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ORIGINAL RESEARCH

Asthma and COVID-19 Outcomes: A Prospective Study in a Large Health Care Delivery System

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Video abstract

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Introduction: Previous studies on the outcomes of asthma and COVID-19 have shown inconsistent results. This study aimed to elucidate the association between asthma and COVID-19 outcomes.

Methods: We conducted a prospective study with a large health plan to compare the incidence of COVID-19 infection, hospitalization and ICU admission in a cohort of 41,282 patients with asthma and a 1:1 age-, sex-, and race-ethnicity-matched cohort without asthma across the following pandemic periods: pre-Delta (03/01/2020 to 05/31/2021), Delta (06/01/2021 to 12/31/2021), and Omicron (01/01/2022 to 08/13/2022). Demographic factors, comorbidities, COVID-19 test results, inpatient utilization, and COVID-19 vaccination status were collected from electronic health records.

Results: Subjects with asthma were more likely than controls to undergo COVID-19 testing during the three pandemic periods and were less likely to test positive in the Omicron period (fully adjusted odds ratio=0.92; 95% CI=0.86–0.98; p=0.01). Relative to controls, patients with asthma had an increased risk of hospitalization for COVID-19 (fully adjusted hazard ratio=1.33; 95% CI=1.08–1.64; p=0.01) and borderline significant (p=0.05) higher rates of ICU admissions in the pre-delta period but not during the delta or Omicron periods. The increased risk of COVID-19 hospitalization associated with asthma was more pronounced in patients with severe asthma and in women compared with men. None of the associations were significantly modified by vaccination status.

Conclusion: Asthma was associated with a lower risk of COVID-19 infection but only during the Omicron period. Asthma was an independent risk factor for hospitalization for COVID-19 in the pre-delta period and this association was stronger for severe asthma and in women.

Keywords: asthma, COVID-19, severe asthma, cohort study

Background

Since the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in December 2019, identifying individuals at risk for severe coronavirus disease (COVID-19) has been a priority. The Centers for Disease Control and Prevention (CDC) have reported several risk factors for COVID-19, including age greater than 65 years, immunosuppression, and chronic conditions.[1] Patients with underlying respiratory disorders, including asthma, were included given their compromised pulmonary system prior to COVID-19.[2]

Asthma is a highly prevalent chronic respiratory condition affecting over 300 million people worldwide.[3] It is well established that asthma exacerbation is associated with respiratory viruses.[4] Furthermore, during the H1N1 2009 influenza pandemic, individuals with asthma were reported to have higher rates of pneumonia and intensive care unit (ICU) admissions.[5] However it remains unclear whether asthma is a risk factor for COVID-19.

The available literature on asthma and COVID-19 outcomes is inconsistent[6–15] and, with one exception,[14] is based on data from the early (pre-delta) stages of the pandemic. Other limitations of prior studies include not considering the deployment of COVID-19 vaccines and not systematically examining possible effect modification by the severity of asthma.

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To shed light on the epidemiological association between asthma and COVID-19 outcomes (infection and hospitalization) and to overcome the limitations of prior research, we conducted a large prospective, longitudinal, population-based cohort study of asthma patients and controls incorporating the three pandemic periods (pre-delta (March 1, 2020, through May 31, 2021), delta (June 1, 2021, through December 31, 2021), and omicron (January 2022 through August 31, 2022), as well as data on COVID-19 vaccines and subgroup analyses by severity of asthma.

Methods

Study Setting and Cohorts

This prospective study utilized data collected using the electronic health record (EHR) and database registries across the Kaiser Permanente Northern California (KPNC) region. The KPNC provides comprehensive healthcare to approximately one-third of the population in the greater San Francisco and Sacramento metropolitan areas. The asthma cohort was identified using the KPNC Adult Asthma Registry on 03/01/2020, which includes patients 18–85 years old meeting at least one HEDIS criteria, namely:1) emergency department visits or hospitalization for asthma; 2) had four or more asthma prescriptions filled in a 12-month period; 3) four or more outpatient asthma visits and filled 2 asthma prescriptions in any 12 months; or 4) prescription of six rescue inhalers in any 12 months or 2 ambulatory corticosteroid treatment prescriptions. Patients with asthma were excluded if they had a prior diagnosis of COPD, interstitial lung disease (ILD), bronchiectasis, or KPNC membership of less than 3 months during the observation period. A consort diagram of the derivation of the asthma cohort is shown in Figure 1. A matched cohort with no evidence of utilization for asthma (outpatient visits, hospitalization, or prescriptions for asthma) or any of the three respiratory conditions listed above was identified and matched 1:1 based on birthyear (± 1 year), sex, and race/ethnicity. An index date was assigned to each control corresponding to the asthma diagnosis date of the matched case, and controls were also required to have at least 3 months of follow-up. This study was approved by the KPNC Regional Institutional Review Board. All the data accessed complied with relevant data protection and privacy regulations.

Data were collected on demographics (age, sex, race/ethnicity), comorbidities (ascertained up to 5 years prior to asthma diagnosis or index date of controls), body mass index (BMI, in Kg/m^2), smoking status, polymerase chain reaction (PCR) COVID-19 tests, hospitalization, ICU admission and death due to COVID-19 from March 1, 2020, through August 31, 2022. A widely used measure of socioeconomic status, the neighborhood deprivation index (NDI),[16,17] was derived for each subject using the 2010 US Census data. For smoking and BMI, we used observations closest to baseline (03/01/2020). Univariate case-control cohort comparisons of baseline characteristics were performed using *t*-tests for continuous variables and chi-square tests for categorical variables. Owing to the changing nature of the COVID-19 pandemic, we stratified the modeling by the predominant COVID-19 variant (Pre-delta, Delta, Omicron). The

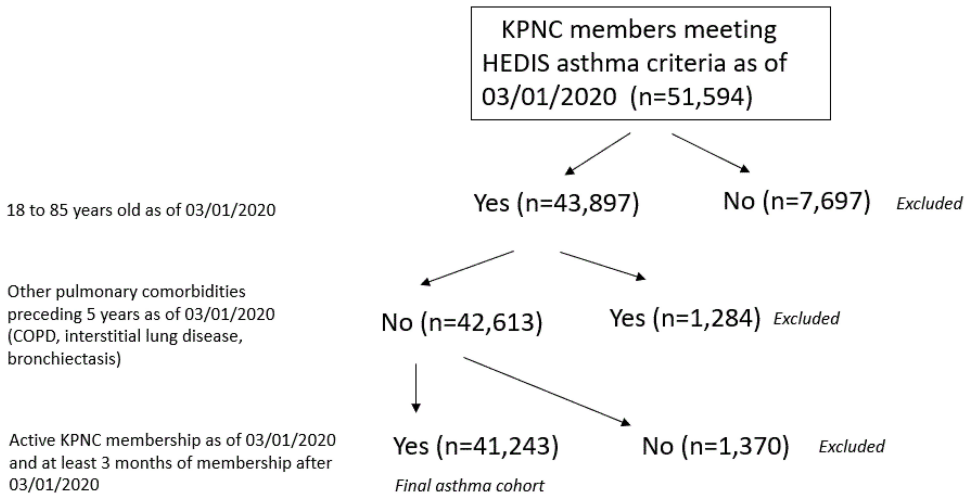

Figure 1 Consort diagram of asthma cohort derivation.

COVID-19 vaccination status was defined as unvaccinated, complete primary series, complete primary series plus any number of boosters, or other (partial, mixed, or unapproved). The primary series consisted of 2 doses of Pfizer, 2 doses of Moderna or 1 dose of Janssen. In each period, the odds of a positive COVID-19 PCR test were estimated using multivariable logistic regression, first adjusted for age, sex, race/ethnicity (these three variables by design), and NDI (Model 1) and then adjusted for Model 1 covariates plus BMI, smoking, number of comorbidities, and vaccination status (Model 2). We also performed a sensitivity analysis including all comorbidities individually as dummy (yes/no) variables, and results did not materially change (data not shown). Vaccination status was entered as a categorical variable with 4 levels, as described above. The hazard ratio of hospitalization for COVID-19 was estimated using Cox proportional hazard regression accounting for matching and sampling[18] and the same model-building strategy as described above for COVID-19 PCR test results. To address missing data on BMI, smoking and NDI we created missing level indicators variable for missingness and entered these variables in the regression models. In addition to stratification by pandemic period, we performed period-specific analysis of the three outcomes stratified by vaccination status, namely those who received complete primary series, complete primary series plus any number of boosters, or other vs those who remained unvaccinated. To further disentangle the complex relationship between asthma and COVID-19, we examined the main clinical endpoint, hospitalization due to COVID-19, stratified by the severity of asthma. To capture severe asthma we built upon a previously validated definition of severe asthma[19] and defined it as a history of asthma exacerbation (ER visit and/or hospital admission for asthma and/or one or more oral steroid bursts) and/or use of biologics (omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab) and/or FEV1 < 70% predicted and/or at least one prescription of oral steroids for ≥ 30 days, all within two years prior to baseline. Finally, because differences exist in the epidemiology of both asthma and COVID-19 by sex, we assessed sex-specific effects of asthma on the risk of COVID-19 hospitalization.

Results

There were 41, 243 subjects in each cohort (Table 1); the mean (SD) age (as of 03/01/2020) in each cohort was 54.7 (15.6) years. In both cohorts, there were more women than men (63 vs 37%) and 45% of the participants were non-white. The asthma cohort had a significantly higher prevalence of obesity and higher percentage of former smokers. Although the overall distributions of NDI differed significantly between asthma cases and controls, there was no difference in the proportions in quintile 5 of the NDI (9% in both cohorts). A higher prevalence of diabetes, hypertension, allergic rhinitis, and respiratory tract infections was observed in the asthma cohort than in the control cohort (Table 1).

Subjects with asthma were more likely to undergo PCR COVID-19 testing during the three pandemic periods (50% vs 36% in pre-delta, 38% vs.25% in delta, and 37 vs 25% in omicron; all p<0.0001) (Table 2). However, there were (consistently across pandemic periods) no statistically significant differences (p>0.05) between the cohorts in the number of positive tests among those tested:10% in pre-delta, 8% in delta and 26–27% in the omicron period (Table 2). The hospitalization rate for COVID-19 was higher in patients with asthma than in controls in the pre-delta period (57.6 vs 33.1 per 10,000 person-years, respectively; P <0.0001). In contrast, the hospitalization rates for COVID-19 were not significantly elevated in the asthma cohort relative to the control cohort in the delta period (49.9 vs 43.1 per 10,000 person-years, respectively; p=0.28) or omicron period (49.0 vs 46.2 per 10,000 person-years, respectively; p=0.60) (Table 2). ICU admissions due to COVID-19 were borderline higher (p=0.05) in asthma subjects compared to controls in the pre-delta period and did not differ between cohorts in the delta and omicron periods (Table 2). Death rates due to COVID-19 were not significantly higher in the asthma cohort than in the control cohort in the pre-delta and delta periods (p≥0.09) and were the same in the omicron period (Table 2). Vaccination status differed significantly between the cohorts in each period (p<0.0001). In the pre-delta period, 18% of asthma patients and 31% of control patients remained unvaccinated. The corresponding figures were 11% and 24% in the delta period and 11% and 23% in the omicron period.

Figure 2 depicts the time course of the COVID-19 pandemic in the asthma cases and controls. Panel A shows the monthly aggregate number of people with positive PCR results. Both groups experienced a pre-delta peak in December 2020, a shallow wave in the delta period (August 2021), the most pronounced peak of the entire pandemic in the omicron period (January 2022), and a second omicron wave in June 2022. The reason why there were more absolute numbers of asthma patients with COVID-19 infection than controls is simply because more asthma patients

Table 1 Baseline Characteristics of Asthma and Control Cohorts

	Asthma Cohort n=41,243	Control Cohort n=41,243	p-value
Age (years), mean ± SD*	54.7 ± 15.6	54.7 ± 15.6	1.00
18–44	10,876 (26%)	10,876 (26%)	
45–64	17,748 (43%)	17,748 (43%)	
≥65	12,619 (31%)	12,619 (31%)	
Sex, n (%)			
Men	15,139 (37%)	15,139 (37%)	1.00
Women	26,104 (63%)	26,104 (63%)	
Race, n (%)			1.00
White	22,729 (55%)	22,729 (55%)	
African-American	3392 (8%)	3392 (8%)	
Asian/PI	6459 (16%)	6459 (16%)	
Multi-racial	2556 (6%)	2556 (6%)	
Native American	249 (1%)	249 (1%)	
Unknown	5861 (14%)	5861 (14%)	
Hispanic Ethnicity	6594 (16%)	6656 (16%)	0.56
BMI (Kg/m^2), n (%)	31.2±7.7	28.7±6.6	<0.0001
< 25	8168 (20%)	10,635 (24%)	<0.0001
25–29.9	12,354 (30%)	11,390 (27%)	
≥ 30	19,692 (47%)	11,727 (28%)	
Missing	1029 (3%)	9192 (22%)	
Smoking Status, n (%)			<0.0001
Never	27,444 (67%)	23,505 (57%)	
Former	11,115 (27%)	8432 (20%)	
Current	1812 (4%)	2169 (5%)	
Missing	872 (2%)	7137 (17%)	
Neighborhood Deprivation Index (NDI)*			<0.0001
Quintile 1	11,419 (28%)	12,345 (30%)	
Quintiles 2–4	26,204 (64%)	24,843 (60%)	
Quintile 5	3554 (9%)	3882 (9%)	
Missing	66 (0%)	163 (0%)	
Prevalent Comorbidities n (%)			
Diabetes	7323 (18%)	5369 (13%)	<0.0001
Hypertension	17,474 (42%)	11,962 (29%)	<0.0001

(*Continued*)

Table 1 (Continued).

	Asthma Cohort n=41,243	Control Cohort n=41,243	p-value
Ischemic heart disease	335 (1%)	400 (1%)	0.01
Stroke	386 (1%)	451 (1%)	0.05
Heart failure	839 (2%)	848 (2%)	0.82
Peripheral arterial disease	1109 (3%)	1081 (3%)	0.54
Atrial fibrillation/flutter	1430 (4%)	1184 (3%)	<0.0001
End-stage renal disease	2799 (7%)	2164 (5%)	<0.0001
Liver disease	1763 (4%)	1131 (3%)	<0.0001
Cancer Except non-melanoma skin cancer	3444 (8%)	3152 (8%)	<0.0001
HIV/AIDS	149 (0%)	119 (0%)	0.07
Allergic rhinitis	19,406 (47%)	5920 (14%)	<0.0001
Respiratory tract infections	22,485 (55%)	11,748 (29%)	<0.0001

Note: *Standard deviation.

Table 2 Study Outcomes and Vaccination Status in the Asthma and Control Cohorts by Pandemic Period

	Asthma Cohort	Control Cohort	P
	n =41,243	n =41,243	
Pre – Delta (March 2020 – May 2021)			
PCR Testing for COVID-19, n (%)			<0.0001
No	20,461 (49.6%)	26,192 (63.5%)	
Yes	20,782 (50.4%)	15,051 (36.5%)	
At least 1 positive test among those tested	2113 (10.2%)	1590 (10.6%)	0.22
Hospitalization for COVID-19, n (rate per 10,000 person-years)	310 (57.6)	178 (33.1)	<0.0001
ICU admission for COVID-19, n (rate per 10,000 person-years)	63 (11)	43 (8)	0.05
Death by COVID-19, n (rate per 10,000 person-years)	41 (5.4)	27 (3.6)	0.09
Vaccination Status			<0.0001
Unvaccinated	7483 (18.1%)	12,900 (31.3%)	
Complete Primary Series	32,280 (78.3%)	26,802 (65.0%)	
Complete Primary Series and (any #) booster	56 (0.1%)	45 (0.1%)	
Other (partial/mixed/unapproved)	1424 (3.4%)	1496 (3.6%)	
	Asthma Cohort	**Control Cohort**	P
	n =40,517	n =40,517	
Delta (June 2021-December 2021)			
PCR Testing for COVID-19, n (%)			<0.0001

(*Continued*)

Table 2 (Continued).

No	25,093 (61.9%)	30,190 (74.5%)	
Yes	15,424 (38.1%)	10,327 (25.5%)	
At least 1 positive test among those tested	1242 (8.0%)	862 (8.3%)	0.39
Prior COVID-19 Infection (at least 90 days prior to current)	17 (0.04%)	19 (0.05%)	0.73
Hospitalization for COVID-19, n (rate per 10,000 person-years)	118 (49.9)	102 (43.1)	0.28
ICU admission for COVID-19, n (rate per 10,000 person-years)	26 (11)	16 (6)	0.12
Death by COVID-19, n (rate per 10,000 person-years)	19 (7.1)	11 (4.1)	0.15
Vaccination Status			<0.0001
Unvaccinated	4604 (11.4%)	9743 (24.0%)	
Complete Primary Series	10,906 (26.9%)	11,553 (28.5%)	
Complete Primary Series and (any #) booster	24,168 (59.6%)	18,387 (45.4%)	
Other (partial/mixed/unapproved)	839 (2.1%)	834 (2.1%)	
	Asthma Cohort	**Control Cohort**	P
	n =40, 169	n =40,169	
Omicron (January 2022 – August 2022)			
PCR Testing for COVID-19, n (%)			<0.0001
No	25,457 (63.4%)	30,424 (75.7)	
Yes	14,712 (36.6%)	9745 (25.0%)	
At least 1 positive test among those tested	3864 (26.3%)	2668 (27.4%)	0.05
Prior COVID-19 Infection (at least 90 days prior to current)	297 (0.7%)	171 (0.4%)	<0.0001
Hospitalization for COVID-19, n (rate per 10,000 person-years)	155 (49.0)	146 (46.2)	0.60
ICU admission for COVID-19, n (rate per 10,000 person-years)	16 (4)	14 (4)	0.71
Death by COVID-19, n (rate per 10,000 person-years)	7 (0.3)	7 (0.3)	0.99
Vaccination Status			<0.0001
Unvaccinated	4327 (10.8%)	99,420 (23.4%)	
Complete Primary Series	5566 (13.9%)	6649 (16.5%)	
Complete Primary Series and (any #) booster	29,477 (73.4%)	23,234 (57.9%)	
Other (partial/mixed/unapproved)	799 (2.0%)	857 (2.1%)	<0.0001

were tested than controls. However, as shown in Table 2, the percentage of patients with a positive test among those tested was lower in patients with asthma (26.3%) than in controls (27.4%). Panel B of Figure 2 shows the number of individuals hospitalized for COVID-19 in the asthma and control cohorts. There were two instances in the pre-delta period where hospitalizations spiked in asthma patients distinctly above controls: first in the summer of 2020 and then in the winter surge from November 2020 to February 2021. In contrast, hospitalization for COVID-19 trends were very similar in patients with asthma and controls in the delta and omicron periods.

Figure 2 COVID-19 infections (**A**) and hospitalization (**B**) in asthma and control cohorts.

There were no statistically significant differences (all p≥0.11) in the odds of a COVID-19 positive test comparing asthma cases and controls in the pre-and delta periods in either Model 1 (adjusted only for sociodemographic factors) or fully adjusted Model 3 (Table 3A). However, in the omicron period, asthma cases had 0.91 lower odds of a positive COVID-19 test result in Model 1 (p=0.001) and 0.92 lower odds in Model 3 (p=0.01). When the cohorts were stratified by vaccination status, lower odds of a positive test among asthma cases were seen in both groups, although it was statistically significant only in the vaccinated group (p=0.01) due to the larger sample size (Table 3B and C).

In the pre-delta period, asthma cases had a statistically significant 1.36-fold elevated hazard ratio of hospitalization for COVID-19 in Model 1 (p=0.001), which was slightly attenuated in model 3 (Table 4A). In contrast, no evidence of a statistically significant increased hazard of hospitalization for COVID-19 in patients with asthma was observed in the delta or omicron periods in the fully adjusted (Model 3) analysis. Notably, there was a statistically significant inverse association (lower hazard) between asthma status and hospitalization for COVID-19 in the omicron period in Model 1, but this association became non-significant after adjustment for vaccination status in Model 3. When the analysis of hospitalization for COVID-19 as an outcome was stratified by vaccination status, the fully adjusted hazard was more pronounced among unvaccinated asthma cases and controls (HR=1.40) than among vaccinated asthma cases and controls (HR=1.29) (Table 4B and C).

Table 3 Odds Ratio for Positive COVID-19 PCR Test in Asthma Patients and Controls Who Underwent COVID-19 PCR Testing at Least Once (Inconclusive COVID-19 PCR Test Results are Excluded) by Pandemic Period

A. In the Entire Sample of Asthma Cases and Controls						
	Pre-Delta (n=35,833) March 2020 – May 2021		**Delta (n=25,751)** June 2021 – December 2021		**Omicron (n=24,457)** January 2022 – August 2022	
	OR (95% CI)	**p**	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
Age, sex, race/ethnicity and NDI	0.94 (0.88, 1.01)	0.11	0.94 (0.86, 1.03)	0.22	0.91 (0.86, 0.97)	0.001
+ BMI, smoking, comorbidities and vaccination status	0.97 (0.89, 1.05)	0.40	1.05 (0.94, 1.16)	0.40	0.92 (0.86, 0.98)	0.01
B. In Asthma Cases and Controls who Received at Least One Vaccine Dose						
	Pre-delta (n=29,631) March 2020 – May 2021		**Delta (n=23,677)** June 2021 – December 2021		**Omicron (n=22,948)** January 2022 – August 2022	
	HR (95% CI)	**p**	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Age, sex, race/ethnicity and NDI	0.99 (0.91, 1.08)	0.88	1.04 (0.93, 1.16)	0.48	0.92 (0.87, 0.98)	0.01
+ BMI, smoking and comorbidities	0.96 (0.87, 1.05)	0.38	1.08 (0.96, 1.21)	0.19	0.92 (0.86, 0.98)	0.02
C. In Asthma Cases and Controls who Remained Unvaccinated						
	Pre-delta (n=6202) March 2020 – May 2021		**Delta (n=2074)** June 2021 – December 2021		**Omicron (n=1509)** January 2022 – August 2022	
	HR (95% CI)	**p**	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Age, sex, race/ethnicity and NDI	1.01 (0.89, 1.15)	0.88	0.95 (0.78, 1.16)	0.62	0.89 (0.71, 1.10)	0.27
+ BMI, smoking and comorbidities	1.00 (0.86, 1.15)	0.97	0.93 (0.73, 1.17)	0.52	0.89 (0.70, 1.13)	0.34

In the analysis considering the severity of asthma in the pre-delta period, the association was more pronounced for severe asthma (fully adjusted HR=1.83) than for non-severe asthma (fully adjusted HR=1.29) (Supplementary Table 1). In the analysis examining sex-specific effects, we found that asthma was significantly associated with COVID-19 hospitalization among women (fully-adjusted HR=1.77; 95% CI, 1.35–2.31; p<0.0001) but not among men (fully-adjusted HR=1.08; 95% CI, 0.78–1.50; p=0.64).

Discussion

Data regarding asthma as a risk factor for COVID-19 are conflicting. Early studies from China showed that the prevalence of chronic respiratory disorders in hospitalized patients with COVID-19 was low.[7,9] Three systematic reviews[11,14,15] have found no clear evidence of increased risk of COVID-19 diagnosis, hospitalization or severity of COVID-19 associated with asthma. One meta-analysis reported that patients with asthma have an increased risk of endotracheal intubation.[10] At the time of submission of this manuscript, there were five published studies that included a group of patients with asthma and a comparison (control) group. One large study from the NHS in the UK reported that asthma with recent oral steroid use was associated with an increased risk of COVID-19 death,[2] whereas another study based on 10 hospitals affiliated with Northwestern University reported no association between asthma and increased risk of hospitalization for COVID-19.[8] A 2021 study from Massachusetts General Hospital reported that asthma was associated with decreased COVID-19 severity, as measured by the WHO Clinical Progression Scale (CPS).[12] A 2022 study from the UK using primary care records found that more severe asthma (defined as regular inhaled corticosteroid use or a history of frequent exacerbations) was associated with severe COVID-19 outcomes (hospital and ICU admission).[6] Finally, another 2022 study from the UK Biobank reported

Table 4 Hazard Ratio of Hospitalization for COVID-19 in Asthma Patients and Controls by Pandemic Period

A. In the Entire Sample of Asthma Cases and Controls						
	Pre-Delta (n=35,833) March 2020 – May 2021		**Delta (n=25,751)** June 2021 – December 2021		**Omicron (n=24,457)** January 2022 – August 2022	
	OR (95% CI)	**p**	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
Age, sex, race/ethnicity and NDI	1.36 (1.12, 1.65)	0.001	0.83 (0.62, 1.10)	0.19	0.73 (0.58, 0.93)	0.01
+ BMI, smoking, comorbidities and vaccination status	1.33 (1.08, 1.64)	0.01	0.95 (0.70, 1.30)	0.75	0.78 (0.61, 1.01)	0.06
B. In Asthma Cases and Controls who Received at Least One Vaccine Dose						
	Pre-delta (n=29,631) March 2020 – May 2021		**Delta (n=23,677)** June 2021 – December 2021		**Omicron (n=22,948)** January 2022 – August 2022	
	HR (95% CI)	**p**	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Age, sex, race/ethnicity and NDI	1.49 (1.16, 1.92)	0.001	0.93 (0.63, 1.36)	0.69	0.80 (0.62, 1.04)	0.10
+ BMI, smoking and comorbidities	1.29 (0.98, 1.70)	0.07	0.88 (0.58, 1.34)	0.56	0.83 (0.63, 1.10)	0.19
C. In Asthma Cases and Controls who Remained Unvaccinated						
	Pre-delta (n=6202) March 2020 – May 2021		**Delta (n=2074)** June 2021 – December 2021		**Omicron (n=1509)** January 2022 – August 2022	
	HR (95% CI)	**p**	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Age, sex, race/ethnicity and NDI	1.60 (1.19, 2.16)	0.001	1.09 (0.72, 1.65)	0.70	0.63 (0.36, 1.11)	0.11
+ BMI, smoking and comorbidities	1.40 (1.01, 1.95)	0.04	1.05 (0.65, 1.69)	0.84	0.60 (0.32, 1.13)	0.11

that having a diagnosis of asthma was associated with a greater chance of COVID-19 hospitalization across all ages.[13]

Our real-world prospective analysis of a large cohort of asthma patients and a matched control cohort within an integrated healthcare system highlights the complexity of the asthma-COVID-19 epidemiological relationship and offers some novel findings in the area. First, patients with asthma were more likely to undergo PCR testing for COVID-19 than matched controls, which was true throughout the pandemic. Among those tested, patients with asthma were significantly less likely to test positive for COVID-19 during the omicron period (regardless of SES background, BMI, smoking status, and comorbidity burden), and this result was not modified by vaccination status. However, there were no significant differences in test positivity between asthma cases and controls in the previous pre-delta and delta periods. Second, asthma was independently associated with a 1.33-fold increased risk of hospitalization for COVID-19 in the pre-delta period. When we stratified the analysis by vaccination status, this increased hazard was present in both vaccinated and unvaccinated subjects, although there was a slightly greater hazard in unvaccinated subjects (HR=1.40) than in vaccinated subjects (HR=1.29). On the other hand, we observed no increased hazard of hospitalization for COVID-19 associated with asthma in the subsequent delta and omicron pandemic periods, and no significant modification of these null results by vaccination status. Finally, the risk of hospitalization due to COVID-19 associated with asthma in the pre-delta period was much more pronounced in the context of severe asthma and was clearly observed in women but not in men.

We can only speculate as to why patients with asthma were more likely to undergo PCR testing for COVID-19 then matched controls, and weigh in the facts that they had more respiratory symptoms due to asthma, or greater concerns because of underlying respiratory disease.

The reasons why asthma was related to hospitalization due to COVID-19 early in the pandemic and not thereafter are unclear. The COVID-19 vaccine received emergency use approval in December 2020 and became available to healthcare workers shortly thereafter. Subsequently, vaccines were rolled out for high-risk populations and then for the general

public. The added protection from COVID-19 vaccines could account for these findings; however, this could also represent the decreased severity of COVID-19 variants. Global studies continue to document differences in COVID-19 outcomes in patients with asthma. For instance, a recent study in the UK showed a correlation between asthma severity, as determined by medication regimen, and COVID-19 severity during the first wave of the pandemic.[6] On the other hand, patients with asthma had lower rates of hospitalization during the first wave in Australia compared to patients without asthma.[14] These global differences can be explained by a multitude of factors, and further investigation of outcomes during the later stages of the pandemic is warranted to ascertain whether these differences persist. Additionally, while behavioral changes within the asthma cohort have not been characterized during the pandemic, it is possible that masking and social distancing practices were different in this patient population, thereby affecting the hospitalization and test positivity rates.

The differences observed in the risk of hospitalization for COVID-19 according to asthma severity were consistent with those observed in prior investigations. Williamson et al reported (using primary care records from the UK) that asthma with recent steroid use was associated with COVID-19 death whereas asthma without recent oral steroid use was not.[2] More severe asthma has also been reported to be associated with more severe COVID-19 outcomes in UK primary-care EHR.[6] The finding of sex-differences in the association of asthma with COVID-19 hospitalization in the pre-delta period (clear association in women, no association in women) is novel and warrants replication in other cohorts and settings before making definitive conclusions. It is noteworthy that the prevalence of asthma and allergic disease is increased in women compared to men, suggesting that sex hormones and other factors may alter pathways important in asthma pathogenesis and allergic disease.

Our study has important strengths, including a large, race/ethnically diverse cohort, and the availability of comprehensive health data through the EHR. Furthermore, we characterized the outcomes through multiple COVID-19 variant periods in a large patient population, allowing us to draw conclusions on how each variant impacted this patient population. We recognize that our study has some limitations. First, our findings may not be generalizable to the uninsured population. Our study was limited to northern California, which may not be generalizable to a wider population and geographic area. However, KPNC membership is similar to the greater San Francisco Bay population in terms of socioeconomic status, with the caveat that KPNC members are less likely to be on either extreme (poverty or wealth).[20] Second, because the study is observational, no causal inference should be derived. Third, we were unable to characterize the association of subgroups of asthma patients such as Th2 high inflammation vs Th2 low inflammation asthma because we lacked the required biomarker data.

In conclusion, our analysis underscores that the epidemiological association between asthma and COVID-19 outcomes is complex and varies across pandemic periods and subgroups. We observed an increased risk of hospitalization associated with asthma for COVID-19 in the pre-delta period and report (in agreement with prior studies) that this risk was particularly salient for severe asthma. On balance, our data should provide reassurance to patients and healthcare providers that asthma does not appear to be a risk factor for COVID-19 outcomes, but continuing surveillance is warranted to delineate the future course of the asthma-COVID-19 relationship.

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