Asthma is not a risk factor for the severity of SARS-CoV-2 infection in the Mexican population

Short title: Asthma and COVID-19

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Author contributions

JMR and MBB were involved in planning and in data collection. All authors were involved in interpretation of results, writing of the manuscript or critically evaluating revisions, and approval of final submission draft.

Abstract

Background. Asthma does not seem to confer a risk for developing a disease caused by 2019 novel coronavirus (COVID-19). The aim of this study was to assess the association between asthma and severity of COVID-19 in the Mexican population.

Methods. In a cross-sectional study, we analyzed the data of the population in Mexico who underwent a test to detect COVID-19 from February 27 to June 21, 2020. The primary outcomes were hospitalization, pneumonia, endotracheal intubation, and death related to COVID-19 in patients with asthma.

Results. Asthma was associated with a lower risk of hospitalization (OR = 0.71, 95% CI 0.66 to 0.76), lower risk of pneumonia (OR = 0.75, 95% CI 0.69 to 0.81), and lower risk of endotracheal intubation (OR = 0.79, 95% CI 0.63 to 0.98). In addition, asthma decreased the risk of dying from COVID-19 (OR = 0.73, 95% CI 0.65 to 0.82). In a subgroup analysis, the same trend was observed in patients who required hospitalization (OR = 0.79, 95% CI 0.69 to 0.90); while in non-hospitalized patients, associations were inconsistent according to the covariates introduced to the models. There was no association between asthma and death in patients admitted to the intensive care unit (ICU); however, in hospitalized patients who did not require ICU management, asthma significantly reduced the risk of dying.

Conclusion. Our results suggest that compared to patients without asthma, patients with asthma are less likely to require hospitalization, develop pneumonia, be intubated endotracheally, or die from COVID-19.

Key words: Asthma; COVID-19; Risk Factors; SARS-CoV-2.

INTRODUCTION

On December 31, 2019, the world learnt about the appearance of an outbreak of atypical pneumonia in China. Soon, it was known that it was caused by a new coronavirus: SARS-CoV-2. It was declared a pandemic by the World Health Organization on March 11, 2020. As of September 18, 2020, more than 30 million cases of COVID-19 had been confirmed in the world, with almost one million deaths.[1] Diabetes, hypertension, heart disease, and obesity are among the comorbid conditions that produce the highest risk of dying from COVID-19.[2,3] Instead, something surprising seems to be happening with asthma patients. It is striking that several reports from different countries indicate that the prevalence of COVID-19 in people with asthma is lower than in the general population;[4] especially since respiratory viruses are among the main agents that exacerbate asthma.[5] With the arrival of SARS-CoV-2; a virus that is transmitted mainly from person to person, it should be expected that a large number of asthmatic patients will be affected; however, this does not appear to be the case. The first analysis that emerged from the place of origin of the epidemic showed that asthma and allergic diseases do not seem to increase the risk of infection by SARS-CoV-2.[4,6,7] On the other hand, some reports have found the opposite.[8,9] Given the inconsistency of results in the literature, the objective of this research is to analyze the association between asthma and the severity of COVID-19 characterized by the need for hospitalization, the requirement for endotracheal intubation, the presence of pneumonia and if it can lead to death.

METHODS

Design

In a cross-sectional design, we analyzed the open database of the Epidemiological Surveillance System for Viral Respiratory Disease in Mexico. The review period ranged from February 27, the date on which the first case of SARS-CoV-2 infection was detected, to June 21, 2020. A total of 479,528 subjects were tested for infection produced by SARS-CoV2.

Sample size

From the total of an initial sample size of 479,528, 62,162 subjects were excluded for any of the following reasons: a) pending test result: 56,590; b) foreign nationality: 2,563; and c) for incomplete data or database failures: 3,009. Finally, of the remaining 417,366 subjects, 239,060 who had a negative result for SARS-CoV-2 were excluded. The final sample consisted of 178,306 confirmed patients.

Data source

The data is extracted from the sentinel surveillance system made up of 475 monitoring units of respiratory diseases (*USMER* as in the Spanish abbreviation), distributed in the 32 states of the national territory. The *USMER* include medical units of the first, second or third level of hospital care. This system allows 10% of cases of ambulatory acute respiratory infections, all severe cases, and associated deaths, to be detected for SARS-CoV-2.

Variables and primary outcomes

The information in the database comes from an epidemiological survey carried out by the Mexican health services that included: age, sex, current smoking history, and comorbidity: asthma, obesity, hypertension, diabetes, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), cardiovascular disease (CVD) and

immunosuppression. It was also questioned whether the patient spoke an indigenous language or not.

When the result of the SARS-CoV-2 test was positive, the following outcomes were recorded: the presence of pneumonia, need for hospitalization, admission to the intensive care unit (ICU), the requirement for endotracheal intubation, and death.

Detection of SARS-CoV-2

The detection of SARS-CoV-2 was carried out by *real-time reverse transcriptase-polymerase chain reaction* (rtRT-PCR*)* in laboratories certified by the National Institute of Diagnosis and Epidemiological Reference.

Ethic

The Government of Mexico, through the General Directorate of Epidemiology, created open-source data regarding COVID-19 cases in the Republic of Mexico which is available to the general population and the scientific community, for public access, use, reuse, and redistribution. In Mexico, the regulation on open data is determined by the decree published in the official gazette of the federation on February 20, 2015. Based on the foregoing, and by article 17 of the Regulations of the General Law of Health in Health Research, the present study is considered without any involvement of a risk as it is a documentary investigation with retrospective analysis of the data. Since its origin, the database does not contain information that allows the identification or location of the subjects under study; and as a result, total confidentiality is guaranteed. The researchers who participated in this analysis declared no conflicts of interest or profit motives.

Data processing

The database was downloaded from the website of the Ministry of Health of the Government of Mexico on June 22, 2020 *(https://www.gob.mx/salud/documentos/datos-abiertos-152127),* which is available in the files with name "*Descriptores_0419.xlsx*" and "*Catalogos_0412.xlsx*" available on the same web page. It was possible to get information about the scale and codes of each variable. The necessary recodifications were made for the statistical analysis.

Statistical analysis

Descriptive statistics were used to express continuous variables and categorical variables. A comparison of proportions between independent groups was performed using the chi-square test. In the univariate analysis, the association between asthma with hospitalization, the development of pneumonia, endotracheal intubation, and patient death was estimated using odds ratios (OR) and a confidence interval (CI) of 95% calculated in a tetrachoric table (2 x 2). In the multivariate analysis, OR and 95% CI were estimated using binary logistic regression. At least one model was completed for the following dependent variables: hospitalization, pneumonia, endotracheal intubation, and death of the patient from COVID-19. The variables introduced in each model were: asthma, diabetes mellitus, hypertension, obesity, COPD, immunosuppression, CVD, CKD, current smoking, belong to any indigenous group of Mexico, sex and age. When the dependent variable was the patient's death, the models also included pneumonia and endotracheal intubation and were performed in the following strata: outpatients, hospitalized patients, admitted to the ICU and not admitted to the ICU. A p-value ≤ 0.05 was considered statistically significant. The data analysis was performed using the IBM SPSS Statistics Version 23.0 software.

RESULTS

Description of the population. 178,306 rtRTPCR-SARS-CoV-2 positive patients were analyzed, most adults (97.7%) and with a slight predominance of men (54.9%). The mean age was 44.1 ± 15.2 years in adults and 8.4 ± 5.8 years in children. In general, the most frequent comorbidity was hypertension (20.2%), followed by obesity (19.7%) and diabetes mellitus (16.6%); the prevalence of asthma was 2.8%. Regarding the severity of COVID-19, 31.5% required hospitalization, 24.5% developed pneumonia, 2.8% required endotracheal intubation, and 12.0% died (Table 1).

Asthma frequency. The frequency of asthma was lower in hospitalized subjects (p < 0.0001), with pneumonia (p < 0.0001), who required endotracheal intubation (p <0.0001) or who died (p <0.0001) (Table 2).

Association of asthma with hospitalization, pneumonia and endotracheal intubation. Table 3 shows that asthma was associated with a lower risk of hospitalization (OR = 0.71, 95% CI 0.66 to 0.76) (Model I), of pneumonia (OR = 0.75, 95% CI 0.69 to 0.81) (Model II) and endotracheal intubation (OR = 0.79, 95% CI 0.63 to 0.98) (Model III). In contrast, diabetes mellitus and obesity were identified as significant risk factors in all three models (OR > 1). On the other hand, hypertension (OR > 1.5), COPD (OR > 2), immunosuppression (OR > 1.5), CVD (OR > 1) and CKD (OR > 1) behaved as risk factors significant for hospitalization and pneumonia, but not for endotracheal intubation. Belonging to one of the original peoples of Mexico and being man were also identified as risk factors in the three models (OR > 1), while adults had a higher risk of hospitalization (OR > 1) and pneumonia (OR > 2). Finally, smoking was not identified as a risk factor, on the contrary, it was associated with a lower probability of hospitalization and pneumonia.

Association of asthma with the death of the patient by COVID-19. Table 4 shows that when analyzing all patients, asthma was identified as a factor that decreased the risk of dying in Model I (OR = 0.78 95% CI 0.70 to 0.87), II (OR = 0.69, 95% CI 0.62 to 0.77), and III (OR = 0.73, 95% CI 0.65 to 0.82). Similar results were observed when analyzing patients whose management was in hospital (models I, II and III: OR = 0.82 95% CI 0.72 to 0.93; OR = 0.76, 95% CI 0.67 to 0.86; and OR = 0.79, 95% CI 0.69 to 0.90; respectively). On the other hand, if only patients who were not hospitalized (outpatient treatment) were analyzed, the association continued with this trend (OR < 1) but only reached statistical significance in model II (p = 0.047). On the other hand, no association was found between asthma and death in patients admitted to the ICU (p> 0.05). Finally, when hospitalized patients who did not require admission to the ICU were analyzed, again asthma behaves; in the three models, as a factor that significantly reduces the risk of dying.

Risk of death from COVID-19 associated with pneumonia and endotracheal intubation. Pneumonia showed a strong association with death in non-hospitalized people (up to OR = 31.17, p < 0.0001 in the model I), but in the presence of endotracheal intubation and other covariates, its association strength decreases. For its part, endotracheal intubation was always associated with death in all models (OR ≈ 4, p <0.0001).

Risk of death from COVID-19 associated with comorbid conditions. Diabetes, hypertension, obesity, COPD, immunosuppression, CVD, and CKD were identified as significant risk factors for patient death in most models. This became more evident when analyzing all the patients excluding the patients admitted to the ICU.

Risk of death associated with other conditions. Belonging to an indigenous group of Mexico, man sex, and adulthood behaved as significant risk factors for death from

COVID-19 in most models. Instead, the patient's current smoking was identified as a factor that decreased the risk of dying in the total sample or in those who took their treatment outside the hospital.

DISCUSSION

Our analysis has shown that the prevalence of asthma in patients with COVID-19 was close to 3%, an amount that is lower when compared to the prevalence reported in adults (5.0%)[10] and children (5.8% to 7.5%)[11] of our country.

Asthma and hospitalization

Previous studies have shown that 35% of patients with COVID-19 have a risk of hospitalization[2] related to age, diabetes, obesity or high blood pressure;[3] but instead, asthma does not seem to increase it due to COVID-19.[6,12] In the United States, emergency medical care needs due to asthma were markedly reduced at the onset of the pandemic.[13] In our analysis, patients with asthma were less likely to be hospitalized, even after adjusting the sex and age. In this regard, tomographic images of patients with asthma and COVID-19 have shown less involvement of lungs,[14,15] which would explain a lower risk of asthma exacerbation. This is very striking if we consider that, in addition to exposure to aeroallergens, viral infections are among the main causes of exacerbation of asthma. Unfortunately, it was not possible to evaluate SARS-CoV-2 infection as a causative agent of asthma exacerbation, and therefore, as a reason for additional hospitalization.

Asthma and pneumonia

We found that asthmatics had a lower probability of developing pneumonia which could explain the lower risk of hospitalization as mentioned previously. In a previous study of 768 hospitalized patients, patients with asthma had less involvement of the lung

parenchyma than controls without asthma,[14,15] which would produce a lower probability of being detected with pneumonia at the time of physical examination. On the other hand, the use of inhaled steroids for asthma control seems to be related to less severity of pneumonia.[15]

Asthma and endotracheal intubation

In our study, the prevalence of patients who required endotracheal intubation (2.8%) was lower than the 4.7% which is reported in China.[4] Furthermore, we observed that patients with asthma had a lower probability of endotracheal intubation. Similarly, two recent studies showed similar findings.[6,16] The protective effect in patients with asthma and the probability of being intubated may arise from the lower severity of COVID-19, as presented in our results.

Asthma and mortality

The development of pneumonia, endotracheal intubation (only in hospitalized patients), a history of diabetes, hypertension, obesity, COPD, immunosuppression, CVD and CKD, in addition to some demographic characteristics such as belonging to an indigenous group, and being an adult man were identified as risk factors for death from COVID-19 in Mexico. But in the case of asthma, it is striking that it remained independently associated with a lower probability of death. Until now, most of the available studies that have investigated this issue have shown inconsistent results. [6,12,16-18] In another investigation, the number of asthma cases was so poor that it did not allow the authors to carry out a conclusive analysis.[19] In England, Williamson et al. analyzed the data corresponding to more than 17 million people to identify factors associated with the death from COVID-19, In the case of asthma, it was asthmatic patients who had previously used systemic steroids who were more likely to die compared with asthmatics

who had not used them.[20] Similar findings were observed in Kuwait.[21] Thus, the protective effect of asthma on the development of SARS-CoV-2 pneumonia and the decrease in the probability of being intubated by COVID-19 seem to be the best explanation for this event.

At the beginning of the pandemic, it was observed in China that people with an allergic disease were not more susceptible to COVID-19.[4,6,7] Some studies have shown inverse results mentioning that the asthma patients are more likely to be hospitalized for severe COVID-19 or have a positive test for SARS-CoV-2; however, when patients are stratified according to the presence of an allergy, it is the non-allergic asthmatics who make the difference.[8,9] An important factor related to a lower risk of SARS-CoV-2 infection is the use of steroids for asthma control; asthmatic patients using inhaled steroids express much less ACE2 and TMPRSS2.[23] Interestingly, patients with asthma or allergic rhinitis tend to express this receptor much less when challenged with aeroallergens.[24] Nasal or airway cells that come from patients with allergic rhinitis or high T2 asthma, and that are stimulated with IL-13 *ex vivo*, have been shown to markedly reduce the expression of ACE2 and increase that of TMPRSS2.[25] On the other hand, viral load is a determining factor that has been related to mortality from COVID-19;[26] thus, as asthmatics express fewer ACE2 receptors, less severe conditions would be expected. Finally, it has been described that innate immunity against the virus in asthma patients is reduced as compared to the non-asthmatics; interferon production is decreased as a consequence of an increase in Th2 pathway signalling and allergic inflammation.[27]

Other findings

It was observed that patients who speak an indigenous language had a higher risk of presenting hospitalization, pneumonia, endotracheal intubation or dying from COVID-19.

Currently, in Mexico, 68 indigenous peoples share risk factors such as language barriers, difficulty in accessing the internet, exposure to biomass, lack of access to health services, and a high prevalence of comorbidity.[28]

In the epidemiological survey, it was the patient himself who made the self-report of asthma. There was also no information to assess the effect on COVID-19 of inhaled or systemic steroids, the presence of an allergy, and the severity of asthma.

Additional limitations were the lack of information on the treatment used to control the remaining comorbidity and COVID-19. Finally, since the sentinel model implemented in our country consist of a sample of 10% of the infected population, deficiencies in the sampling may limit our statistical extrapolations.

Our results suggest that patients with asthma are less likely to require hospitalization, develop pneumonia, be intubated, or die from COVID-19 than those without asthma. As is the case in most emerging disease epidemics, knowledge changes day by day and advances at dizzying steps, so more studies are required to demonstrate the consistency with our findings.

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Table 1. Characteristics of patients with COVID-19

	Total n = 178, 306	
	n	%
Sex, men	97,912	54.9
Age category		
Pediatric	4,140	2.3
Adult	174, 166	97.7
Indigenous languages	2,028	1.1
Current smoker	14,142	7.9
Asthma	4,942	2.8
Diabetes	29,587	16.6
Hypertension	35,953	20.2
Obesity	35,212	19.7
COPD	3,019	1.7
Immunosuppression	2,489	1.4
CVD	4,258	2.4
CKD	3,920	2.2
Severity of COVID-19		
Pneumonia	43,639	24.5
Hospitalization	56,190	31.5
ICU	4,883	2.7
Endotracheal intubation	5,004	2.8
Death	21,444	12.0

COVID-19: Coronavirus disease-19.

COPD: Chronic obstructive pulmonary disease.

CVD: Cardiovascular disease.

CKD: Chronic kidney disease.

ICU: Intensive care unite.

Table 2. Univariate analysis between asthma and COVID-19 severity in 178,306 rtRT-PCR-SARS-CoV-2 positive patients

			OR	95% CI	*p*
Asthma, n (%)	Hospitalized patients n = 56,190	Non-hospitalized patients n = 122,116			
Yes	1,287 (2.3)	3,655 (3.0)	0.76	0.71 – 0.81	< 0.0001
No	54,903 (97.7)	118,461 (97.0)	1		
	Pneumonia n = 43,639	Non-pneumonia n = 134,667			
Yes	1,008 (2.3)	3,934 (2.9)	0.79	0.73 – 0.84	< 0.0001
No	42,631 (97.7)	130,733 (97.1)	1		
	Endotracheal intubation * n = 5,004	Non-endotracheal intubation * n = 51,130			
Yes	93 (1.9)	1,193 (2.3)	0.79	0.64 – 0.98	0.032
No	4,911 (98.1)	49,937 (97.5)	1		
	Death n = 21,444	Survived n = 156,862			
Yes	440 (2.1)	4,502 (2.9)	0.71	0.64 – 0.78	< 0.0001
No	21,004 (97.9)	152,360 (97.1)	1		

* Calculated only in those patients who were hospitalized (n = 56,190) of which 56 subjects were excluded because it was not known whether they required endotracheal intubation.

Table 3. Multivariate analysis of the association between asthma with hospitalization, pneumonia and endotracheal intubation in patients with COVID-19

	Model I Dependent variable: Hospitalized patients n = 173, 535*			Model II Dependent variable: pneumonia n = 173,535*			Model III Dependent variable: endotracheal intubation n = 54,859**		
	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*
Asthma									
Yes	0.71	0.66 – 0.76	< 0.0001	0.75	0.69 – 0.81	< 0.0001	0.79	0.63 – 0.98	0.033
No	1			1			1		
Diabetes									
Yes	2.74	2.66 – 2.82	< 0.0001	2.35	2.29 – 2.42	< 0.0001	1.25	1.17 – 1.34	< 0.0001
No	1			1			1		
Hypertension									
Yes	2.13	2.07 – 2.19	< 0.0001	1.84	1.79 – 1.89	< 0.0001	1.03	0.96 – 1.10	0.402
No	1			1			1		
Obesity									
Yes	1.16	1.13 – 1.19	< 0.0001	1.25	1.22 – 1.29	< 0.0001	1.36	1.28 – 1.46	< 0.0001
No	1			1			1		
COPD									
Yes	2.71	2.49 – 2.94	< 0.0001	2.04	1.88 – 2.20	< 0.0001	1.12	0.96 – 1.31	0.156
No	1			1			1		
Immunosuppression									
Yes	2.17	1.99 – 2.37	< 0.0001	1.74	1.59 – 1.90	< 0.0001	0.84	0.68 – 1.03	0.084
No	1			1			1		

CVD									
Yes	1.45	1.35 – 1.55	< 0.0001	1.32	1.23 – 1.41	< 0.0001	1.09	0.94 – 1.25	0.257
No	1			1			1		
CKD									
Yes	2.39	2.22 – 2.58	< 0.0001	1.59	1.49 – 1.71	< 0.0001	0.97	0.84 – 1.12	0.675
No	1			1					
Current smoker									
Yes	0.89	0.85 – 0.92	< 0.0001	0.96	0.92 – 0.996	0.032	0.95	0.86 – 1.06	0.362
No	1			1			1		
Indigenous languages									
Yes	1.43	1.30 – 1.57	< 0.0001	1.60	1.45 – 1.76	< 0.0001	1.39	1.12 – 1.71	0.002
No	1			1			1		
Sex									
Men	1.69	1.66 – 1.73	< 0.0001	1.60	1.56 – 1.63	< 0.0001	1.40	1.32 – 1.50	< 0.0001
Women	1			1			1		
Age category									
Adult	1.42	1.31 – 1.54	< 0.0001	2.44	2.18 – 2.73	< 0.0001	0.81	0.63 – 1.05	0.115
Pediatric	1			1			1		

OR calculated by logistic regression. Reference category: OR = 1. The variables were entered using the Enter method in successive blocks until the final model presented is reached.

* Missing values: n = 4771. ** Missing values: n = 1331

COPD: Chronic obstructive pulmonary disease

CVD: Cardiovascular disease.

CKD: Chronic kidney disease.

Table 4. Multivariate models of the association between asthma and death of COVID-19 adjusting by comorbidity, severity disease, language, smoking, age and sex

	Model I			Model II			Model III		
	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*
All patients*									
Asthma	0.78	0.70 – 0.87	< 0.0001	0.69	0.62 – 0.77	< 0.0001	0.73	0.65 – 0.82	< 0.0001
Pneumonia	14.70	14.21 – 15.21	< 0.0001	12.00	11.60 – 12.43	< 0.0001	11.40	11.01 – 11.81	< 0.0001
Diabetes				1.70	1.63 – 1.76	< 0.0001	1.71	1.65 – 1.78	< 0.0001
Hypertension				1.87	1.81 – 1.94	< 0.0001	1.90	1.83 – 1.97	< 0.0001
Obesity				1.04	1.01 – 1.09	0.028	1.06	1.02 – 1.10	0.003
COPD				1.95	1.78 – 2.14	< 0.0001	2.02	1.84 – 2.22	< 0.0001
Immunosuppression				1.27	1.13 – 1.41	< 0.0001	1.32	1.18 – 1.47	< 0.0001
CVD				1.27	1.17 – 1.39	< 0.0001	1.29	1.19 – 1.41	< 0.0001
CKD				1.95	1.79 – 2.11	< 0.0001	1.93	1.78 – 2.10	< 0.0001
Current smoker							0.90	0.85 – 0.95	< 0.0001
Indigenous languages							1.23	1.08 – 1.41	0.002
Sex (men)							1.54	1.48 – 1.59	< 0.0001
Adult							3.01	2.39 – 3.80	< 0.0001
Non-hospitalized patients **									
Asthma	0.91	0.70 – 1.18	0.459	0.76	0.58 – 0.997	0.047	0.79	0.60 – 1.05	0.104
Pneumonia	31.17	28.56 – 34.02	< 0.0001	25.91	23.67 – 28.36	< 0.0001	25.17	22.96 – 27.60	< 0.0001
Diabetes				2.55	2.29 – 2.84	< 0.0001	2.58	2.31 – 2.87	< 0.0001
Hypertension				2.26	2.04 – 2.51	< 0.0001	2.27	2.04 – 2.53	< 0.0001
Obesity				1.28	1.15 – 1.42	< 0.0001	1.32	1.19 – 1.47	< 0.0001
COPD				2.85	2.24 – 3.62	< 0.0001	3.09	2.42 – 3.95	< 0.0001
Immunosuppression				1.16	0.84 – 1.61	0.360	1.18	0.85 – 1.66	0.326
CVD				1.15	0.91 – 1.46	0.250	1.18	0.92 – 1.50	0.186
CKD				2.53	2.00 – 3.19	< 0.0001	2.66	2.10 – 3.37	< 0.0001
Current smoker							0.74	0.62 – 0.88	0.001
Indigenous languages							1.93	1.40 – 2.67	< 0.0001
Sex (men)							2.08	1.89 – 2.30	< 0.0001
Adult							5.29	2.19 – 12.80	< 0.0001
Hospitalized patients ***									

Table 4. Multivariate models of the association between asthma and death of COVID-19 adjusting by comorbidity, severity disease, language, smoking, age and sex

	Model I			Model II			Model III		
	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*
Asthma	0.82	0.72 – 0.93	0.002	0.76	0.67 – 0.86	< 0.0001	0.79	0.69 – 0.90	< 0.0001
Pneumonia	1.94	1.86 – 2.02	< 0.0001	1.91	1.84 – 2.00	< 0.0001	1.89	1.81 – 1.97	< 0.0001
Endotracheal intubation	4.00	3.75 – 4.26	< 0.0001	4.06	3.81 – 4.33	< 0.0001	3.97	3.72 – 4.24	< 0.0001
Diabetes				1.29	1.23 – 1.34	< 0.0001	1.29	1.24 – 1.34	< 0.0001
Hypertension				1.54	1.48 – 1.61	< 0.0001	1.55	1.48 – 1.61	< 0.0001
Obesity				0.97	0.93 – 1.01	0.169	0.98	0.93 – 1.02	0.257
COPD				1.49	1.36 – 1.64	< 0.0001	1.50	1.37 – 1.66	< 0.0001
Immunosuppression				1.11	0.99 – 1.25	0.075	1.17	1.04 – 1.31	0.010
CVD				1.19	1.09 – 1.30	< 0.0001	1.21	1.11 – 1.32	< 0.0001
CKD				1.53	1.41 – 1.67	< 0.0001	1.51	1.39 – 1.65	< 0.0001
Current smoker							0.98	0.92 – 1.05	0.591
Indigenous languages							1.09	0.94 – 1.27	0.234
Sex (men)							1.24	1.19 – 1.29	< 0.0001
Adult							3.51	2.73 – 4.51	< 0.0001

Table 4. Multivariate models of the association between asthma and death of COVID-19 adjusting by comorbidity, severity disease, language, smoking, age and sex

	Model I			Model II			Model III		
	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*
ICU[‡]	1.12	0.76 – 1.66	0.561	1.001	0.68 – 1.48	0.995	0.96	0.64 – 1.43	0.826
Asthma	2.44	1.95 – 3.05	< 0.0001	2.39	1.91 – 3.00	< 0.0001	2.23	1.77 – 2.81	< 0.0001
Pneumonia	4.62	4.07 – 5.23	< 0.0001	4.62	4.07 – 5.25	< 0.0001	4.45	3.91 – 5.06	< 0.0001
Endotracheal intubation				1.12	0.98 – 1.29	0.097	1.09	0.95 – 1.26	0.225
Diabetes				1.39	1.21 – 1.59	< 0.0001	1.36	1.18 – 1.56	< 0.0001
Hypertension				1.04	0.91 – 1.20	0.560	1.03	0.90 – 1.19	0.661
Obesity				1.54	1.08 – 2.18	0.017	1.57	1.09 – 2.25	0.015
COPD				1.17	0.80 – 1.72	0.413	1.31	0.88 – 1.94	0.180
Immunosuppression				0.92	0.68 – 1.23	0.555	0.94	0.70 – 1.27	0.692
CVD				1.36	0.99 – 1.87	0.059	1.34	0.97 – 1.85	0.076
CKD							0.99	0.78 – 1.25	0.903
Current smoker							1.20	0.74 – 1.94	0.457
Indigenous languages							1.08	0.94 – 1.24	0.285
Sex (men)							3.64	2.23 – 5.94	< 0.0001
Adult									
Non-ICU[‡‡]									
Asthma	0.80	0.70 – 0.91	0.001	0.74	0.64 – 0.85	< 0.0001	0.77	0.68 – 0.89	< 0.0001
Pneumonia	1.93	1.85 – 2.02	< 0.0001	1.91	1.83 – 1.99	< 0.0001	1.88	1.80 – 1.97	< 0.0001
Endotracheal intubation	3.80	3.48 – 4.16	< 0.0001	3.85	3.52 – 4.21	< 0.0001	3.73	3.41 – 4.10	< 0.0001
Diabetes				1.30	1.25 – 1.36	< 0.0001	1.31	1.25 – 1.37	< 0.0001
Hypertension				1.56	1.49 – 1.63	< 0.0001	1.56	1.50 – 1.63	< 0.0001
Obesity				0.96	0.92 – 1.01	0.100	0.97	0.92 – 1.01	0.172
COPD				1.49	1.35 – 1.64	< 0.0001	1.50	1.35 – 1.65	< 0.0001
Immunosuppression				1.10	0.98 – 1.24	0.118	1.15	1.02 – 1.30	0.027
CVD				1.23	1.12 – 1.35	< 0.0001	1.24	1.13 – 1.37	< 0.0001
CKD				1.54	1.41 – 1.68	< 0.0001	1.52	1.39 – 1.66	< 0.0001
Current smoker							0.98	0.92 – 1.05	0.598
Indigenous languages							1.08	0.93– 1.26	0.318
Sex (men)							1.26	1.21 – 1.31	< 0.0001

Table 4. Multivariate models of the association between asthma and death of COVID-19 adjusting by comorbidity, severity disease, language, smoking, age and sex

	Model I			Model II			Model III		
	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*
Adult							3.52	2.62 – 4.74	< 0.0001

COPD: Chronic obstructive pulmonary disease. CVD: Cardiovascular disease. CKD: Chronic kidney disease. ICU: Intensive Care Unit.
OR: odds ratio calculated by logistic regression. The variables entered were dichotomous. In each variable, the reference group is the complementary category. The selection of the variables of each model was carried out using the "Enter method" in successive blocks until reaching the final model that is presented.
Model II: adjusted for comorbidity.
Model III: also adjusted for smoking, indigenous language, age and sex.
Sample size of the models:
*All patients: n = 178,306, except in model III where n = 173,535
** Non-hospitalized patients: n = 122,116, except in model III where n = 118,625
*** Hospitalized patients: n = 56,134, except in model III where n = 54,859
‡ Hospitalized patients who required admission to the ICU: n = 4,883, except in model III where n = 4714
‡‡ Hospitalized patients who did not require admission to the ICU: n = 51,251, except in model III where n = 50,145.