.

Methods

We performed a retrospective cohort study investigating development of severe outcomes of COVID-19 in patients with COPD and asthma registered in the Danish health care system during the COVID-19 pandemic. Patients were included between February 1, 2020 and July 10, 2020. At end of follow-up, 13 015 (0.2%) of the Danish population had tested positive for COVID-19. In Denmark, ethical approval is not necessary for retrospective studies. However, the study was approved by the data responsible institute (The Capital Region of Denmark – approval number P-2019-191). The authors vouch for the integrity of the data and the analyses.

Data sources

We used unique personal identifiers (encrypted CPR) from the Danish administrative registries to link pseudoanonymized data to individual persons. Thereby, data concerning diagnoses from outpatient and hospitalization contacts, hospital procedures, prescription fills, civil and vital status, as well as income and education were collected. From the Danish registries, data on diagnoses from hospitalizations are available from 1978 as well as diagnoses from outpatient contacts are available since 1996; similarly, all procedures are available since 1996 and all prescriptions filled since 1995 can be assessed. The Danish registries have been described in detail previously[9].

Study patients and COVID-19

We included all Danish residents receiving a COVID-19 diagnosis (International classification of diseases, 10th edition (ICD-10): B342A, B972, and B972A). The index date was day of diagnosis/admission for COVID-19.

Severe combined endpoint of COVID-19

We defined a severe combined endpoint of COVID-19 which included diagnosis of COVID-19 with severe respiratory syndrome (ICD-10 code B972A), admission to an intensive care unit (ICU), or death, whichever came first.

Asthma and COPD

Asthma and COPD were primarily defined from ICD-10 codes J43-45. Patients with asthma who were not identified by ICD-code for asthma, due to primary asthma management outside hospital, were defined as asthma based on prescribed medication if they within the last year had filled a minimum of two prescriptions of inhaled corticosteroids[10] or leukotriene receptor antagonists without concurrent use of long-acting muscarinergic antagonists (Figure 1). Patients with COPD who were not identified by ICD-code in a hospital setting for COPD were defined as having COPD based on prescribed medication if they within the last year had filled minimum two prescriptions of long acting beta-agonists or long-acting muscarinergic antagonists without concurrent use of inhaled corticosteroids within the last 12 months. Patients over 60 years with use of long-acting beta agonists in combination with inhaled corticosteroids were considered as COPD. If a patient was diagnosed with both COPD and asthma, the patient was considered as having COPD. To compare our population to the general population, we estimated prevalence of COPD and asthma in the general population by the same criteria. All ICD-10 codes used are displayed in the supplementary material (Supplementary 1 and 2).

Covariates

We estimated current education level; household income; civil status defined as either "Single" or "Cohabiting" and origin defined as either "Danish" or "Immigrant or descendants". Lastly, we calculated comorbidities from the last 10 years based on diagnosis from admissions and filled prescriptions. All definitions and ICD-10 codes for comorbidities are supplied in the supplementary material (Supplementary 1 and 2).

Type 2-inflammation

To evaluate Type 2-inflammation, we included blood eosinophils in our analysis. Blood eosinophil counts were collected from the last five years and the most recent value was chosen for analysis. For analysis, values were factorized into <0.3 x 10^9 and ≥0.3 x 10^9 cells/liter.

Statistical considerations

Comparisons of characteristics among included patients were analyzed by Chi-square-test for categorical variables or Student's t-test for continuous variables. Our primary endpoint was standardized absolute risk for the severe combined endpoint at day 30 after first diagnosis of COVID-19 among patients with asthma, COPD or no obstructive lung disease. We calculated a standardized absolute risk at 30 days after COVID-19 diagnosis for the whole population by using g-formula methods based on multivariable Cox regression[11,12].The Cox proportional hazards model was adjusted for age, sex, education level and a combined covariate for cardiac disease (heart failure, atrial fibrillation or flutter, or ischemic heart disease)[11,13,14]. Variables and comorbidities included in the model were chosen based on that they could impact both the exposure and outcome and that they were available using a directed acyclic graph approach[15,16] (see Figure 4 in Supplementary material). To analyze the impact of increasing age on outcomes of COVID-19 in patients with asthma and COPD, we estimated the age standardized absolute risk of the combined outcome at day 30 and its individual components. This analysis assumes that each patient with COVID-19 could have all ages between 30 and 100 years and calculates the standardized absolute risk given that the patient had the assumed age. The applied Cox proportional hazards model was adjusted for sex, cardiac disease and education level. Lastly, in a complete-case analysis stratified by disease group, we estimated the standardized absolute risk of severe outcomes of COVID-19 at day 30 among patients with low and high levels of eosinophilia in their blood. We calculated an average absolute risk at 30 days after COVID-19 diagnosis for the whole population by using g-formula methods based on multivariable Cox regression[11,12]. Missingness

was rare (<1%), therefore imputation methods were not necessary and all analyses represent complete-case analysis.

All analyses were performed using R Core Team (2019). R: A language and environment for statistical computing. Vienna, Austria. URL https://www.R-project.org/[17].

Results

In this nationwide cohort study, we included 5104 patients with confirmed COVID-19 (Table 1). From these, 354 (6.9%) were defined as having asthma and 432 (8.5%) as having COPD. When using the same diagnostic criteria in the general population we found that 90492/5920253 (1.5%) had COPD and 270772 (4.6%) had asthma. These results indicate that obstructive lung diseases are significantly overrepresented in our sample population (P<0.001) (Figure 1).

Patients with COPD were considerably older at admission compared with patients with asthma and patients without obstructive lung disease (median age 76.8, 47.5 and 53.0 years, respectively) (P<0.001). Level of education and mean household income were generally lower among patients with COPD compared with the other groups. Among patients with asthma, 217/354 (61.3%) were women while patients with COPD and patients without obstructive lung disease showed no obvious differences in sex distribution. In total, 913/5104 (17.9%) were immigrants or descendants of immigrants.

Only 73/432 (16.9%) of COPD patients were under 65 years of age while 291/354 (82.2%) of patients with asthma were younger than 65 years. In comparison, only 33/354 (9.3%) were 75 years or older while among the patients with COPD, 241/432 (55.8%) were 75 years or older.

We estimated use of respiratory treatments within the last 12 months among patients with asthma and COPD split into each generic pharmaceutical substance. In patients with asthma, inhaled corticosteroids of any kind were used by 178/354 patients (50.3%). Compared with patients with COPD, use of leukotriene receptor antagonists, antihistamines and inhaled corticosteroids were more common among patients with asthma. Use of systemic corticosteroids, long-acting beta agonists and long-acting muscarinergic antagonists were more common among patients with COPD compared with patients with asthma. From patients without asthma or COPD, 171/4318 (3.4%) patients had received inhalation therapy of any kind within the last 12 months.

We estimated the standardized absolute risk of the severe combined endpoint within the first 30 days (Figure 2). At day 30, the risk of developing the combined endpoint was 21.2% (95% CI 18.8 to 23.6) in patients with COPD; 18.5% (95% CI 14.3 to 22.7) in patients with asthma and 17.2% (95% CI 16.1 to 18.3) in patients with no asthma or COPD. Patients with COPD had significantly higher risk of developing the combined endpoint than patients without asthma or COPD with a risk difference of 4.0% (95% CI 1.3 to 6.6; P=0.003). There was no significant risk difference for patients with asthma compared with patients without asthma or COPD (1.3%, 95% CI -3.1 to 5.6; P=0.57).

We calculated standardized risks of the individual components of the combined endpoint. We found that patients with COPD had significantly higher risk of being diagnosed with "Severe COVID-19" compared with patients without obstructive lung diseases with a risk difference of 4.7% (95 % CI 1.8 to 7.6; P=0.001). For patients with asthma, the risk difference was 2.1% (95% CI -2.0 to 6.1; P=0.32). Risk of death was higher among patients with COPD compared with patients without asthma or COPD (1.9%, 95%CI 0.1 to 3.6; P=0.035) while patients with asthma did not have increased risk. We observed no differences in risk of admission to ICU between the disease groups.

We calculated standardized risk for the combined outcome at day 30 after diagnosis of COVID-19 assuming that a patient could have all ages between 30 and 100 years (Figure 3). At age 30 years, patients without obstructive lung disease had a mean risk of 2.9% (95% CI 1.8 to 3.9); patients with asthma had a mean risk of 3.2% (95% CI 0.7 to 5.8) and patients with COPD had a standardized risk of 14.1% (95% CI 2.3 to 25.8). At age 50 years, the risk increased to 10.1% (95% CI 8.6 to 11.5) for patients without lung disease; 14.5% (95% CI 6.7 to 22.3) for patients with asthma and 21.0% (95% CI 9.9 to 32.2) for patients with COPD. At age 70, the risk of the combined outcome further increased to 29.2% (95% CI 21.3 to 37.2) for patients without lung disease; 46.6% (95% CI 14.7 to 78.5) for patients with asthma and 33.0% (95% CI 25.3 to 40.7) for patients with COPD. Age standardized risks of the individual components of the combined outcome of severe COVID-

19 were estimated (Figure 4). At age 70, patients with COPD had significantly lower risk of being admitted to an intensive care unit compared with both patients with asthma and no lung disease (P<0.001). Risk of death increased with age in all disease groups. Standardized absolute risks at specific age points with confidence intervals are supplied in the supplementary material (Supplementary 5).

Eosinophilic inflammation

From the total population, 2923/5104 had measured blood eosinophil levels within the last five years. In a complete-case analysis, we estimated the standardized absolute risk at 30 days after diagnosis of COVID-19 in four groups: asthma, COPD, asthma/COPD combined and no asthma/COPD (Figure 6). In patients with COPD, low counts of eosinophils in blood were associated with increased risk of the combined outcome with a risk difference of 18.5% (95%CI 5.9 to 31.1; P=0.002). The same pattern with high eosinophils being protective against severe disease was seen when patients with asthma and COPD were combined (Risk difference 13.6%; 95%CI 4.3 to 22.9; P=0.002).

Discussion

In this retrospective cohort study of Danish COVID-19 patients with asthma, COPD or no obstructive lung disease, we found that patients with COPD had slightly increased risk of a severe combined outcome of COVID-19 while patients with asthma showed no increased risk. When the analyses were standardized by age, the risk differences disappeared. Compared with the general population, patients with asthma and COPD were overrepresented suggesting that they could be more susceptible to COVID-19 requiring hospitalization or medical assistance. Lastly, we found that low counts of blood eosinophils were associated with worse outcomes of COVID-19 in patients with COPD.

Patients with COPD had increased absolute risk of severe COVID-19. However, in age standardized analysis, there were no significant differences in risk between patients with asthma, COPD or no obstructive lung disease suggesting that asthma and COPD might not be independent risk factors for adverse outcomes of COVID-19. Further, patients with COPD were less likely to be admitted to an intensive care unit. This is probably because of the presence of other comorbid conditions which indicates that their recovery potential is low. However, as the primary outcome in this study was a combined outcome of three COVID-19 outcomes, patients with COPD were still at risk of severe COVID-19 and death.

We observed no significant differences in age standardized risk for the combined severe COVID-19 outcome between the disease groups. However, in patients with asthma at age 70 the standardized risk for the combined outcome day 30 increased dramatically to 46.6% but as the confidence intervals are broad, because of the low incidence of COVID-19 in Denmark, this difference was not significant. Further studies investigating outcomes of patients with asthma are warranted to determine whether patients with asthma are at higher risk of severe outcomes of COVID-19.

Interestingly, we found that blood eosinophils were associated with disease outcome among patients with COVID-19 and COPD. It is notable that low levels of eosinophils were associated with worse outcomes of COVID-19 since high levels of eosinophilia is associated with detrimental effects in COPD. It is therefore imperative that the mechanisms and relationships between Type 2-inflammation and outcomes of COVID-19 are assessed in future prospective studies among patients with obstructive lung diseases.

When applying our definition of asthma and COPD to the general population, we observed a relatively low number of patiens with asthma and COPD. A reason for this could be that we did not include short-acting beta agonists as a diagnostic criterion for asthma and COPD since it is difficult to determine whether it was initiated due to asthma, COPD or other reasons.

It is surprising that only 50% of the population with asthma had filled prescriptions with inhaled corticosteroids within the last 12 months as inhaled corticosteroids are considered the cornerstone treatment in asthma. This raises questions whether they are former asthma patients or if it is a matter of poor adherence. From a pulmonary perspective the latter does not seem unlikely and it is possible that this could be associated with their high admission rate[18]. However, it could be that patients with asthma are more aware of their respiratory symptoms and thus are more likely to seek medical care.

A strength with our study is that we can include all patients registered in the Danish registers diagnosed with COVID-19. The Danish health-care system is tax-financed with free universal access and is linked with a personal identification number. This makes us able to connect their COVID-19 diagnose to socioeconomic and medical data before the specific outcome. Therefore, our description of the included population is precise, objective and generalizable.

Our study is limited by its observational nature and as with all register-based studies we are reliant on precise data from clinicians and health-care systems nationwide. This means that our diseases of interest (asthma and COPD) can have been both over- and underdiagnosed. Further, we had no

access to data on degree of airflow limitation and thus, severity of COPD and asthma could only be determined by medication use. In our study, only patients registered with COVID-19 in a hospital setting are included. This means that patients in this study probably have a higher burden of disease and comorbidities compared with COVID-19 patients outside the hospital system. However, during the current pandemic clear guidelines on reporting COVID-19 and related outcomes have been established and this makes us believe that the diagnoses and reporting of severe COVID-19 are precise[19].

In conclusion, patients with COPD had slightly increased standardized absolute risk of a combined outcome of COVID-19 compared with patients without asthma and COPD. However, in age standardized analysis, there were no significant differences disappeared. This suggests that asthma and COPD are not independent risk factors for adverse outcomes of COVID-19. However, patients with asthma and COPD were overrepresented in our population suggesting that patients with pulmonary disease are more susceptible to COVID-19 demanding hospitalization and this should be investigated further.

Acknowledgements

Conflicts of interest

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare no support from any organisation for the submitted work; Dr Hansen has nothing to disclose; Ms Lykkemark Moeller has nothing to disclose; Dr. Backer reports grants, personal fees and other from GSK, Chiesi, Novartis, AstraZeneca, Sanofi, MSD and TEVA; Mr Porsborg-Andersen has nothing to disclose; Dr Kober have received speakers honorarium from Novo Nordisk, Novartis, AstraZeneca and Boehringer unrelated to this manuscript; Dr. Kragholm has received speaker's honoraria from Novartis outside the submitted work; Dr Torp-Pedersen have received study funding from Bayern and Novo Nordisk outside the submitted work. Otherwise, there were no financial relationships over the previous three years with any organisations that might have an interest in the submitted work; and no other relationships or activities that could appear to have influenced the submitted work.

Author contributions

ESH, AML, CTP and VB initiated the study. ESH and AML produced the initial manuscript. ESH, AML and CTP made the initial analyses. All authors contributed to the interpretation of the data and manuscript writing. All authors approved the final manuscript before submitting for publication. ESH and CTP take full responsibility for the results.

Transparency declaration

ESH and CTP affirm that this manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

References

1.   Ntritsos G, Franek J, Belbasis L, et al. Gender-specific estimates of COPD prevalence: A systematic review and meta-analysis. *Int J COPD*. 2018;13:1507-1514. doi:10.2147/COPD.S146390

2.   Hosseini M, Almasi-Hashiani A, Sepidarkish M, Maroufizadeh S. Global prevalence of asthma-COPD overlap (ACO) in the general population: A systematic review and meta-analysis. *Respir Res*. 2019;20(1):4-13. doi:10.1186/s12931-019-1198-4

3.   Wedzicha JA, Seemungal TA. COPD exacerbations: defining their cause and prevention. *Lancet*. 2007;370(9589):786-796. doi:10.1016/S0140-6736(07)61382-8

4.   Rabe KF, Watz H. Chronic obstructive pulmonary disease. *Lancet*. 2017;389(10082):1931-1940. doi:10.1016/S0140-6736(17)31222-9

5.   W.-J. G, W.-H. L, Y. Z, et al. *Comorbidity and Its Impact on 1590 Patients with Covid-19 in China: A Nationwide Analysis*.; 2020. doi:10.1183/13993003.00547-2020

6.   Docherty AB, Harrison EM, Green CA, et al. Features of 16,749 hospitalised UK patients with COVID-19 using the ISARIC WHO Clinical Characterisation Protocol. *medRxiv*. 2020;2(March):2020.04.23.20076042. doi:10.1101/2020.04.23.20076042

7.   Bafadhel M, Peterson S, De Blas MA, et al. Predictors of exacerbation risk and response to budesonide in patients with chronic obstructive pulmonary disease: a post-hoc analysis of three randomised trials. *Lancet Respir Med*. 2018;6(2):117-126. doi:10.1016/S2213-2600(18)30006-7

8. Chhiba KD, Patel GB, Vu THT, et al. Prevalence and characterization of asthma in hospitalized and nonhospitalized patients with COVID-19. *J Allergy Clin Immunol.* 2020;146(2):307-314.e4. doi:10.1016/j.jaci.2020.06.010

9. Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National patient registry: A review of content, data quality, and research potential. *Clin Epidemiol.* 2015;7:449-490. doi:10.2147/CLEP.S91125

10. Backer V, Lykkegaard J, Bodtger U, Agertoft L, Korshoej L, Braüner EV. The Danish national database for asthma. *Clin Epidemiol.* 2016;8:601-606. doi:10.2147/CLEP.S99494

11. Andersen PK, Gill RD. Cox's Regression Model for Counting Processes: A Large Sample Study. *Ann Stat.* 1982;10(4):1100-1120. doi:10.1214/aos/1176345976

12. Hernán M, Robins J. *Causal Inference - Part 2*. Boca Raton: Chapman & Hall/CRC; 2018.

13. COPD Global Initiative. 2020 Report. *Glob Initiat Chronic Obstr Lung Dis.* 2020. https://goldcopd.org/wp-content/uploads/2019/11/GOLD-2020-REPORT-ver1.0wms.pdf Accessed May 19, 2020.

14. Eisner MD, Blanc PD, Omachi TA, et al. Socioeconomic status, race and COPD health outcomes. *J Epidemiol Community Health.* 2011;65(1):26-34. doi:10.1136/jech.2009.089722

15. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. *Epidemiology.* 1999;10(1):37-48. doi:10.1097/00001648-199901000-00008

16. Textor J, van der Zander B, Gilthorpe MS, Liśkiewicz M, Ellison GT. Robust causal inference using directed acyclic graphs: The R package "dagitty." *Int J Epidemiol.* 2016;45(6):1887-1894. doi:10.1093/ije/dyw341

17. R Core Team. R: A language and Environment for Statistical Computing. 2019. https://www.r-project.org/.

18. Mäkelä MJ, Backer V, Hedegaard M, Larsson K. Adherence to inhaled therapies, health

outcomes and costs in patients with asthma and COPD. *Respir Med.* 2013;107(10):1481-

1490. doi:10.1016/j.rmed.2013.04.005

19. Fosbøl EL, Butt JH, Østergaard L, et al. Association of Angiotensin-Converting Enzyme

Inhibitor or Angiotensin Receptor Blocker Use with COVID-19 Diagnosis and Mortality.

JAMA - J Am Med Assoc. 2020;324(2):168-177. doi:10.1001/jama.2020.11301

Figure 1: Flowchart of study population

Figure 1: Flowchart of diagnoses in the study population. First, patients were selected based on ICD-codes. Secondly, we went through medication history to identify patients with asthma or COPD without an ICD-code. Patients identified by ICD-codes did not necessarily use inhaled medication.

Abbreviations: ICD, International classification of diseases, 10th edition; COPD, chronic obstructive pulmonary disease

Figure 2: Prevalence of asthma and COPD in sample population versus general population

Figure 2: Prevalance of COPD and asthma in percents in the sample population versus the general population at May 20, 2020 when using the same definition as in our sample population.

Abbreviations: COVID-19, coronavirus disease; COPD, chronic obstructive pulmonary disease

Figure 3: Standardized absolute risk of combined endpoint for COVID-19 in the first 30 days after diagnosis

Figure 3: Standardized absolute risk of the combined endpoint of COVID-19 in the first 30 days after diagnosis. The lower panel showing the individual parts of the combined endpoints.

Abbreviations: COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease

Figure 4: Standardized absolute risk of the combined outcome of COVID-19 at 30 days by

age

Figure 4: Displayed is the standardized absolute risk showing the relationship between type of chronic disease and risk of the combined endpoint of COVID-19 at day 30 between age 30 years and 100 years. The combined endpoint is a combination of death, severe respiratory syndrome in COVID-19 by ICD-10 codes and admission in an intensive care unit.

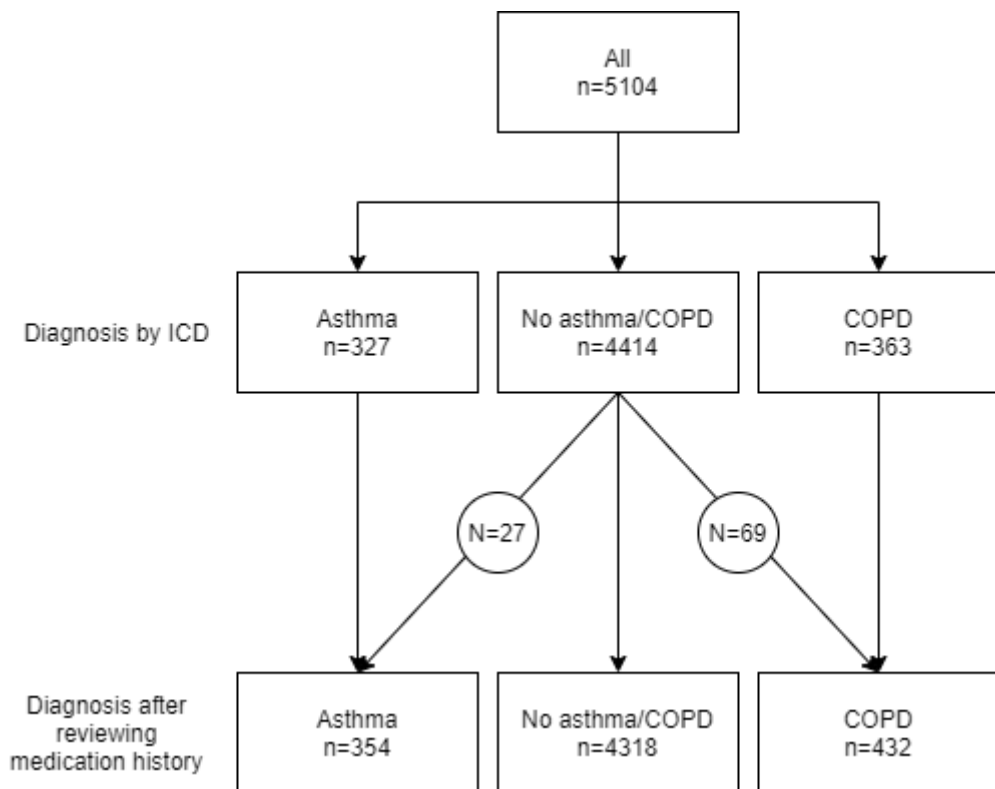Abbreviations: COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease

Figure 5: Components of the standardized risk of the combined outcome of COVID-19 at 30
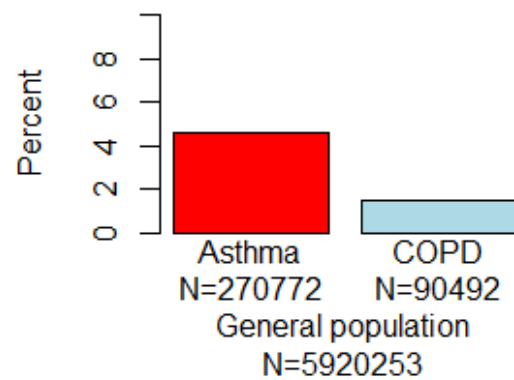
days by age

Figure 5: Displayed is the absolute risk of the individual components of the combined outcome standardized by age.

Abbreviations: COVID-19, coronavirus disease; ICU, intensive care unit; COPD, chronic obstructive pulmonary disease

Figure 6: Risk of severe outcomes of COVID-19 and blood eosinophil values

Figure 6: Displayed are the standardized absolute risks of the combined outcome of COVID-19 given that a patient had low or high levels of blood eosinophils (< or ≥ 0.3 x 10^9 cells/liter). The estimations displayed are the risks at day 30 after first diagnosis of COVID-19.

Combined

ICU

Severe COVID-19

Death

95% confidence band

Disease
Asthma
COPD
No asthma/COPD

Disease	Eos		Estimate (CI$_{95}$)
No asthma/COPD	Normal		24.8 (23.1-26.6)
	Elevated		24.6 (18.6-30.5)
COPD	Normal		44.8 (39.9-49.7)
	Elevated		26.4 (14.6-38.3)
Asthma	Normal		17.0 (12.0-21.9)
	Elevated		9.5 (0.0-19.4)
Asthma/COPD combined	Normal		33.8 (30.1-37.6)
	Elevated		20.2 (11.7-28.8)

Mean risk(%)

0   20   40   60
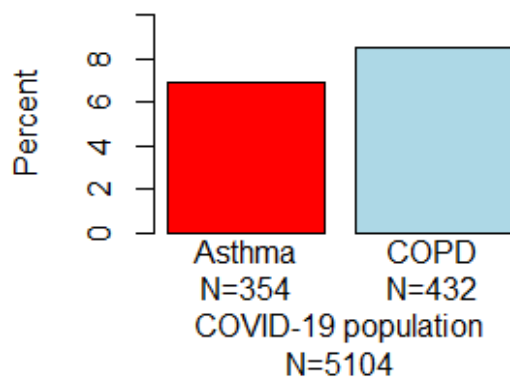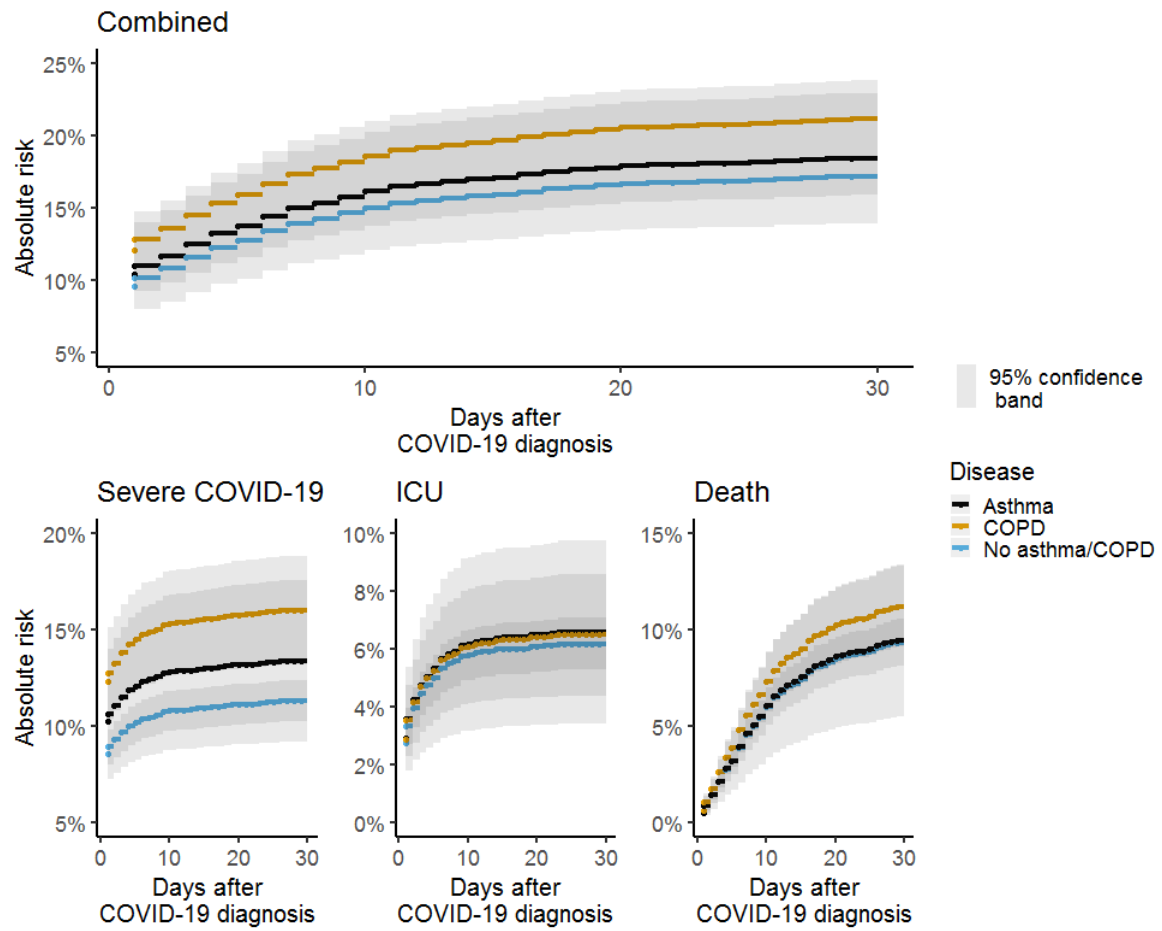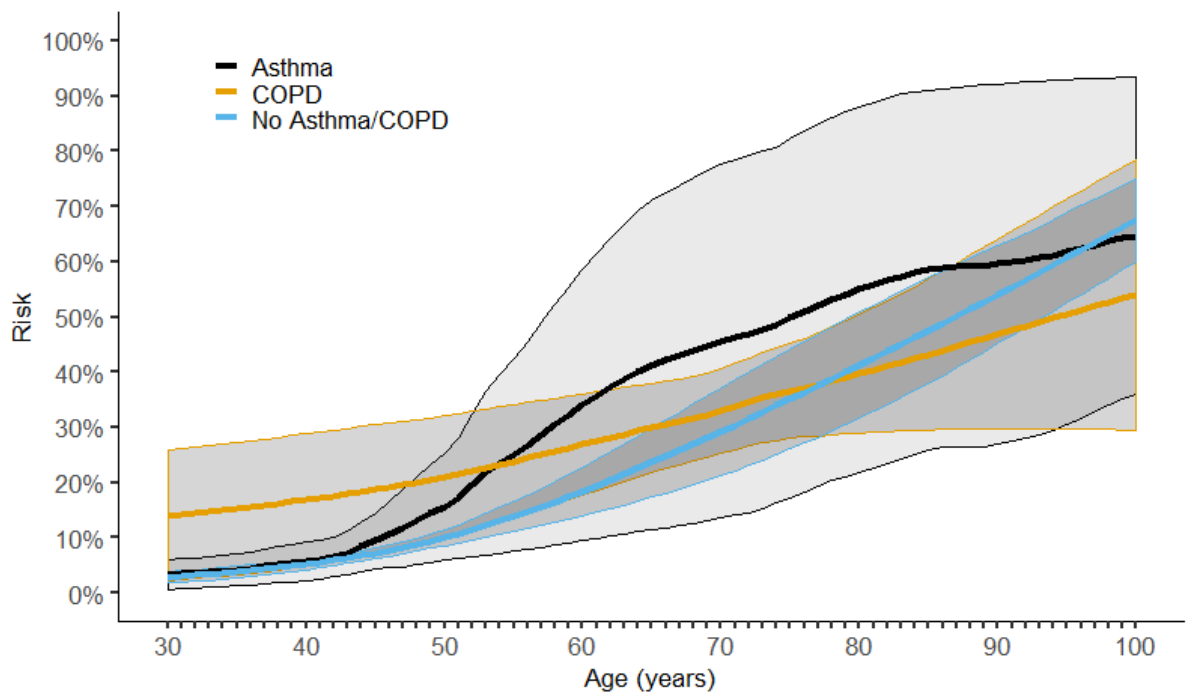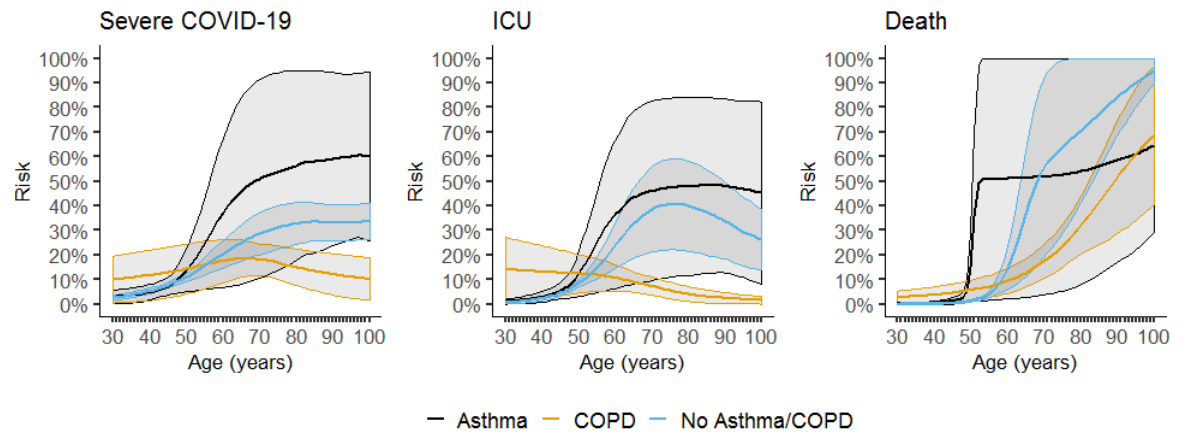
Table 1: Characteristics of included COVID-19 population

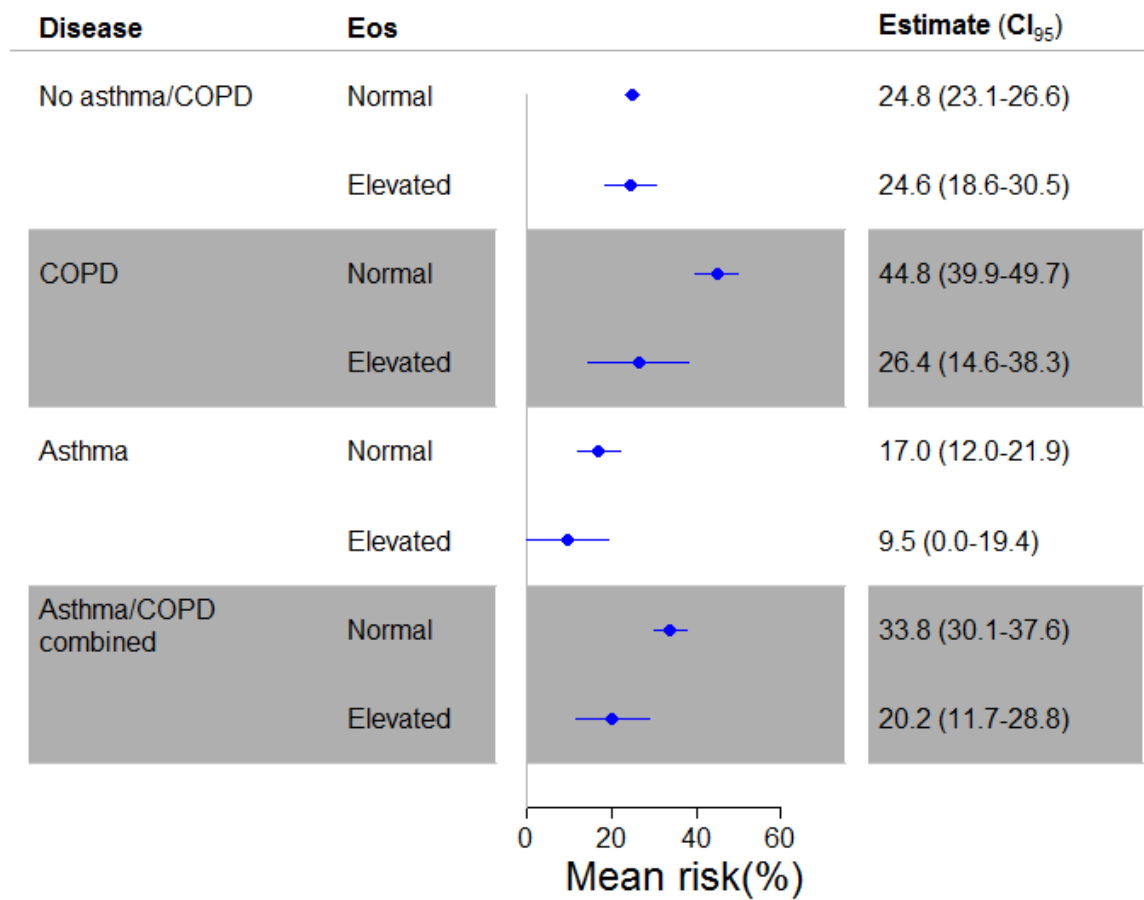| Characteristics	Asthma (n=354)	COPD (n=432)	No asthma or COPD (n=4318)	P-values
Age, median (IQR)	47.5 (24.1)	76.8 (13.7)	53.0 (30.0)	P<0.001
Age groups, No. (%), years				P<0.001
<65	291 (82.2)	73 (16.9)	3036 (70.3)	
65-74	30 (8.5)	118 (27.3)	495 (11.5)	
≥ 75	33 (9.3)	241 (55.8)	787 (18.2)	
Sex, No. (%)				
Female	217 (61.3)	220 (50.9)	2268 (52.5)	
Household income, No. (%), quartiles				P<0.004
Lowest	79 (22.3)	154 (35.6)	1043 (24.1)	
Second lowest	75 (21.2)	176 (40.7)	1025 (23.7)	
Second highest	95 (26.8)	75 (17.4)	1106 (25.6)	
Highest	105 (29.7)	27 (6.2)	1144 (26.5)	
Highest completed education, No. (%)				P<0.001
Upper or lower secondary school	85 (24.0)	188 (43.5)	1096 (25.4)	
Vocational upper secondary school	108 (30.5)	182 (42.1)	1616 (37.4)	
Medium-cycle higher education or bachelors' degree	109 (30.8)	49 (11.3)	1100 (25.5)	
Long-cycle higher education	52 (14.7)	13 (3.0)	506 (11.7)	
Civil status, No. (%)				
Single	116 (32.8)	217 (50.2)	1544 (35.8)	P<0.001
Married or cohabiting	238 (67.2)	215 (49.8)	2774 (64.2)	
Origin, No. (%)				
Danish	281 (79.4)	392 (90.7)	3518 (81.5)	P<0.001
Immigrants or immigrants' descendants	73 (20.6)	40 (9.3)	800 (18.5)	
Comorbidities, No. (%)				
Ischemic heart disease	10 (2.8)	98 (22.7)	271 (6.3)	P<0.001
Previous myocardial infarction	9 (2.5)	96 (22.2)	232 (5.4)	P<0.001
Heart failure	7 (2.0)	83 (19.2)	147 (3.4)	P<0.001
Atrial fibrillation or flutter	27 (7.6)	139 (32.2)	474 (11.0)	P<0.001
Cerebral vascular disease	13 (3.7)	91 (21.1)	276 (6.4)	P<0.001
Diabetes	34 (9.6)	109 (25.2)	455 (10.5)	P<0.001
Chronic kidney disease	7 (2.0)	63 (14.6)	214 (5.0)	P<0.001
Eosinophilic inflammation, mean (SD) [a]				
Blood eosinophilia (x 10^9 cells/liter)	0.17 (0.21)	0.15 (0.14)	0.13 (0.17)	P<0.001
Treatment, No. (%)[b]				
Short-acting beta agonists	112 (31.6)	169 (39.1)	98 (2.3)	P<0.001

Long-acting beta agonist	130 (36.7)	260 (60.2)	23 (0.5)	P<0.001
Long-acting muscarinergic antagonists	17 (4.8)	200 (46.3)	10 (0.2)	P<0.001
Inhaled corticosteroids	178 (50.3)	187 (43.3)	40 (0.9)	P<0.001
Leukotriene receptor antagonists	42 (11.9)	12 (2.8)	0 (0)	P<0.001
Antihistamines	67 (18.9)	47 (10.9)	261 (6.0)	P<0.001
Systemic corticosteroids	41 (11.6)	90 (20.8)	156 (3.6)	P<0.001

Table 1: Total N=5104. Abbreviations: COPD, Chronic obstructive pulmonary disease; No, number; IQR, inter quartile range

[a]From the total population, 2923 patients with COVID-19 had measures of blood eosinophilia within the last five years.

[b]Frequency of different types of medication from the last 12 months were estimated. If a patient received combination therapy, for example inhaled corticosteroids and a long-acting beta-agonist, the medications were split up into their generic forms. Treatment with systemic corticosteroids was defined as any prescription filled within the last 12 months.

Supplementary material

Supplementary 1: Codes used for diseases

Main diseases	
COPD	J43-44
Asthma	J45
Comorbodities	
Ischemic heart disease	I20, I24, I251, I253, I254, I255, I256, I258, I259
Previous myocardial infarction	I21, I22, I25
Heart failure	I099, I110, I130, I132, I255, I425, I426, I427, I429, I428A, P290, I43, I50
Atrial fibrillation or flutter	I48
Cerebral vascular disease	I6, G45, G46, H340
Diabetes	Determined from prescriptions of ATC-codes starting with A10
Chronic kidney disease	N03, N05, Z490, Z491, Z492, N18, N19, I120, I131, N250, Z940, Z992

Supplementary 2: ATC-codes used for medication

|	
Respiratory drugs	R03
Antihistamines	R06
Systemic corticosteroids	H02
Diabetes drugs	A10
Biologic therapies in asthma	Opr-codes under "BOHJ" with diagnosis of action being DJ45

Supplementary 3: Hazard ratios from adjusted Cox's regression model used for risk estimation

Outcome	Disease	Events	P value		Estimate (CI$_{95}$)
Combined	No asthma/COPD	741	1.00		Ref
	Asthma	47	0.56		1.09 (0.81-1.47)
	COPD	198	0.002		1.30 (1.10-1.53)
Severe COVID-19	No asthma/COPD	462	1.00		Ref
	Asthma	35	0.28		1.21 (0.86-1.71)
	COPD	116	<0.001		1.48 (1.20-1.84)
ICU	No asthma/COPD	252	1.00		Ref
	Asthma	17	0.79		1.07 (0.65-1.75)
	COPD	47	0.75		1.05 (0.76-1.46)
Death	No asthma/COPD	419	1.00		Ref
	Asthma	22	0.95		1.01 (0.66-1.56)
	COPD	141	0.028		1.25 (1.02-1.51)

Hazard ratio axis: 0.6 1.0 1.4 1.8

Adjusted hazard ratios for the severe combined outome of COVID-19 from a multivariable Cox's regression model.

Abbreviations: COPD, chronic obstructive pulmonary disease; ICU, Intensive care unit; COVID-19, coronavirus disease.

Supplementary 4: Directed acyclic graph
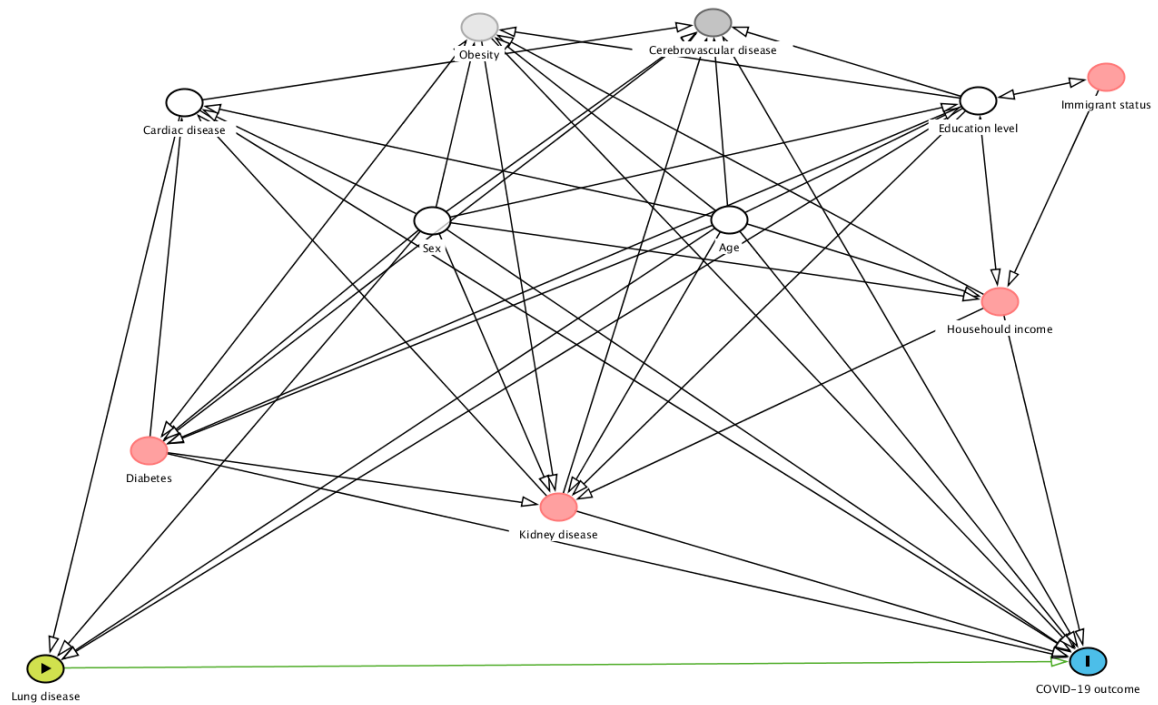
Directed acyclic graph used for assessment of covariates. Minimal required adjustment for model included cardiac disease, age, sex and education level.

Abbreviations: COVID-19, coronavirus disease.

Supplementary 5: Tables of risk estimates at specific ages in the age standardized analysis

Table of standardized risk for the components of the combined endpoint by age for patients with asthma

Age	Severe COVID-19 % (95% CI)	ICU % (95%CI)	Death % (95%CI)
30 years	2.9 (0.1-5.6)	1.1 (0.0-2.1)	0.4 (0.0-0.7)
50 years	13.8 (5.0-22.5)	12.5 (3.1-21.8)	15.2 (1.0-29.4)
70 years	50.8 (10.4-91.2)	46.1 (9.6-82.5)	51.9 (3.7-100.0)

Table of standardized risk for the components of the combined endpoint by age for patients with COPD

Age	Severe COVID-19 % (95% CI)	ICU % (95%CI)	Death % (95%CI)
30 years	10.0 (0.5-19.6)	14.2 (12.3-27.2)	2.8 (0.2-5.4)
50 years	14.3 (4.1-24.4)	12.3 (4.5-20.1)	5.7 (1.6-9.8)
70 years	18.1 (11.7-24.4)	7.3 (3.6-11.0)	17.4 (10.4-24.3)

Table of standardized risk for the components of the combined endpoint by age for patients without asthma or COPD

Age	Severe COVID-19 % (95% CI)	ICU % (95%CI)	Death % (95%CI)
30 years	2.5 (1.5-3.6)	0.7 (0.2-1.2)	0.0 (0.0-0.7)
50 years	10.8 (9.0-12.7)	8.5 (6.9-10.1)	1.3 (0.8-1.8)
70 years	28.6 (20.1-37.1)	38.6 (21.2-55.9)	55.2 (18.8-91.6)