Author Manuscript
Author Manuscript
Author Manuscript
Author Manuscript

HHS Public Access

Author manuscript

Mycoses. Author manuscript; available in PMC 2025 December 01.

Published in final edited form as:

Mycoses. 2025 September ; 68(9): e70109. doi:10.1111/myc.70109.

New asthma diagnosis codes or short-acting β2 agonist prescriptions after histoplasmosis among patients with commercial health insurance, United States, 2018–2023

Ian Hennessee,
Centers for Disease Control and Prevention, Atlanta, Georgia, USA

Kaitlin Benedict,
Centers for Disease Control and Prevention, Atlanta, Georgia, USA

Dallas J. Smith,
Centers for Disease Control and Prevention, Atlanta, Georgia, USA

Nicolas Barros
Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana, USA

Abstract

Background: Although several fungal infections have been linked to asthma development, the relationship between histoplasmosis and asthma development has not been fully described.

Objectives: To assess the incidence of new asthma diagnosis codes or short-acting β_2 agonist (SABA) prescription in the year following histoplasmosis diagnosis and identify potentially related factors.

Methods: We used a large health insurance claims database to identify patients with histoplasmosis with and without an asthma diagnosis code or a short-acting $\beta 2$ agonist prescription in the year after diagnosis.

Results: Among 1,819 patients diagnosed with histoplasmosis, 252 (13.9%) received a new asthma diagnosis or SABA prescription in the subsequent year, more than double the proportion in the general population (5.8%). Pulmonary histoplasmosis and symptoms such as dyspnea and wheezing were associated with asthma diagnosis or SABA receipt.

Conclusion: These findings suggest that histoplasmosis may predispose certain patients to airway hyperreactivity, particularly those with acute pulmonary symptoms. Further research is needed to elucidate potential mechanisms underlying these findings, which could inform strategies to mitigate post-infectious airway disease in affected patients.

Corresponding author: Kaitlin Benedict, MPH, jsy8@cdc.gov, Centers for Disease Control and Prevention, 1600 Clifton Road NE, Mailstop H24-11, Atlanta, Georgia, USA 30329.

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Conflict of interest: Nicolas Barros serves as a Medical Liaison for Miravista Diagnostics, a company involved in fungal diagnostics. All other authors report no conflicts of interest.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Keywords

histoplasmosis; asthma; insurance; health; United States

Introduction

Viral infections and atypical bacterial infections, including *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*, have been implicated in the development of asthma due to inflammatory damage to airway tissues (1–4). Some studies also suggest that typical bacterial pathogens, such as *Streptococcus pneumoniae*, may contribute to asthma development through similar mechanisms (3).

In addition to bacterial and viral pathogens, several fungal mold infections such as aspergillosis and infections due to *Alternaria spp.* and *Cladosporium spp.* are known to predispose individuals to asthma development or exacerbations, largely due to hypersensitization to fungal antigens (5). A recent study reported an increased incidence of asthma diagnosis or treatment following infection due to *Coccidioides*, a dimorphic fungus similar to *Histoplasma* (6). However, data on the incidence of asthma following histoplasmosis are lacking.

Asthma is considered a risk factor for histoplasmosis, possibly due to altered respiratory tract immunity or the frequent use of chronic corticosteroid in asthma management (7,8). Histoplasmosis can also damage airway tissues and trigger a robust inflammatory immune response (9,10). This may predispose patients to later airway hyperreactivity due to mechanisms described in other fungal infections (5,6). We used a large U.S. health insurance claims database to estimate the frequency of new-onset asthma diagnosis or initiation of asthma treatment following histoplasmosis and assess potentially associated factors.

Methods

We used the Merative™ Marketscan® Commercial/Medicare Database (https://www.merative.com/documents/brief/marketscan-explainer-general), which includes health insurance claims data for over 45 million patients across the United States with employer-sponsored plans including Medicare Supplemental and Medicare Advantage plans. We identified patients diagnosed with histoplasmosis (n=12,832) during January 01, 2018, to June 30, 2023, using International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes (Supplemental Table 1). To improve diagnostic accuracy, we excluded patients with codes listed only on laboratory or imaging claims alone, as these may reflect rule-out diagnoses. The index date was the date the histoplasmosis code was first used during the study window.

We also excluded 7,783 patients whose histoplasmosis code was assigned by an eye care provider, to remove cases of presumed ocular histoplasmosis. We required continuous health plan enrollment for one year before and one year after the histoplasmosis index date, which excluded an additional 2,288 patients due to lack of continuous enrollment. To identify new-onset asthma diagnoses, we excluded 713 patients with a prior asthma diagnosis or

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

an outpatient prescription for a short-acting β_2 agonist (SABA; i.e., albuterol, albuterol sulphate, or levalbuterol), a standard treatment for asthma, within the year before their index date. Finally, we excluded 229 patients who had a histoplasmosis code in the year before the index date to ensure incident case capture (Supplemental figure 1).

Next, we assessed factors associated with an asthma diagnosis code or a new SABA prescription in the year following the histoplasmosis index date. We assessed patient demographics, provider specialty on the index date, histoplasmosis form, presenting symptoms, clinical findings, and other selected comorbid conditions documented within the 90 days before or on the index date, using ICD-10-CM codes (Supplemental Table 1). We assessed bivariable associations using chi-squared tests, Fisher's exact tests, and t-tests with a significance threshold of p<0.05. Bivariable associations with p-values <0.2 were included in a stepwise multivariable regression model to estimate adjusted odds ratios (aORs) and 95% confidence intervals (95% CIs) for independent associations between key demographic and clinical factors and asthma diagnosis or SABA prescription.

Finally, we constructed several comparison cohorts. These included: 1) patients with healthcare visits for any reason, to estimate asthma incidence among the general population of commercially insured patients; 2) patients with other thermally dimorphic fungal infections, such as blastomycosis or coccidioidomycosis; 3) patients with aspergillosis, a known fungal infection linked to asthma development and exacerbation (5); 4) patients with influenza infection or COVID-19 diagnoses, which are viral infections linked to asthma development and exacerbation in adults (2,11); and 5) patients with pneumonia due to *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, or *Streptococcus pneumoniae,* which are pathogens associated with asthma development (3). We constructed the cohorts in the same manner as described above (Supplemental Table 2).

Results

Among 1,819 patients with histoplasmosis who met the inclusion criteria, 252 (13.9%, 95% CI:12.3–15.4) had a new asthma diagnosis code (n=93, 5.1%) or a new SABA prescription (n=197, 10.8%) within one year of their index date; n=38 had both a new asthma diagnosis code and a new SABA prescription (Table 1, Figure 1). Of the 93 patients with asthma diagnosis codes, 26 (28%) were classified as mild, 18 (19%) as moderate, 1 (0.4%) as severe, and 58 (62%) were of unspecified severity (Supplemental Table 3). The median time from histoplasmosis to first asthma diagnosis code or new SABA prescription was 130 days (interquartile range [IQR]: 49.5–239.5).

Patients with histoplasmosis had an even sex distribution (50% male, 50% female), with a median age of 57 years (IQR: 43–69). Patients were primarily from the Midwest (51%) and South (38%) census regions (Table 1). Patients with a new asthma diagnosis code or SABA prescription were more likely than those who did not to have been seen at an acute care hospital (40% vs. 33%, p=0.026) or by a pulmonary specialist on the index date (16% vs. 10%, p=0.004). They were also more likely to have pulmonary histoplasmosis (35% vs. 26%, p=0.003), an unspecified histoplasmosis form (19% vs. 13%, p=0.006), or to have been hospitalized on the index date (19% vs. 13%, p=0.006) (Table 1).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Several pulmonary symptoms and clinical findings were more common among patients who had a new asthma diagnosis code or SABA prescription. This included dyspnea (28% vs. 17%, $p<0.001$), wheezing (3% vs. 1%, $p=0.007$), chest pain (18% vs. 13%, $p=0.04$), hypoxemia (7% vs. 3%, $p<0.001$), acute respiratory failure (3% vs. 1%, $p=0.007$), and pleural effusion (11% vs. 6%, $p=0.008$). Most systemic symptoms were not associated with receiving a new asthma diagnosis code or SABA prescription. Diagnoses in the 90 days before the index date that were associated with receiving an asthma diagnosis code or SABA prescription included allergic rhinitis (7% vs. 4%, $p=0.045$), anxiety disorder (14% vs. 10%, $p=0.029$), chronic obstructive pulmonary disease (16% vs. 8%, $p<0.001$), COVID-19 (9% vs. 4%, $p=0.009$), depression (14% vs. 8%, $p=0.009$), and pneumonia (18% vs. 11%, $p=0.002$). Diagnostic procedures including chest computed tomography (44% vs. 32%, $p<0.001$), spirometry (33% vs. 9%, $p<0.001$), or nitric oxide expired gas determination (2%. vs. 0.3%, $p=0.007$) were more common among patients who received a new asthma diagnosis code or SABA prescription; receipt of antifungal treatment was not associated.

In multivariable logistic regression, pulmonary histoplasmosis was independently associated with higher odds of receiving a new asthma diagnosis code or SABA prescription (adjusted odds ratio (aOR)=1.7, 95% CI: 1.3–2.4), as was dyspnea (aOR=1.7, 95% CI: 1.2–2.4) and wheezing (aOR=4.1, 95% CI: 1.3–12.8) (Supplemental Table 3). Other significant predictors included pericarditis (aOR=11.6, 95% CI: 1.0–131.9), COVID-19 (aOR=2.4, 95% CI: 1.0–5.2), and depression (aOR=1.7, 95% CI: 1.1–2.8).

In the comparison cohorts, the proportion of patients with a new asthma diagnosis code or SABA prescription within the year following the index date was 5.8% (95% CI: 5.8–5.9) among the general population, 8.0% (95% CI: 4.9–11.1) among patients with blastomycosis, 12.9% (95% CI: 11.3–14.6) among patients with coccidioidomycosis, and 19.4% (95% CI: 17.3–21.4) among patients with aspergillosis (Figure 1). Among patients with viral infections, the proportion was 9.3% (95% CI: 9.2–9.3) for those with influenza and 11.4% (95% CI: 11.3–11.4) for those with COVID-19. Finally, among patients with bacterial pneumonia, the proportion was 24.5% (95% CI: 20.1–28.9) for those with *Chlamydia pneumoniae*, 19.5% (95% CI: 18.8–20.3) for those with *Mycoplasma pneumoniae*, and 25.4% (95% CI: 23.9–26.8) for those with *Streptococcus pneumoniae*. When restricting the histoplasmosis cohort to patients who also had a diagnosis code for "unspecified pneumonia," 20.1% (95% CI: 14.5%–25.7%) received a new asthma diagnosis code or SABA prescription.

Discussion

In this analysis of patients with commercial insurance, nearly 14% of patients diagnosed with histoplasmosis received either a new asthma diagnosis code or a short-acting beta-agonist (SABA) prescription within the following year. This rate was more than twice that of the general population, higher than observed following infections due to influenza and COVID-19, and similar to that observed after coccidioidomycosis. Furthermore, among patients with histoplasmosis and "unspecified pneumonia" diagnoses, the proportion with a new asthma diagnosis code or SABA prescription was similar to that seen with certain bacterial pneumonias, conditions for which associations with new-onset asthma are well

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

described (1–3,5). Although this is an exploratory study not meant to establish causality, these findings suggest that histoplasmosis, particularly when presenting with pulmonary symptoms or pneumonia, may predispose patients to developing inflammation-mediated airway hyperresponsiveness.

Several potential mechanisms could explain this finding (Table 2). One possibility is that *Histoplasma capsulatum* infection damages airway epithelial cells, leading to persistent inflammation and a cascade of immune responses that promote airway remodeling and hyperreactivity. In allergic bronchopulmonary aspergillosis (ABPA), for example, *Aspergillus* proteases provoke prolonged T helper 2 (Th2)-skewed immune responses, mucosal inflammation, and structural airway changes, including smooth muscle hyperplasia and goblet cell metaplasia (5,12,13). *Histoplasma* expresses several orthologous proteins—including heat shock protein 60, 60S ribosomal protein L3, and fructose 1,6-bisphosphate aldolase (14–16), that could act through similar pathophysiologic mechanisms to stimulate Th2 responses and contribute to asthma pathogenesis. Additionally, fungal cell wall components such as β-glucans, chitin, and mannans can serve as potent pathogen-associated molecular patterns, activating innate immune pathways (e.g., Dectin-1, TLR2/4) and promoting chronic airway inflammation (17). Damaged respiratory epithelia may also release alarmins such as IL-25, IL-33, and thymic stromal lymphopoietin (TSLP), which activate group 2 innate lymphoid cells (ILC2s), critical drivers of allergic inflammation and asthma (18). These responses may be further amplified in individuals with predisposing immune profiles. Another contributing factor may be disruption of the airway epithelial barrier following fungal infection, increasing exposure to inhaled allergens and environmental irritants (19). This sensitization could predispose to de novo asthma or exacerbate subclinical disease. Fungal infections may also alter the composition of the lung microbiome, favoring colonization by bacteria associated with airway inflammation and dysregulated immune responses (20). Moreover, certain fungal proteases may activate protease-activated receptors on airway nerves or smooth muscle, triggering bronchospasm and enhancing neuroimmune signaling that promotes airway hyperresponsiveness (21). Latent persistence of *Histoplasma* in lung tissues or macrophages could provide a chronic source of antigenic stimulation, sustaining inflammation long after the initial infection. This mechanism has been proposed in other fungal-related pulmonary diseases, such as chronic pulmonary aspergillosis and fungal bronchitis (22).

These hypotheses are supported by our findings that receiving a new asthma diagnosis code or SABA was more common in patients with pulmonary histoplasmosis (compared with other histoplasmosis forms), and in those with pulmonary symptoms and findings (e.g., dyspnea, wheezing, and pneumonia) and potentially more severe disease, as indicated by hospitalization. The independent association we observed between pericarditis and asthma diagnosis or SABA also supports the idea that a heightened systemic inflammatory response may contribute to airway dysfunction (10,23). Similarly, a recent study of coccidioidomycosis showed that patients with more severe pulmonary disease were more likely to receive asthma diagnosis codes or SABA prescriptions (6). Further studies are needed to assess whether there are unique processes related to asthma development following dimorphic fungal infection, or if the processes are similar to those in other respiratory infections (3,4,11,24).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Alternatively, our findings might reflect that histoplasmosis unmasked previously undiagnosed asthma, especially among patients with pre-existing Th2-dominant immune profiles. Because the adaptive immune response to *Histoplasma* typically requires a Th1 response (9), it is possible that histoplasmosis could occur more frequently in patients who have Th2-dominated immune responses and are more likely to develop asthma regardless of histoplasmosis infection. Approximately 75% of asthma diagnoses or SABA prescriptions in our study occurred 49 days or more after the diagnosis of histoplasmosis, suggesting they were not incidental findings during initial histoplasmosis evaluation. However, patients seen by pulmonologists or allergists during histoplasmosis follow-up may have had a higher likelihood of being evaluated for asthma, potentially leading to detection bias.

Somewhat unexpectedly, we found that depression was independently associated with receiving a new asthma diagnosis code or SABA. Psychological stress has been increasingly recognized as a contributor to asthma incidence and exacerbations, possibly through dysregulation of hypothalamic-pituitary-adrenal axis signaling and immune responses (25). However, further studies are needed to assess what, if any, role histoplasmosis plays in the relationship between depression and asthma.

A primary limitation of our study is the reliance on ICD-10 codes, which are subject to misclassification and under-coding of symptoms. Not all patients with ICD-10 codes for asthma had spirometry-confirmed diagnoses; however, prior studies have validated the use of administrative claims data for asthma research (26). We included SABA prescriptions in our study to improve case detection (26); approximately two-thirds of patients in our study met the case definition by having a SABA prescription and no asthma diagnosis code. However, another study limitation is the lack of information about SABA indication. SABAs can also be prescribed for chronic obstructive pulmonary disease or might reflect off-label use for histoplasmosis-related symptoms (e.g., wheezing or dyspnea) during recovery from histoplasmosis. This could have led to an over-estimation of the outcome of interest. Additionally, we may have overestimated new asthma diagnoses in patients with a history of asthma or SABA use >1 year before histoplasmosis diagnosis.

In summary, this retrospective cohort study found that nearly 14% of patients with histoplasmosis received a new asthma diagnosis or SABA prescription. Further studies could shed light on mechanistic drivers of the association between histoplasmosis and subsequent asthma or SABA prescription, and whether they are unique to thermally dimorphic fungal infections or a broader phenomenon seen with other respiratory pathogens. Understanding these mechanisms may help inform strategies to mitigate post-infectious airway disease in affected populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

This activity was reviewed by the CDC and was conducted consistent with applicable federal law and CDC policy (e.g., 45 C.F.R. part 46.102(l)(2), 21 C.F.R. part 56; 42 U.S.C. §241(d); 5 U.S.C. §552a; 44 U.S.C. §3501 et seq.).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Because MarketScan data are fully de-identified, this analysis was not subject to review by the Centers for Disease Control and Prevention (CDC) institutional review board.

Financial support:

No specific funding was received for this work.

References

1. MacDowell AL, Bacharier LB. Infectious triggers of asthma. Immunology and Allergy Clinics of North America. 2005 Feb;25(1):45–66. [PubMed: 15579364]
2. Pelaia G, Vatrella A, Gallelli L, Renda T, Cazzola M, Maselli R, et al. Respiratory infections and asthma. Respiratory Medicine. 2006 May;100(5):775–84. [PubMed: 16289785]
3. Webley WC, Hahn DL. Infection-mediated asthma: etiology, mechanisms and treatment options, with focus on Chlamydia pneumoniae and macrolides. Respir Res. 2017 Dec;18(1):98. [PubMed: 28526018]
4. Sigurs N, Bjarnason R, Sigurbergsson F, Kjellman B. Respiratory Syncytial Virus Bronchiolitis in Infancy Is an Important Risk Factor for Asthma and Allergy at Age 7. Am J Respir Crit Care Med. 2000 May 1;161(5):1501–7. [PubMed: 10806145]
5. Denning DW, O'Driscoll BR, Hogaboam CM, Bowyer P, Niven RM. The link between fungi and severe asthma: a summary of the evidence. Eur Respir J. 2006 Mar;27(3):615–26. [PubMed: 16507864]
6. Benedict K, Smith DJ, Haczku A, Zeki AA, Hsu J, Toda M, et al. Investigating Asthma After Coccidioidomycosis Among Patients With Commercial Health Insurance, United States, 2017–2022. Mycoses. 2025 Feb;68(2):e70033. [PubMed: 39956956]
7. Bueter CL, Deepe GS. Aeroallergens Exacerbate *Histoplasma capsulatum* Infection. The Journal of Immunology. 2018 Dec 1;201(11):3352–61. [PubMed: 30348735]
8. Gudala M Delayed Diagnosis of Pulmonary Histoplasmosis in an Immunocompetent Young Asthmatic Female from Florida, a Non-Endemic Area for Histoplasma Capsulatum. Mycology [Internet]. 2015 [cited 2025 Mar 31];1(1). Available from: http://mycology.imedpub.com/delayed-diagnosis-ofpulmonary-histoplasmosis-inan-immunocompetent-youngasthmatic-female-from-floridaa-nonendemic-area-forhistoplasma-capsulatum.php?aid=7205
9. Barros N, Wheat JL, Hage C. Pulmonary Histoplasmosis: A Clinical Update. J Fungi (Basel). 2023 Feb 10;9(2):236.
10. Kauffman CA. Histoplasmosis: a Clinical and Laboratory Update. Clin Microbiol Rev. 2007 Jan;20(1):115–32. [PubMed: 17223625]
11. Kim BG, Lee H, Yeom SW, Jeong CY, Park DW, Park TS, et al. Increased Risk of New-Onset Asthma After COVID-19: A Nationwide Population-Based Cohort Study. The Journal of Allergy and Clinical Immunology: In Practice. 2024 Jan 1;12(1):120–132.e5. [PubMed: 37774780]
12. Oguma T, Asano K, Tomomatsu K, Kodama M, Fukunaga K, Shiomi T, et al. Induction of Mucin and MUC5AC Expression by the Protease Activity of *Aspergillus fumigatus* in Airway Epithelial Cells. The Journal of Immunology. 2011 Jul 15;187(2):999–1005. [PubMed: 21685325]
13. Wiesner DL, Merkhofer RM, Ober C, Kujoth GC, Niu M, Keller NP, et al. Club Cell TRPV4 Serves as a Damage Sensor Driving Lung Allergic Inflammation. Cell Host & Microbe. 2020 Apr;27(4):614–628.e6. [PubMed: 32130954]
14. Long KH, Gomez FJ, Morris RE, Newman SL. Identification of Heat Shock Protein 60 as the Ligand on *Histoplasma capsulatum* That Mediates Binding to CD18 Receptors on Human Macrophages. The Journal of Immunology. 2003 Jan 1;170(1):487–94. [PubMed: 12496435]
15. Matos Baltazar L, Nakayasu ES, Sobreira TJP, Choi H, Casadevall A, Nimrichter L, et al. Antibody Binding Alters the Characteristics and Contents of Extracellular Vesicles Released by Histoplasma capsulatum. mSphere. 2016;1(2):e00085–15.
16. Almeida MA, Baeza LC, Almeida-Paes R, Bailão AM, Borges CL, Guimarães AJ, et al. Comparative Proteomic Analysis of Histoplasma capsulatum Yeast and Mycelium Reveals Differential Metabolic Shifts and Cell Wall Remodeling Processes in the Different Morphotypes. Front Microbiol. 2021;12:640931. [PubMed: 34177824]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

17. Brown GD. Innate antifungal immunity: the key role of phagocytes. Annu Rev Immunol. 2011;29:1–21. [PubMed: 20936972]
18. Licona-Limón P, Kim LK, Palm NW, Flavell RA. TH2, allergy and group 2 innate lymphoid cells. Nat Immunol. 2013 Jun;14(6):536–42. [PubMed: 23685824]
19. Heijink IH, Kuchibhotla VNS, Roffel MP, Maes T, Knight DA, Sayers I, et al. Epithelial cell dysfunction, a major driver of asthma development. Allergy. 2020 Aug;75(8):1902–17. [PubMed: 32460363]
20. Campbell CD, Gleeson M, Sulaiman I. The role of the respiratory microbiome in asthma. Front Allergy. 2023;4:1120999. [PubMed: 37324782]
21. Balenga NA, Klichinsky M, Xie Z, Chan EC, Zhao M, Jude J, et al. A fungal protease allergen provokes airway hyper-responsiveness in asthma. Nat Commun. 2015 Apr 13;6:6763. [PubMed: 25865874]
22. Rapeport WG, Ito K, Denning DW. The role of antifungals in the management of patients with severe asthma. Clin Transl Allergy. 2020 Nov 6;10(1):46. [PubMed: 33292524]
23. Wang JJ, Reimold SC. Chest Pain Resulting From Histoplasmosis Pericarditis: A Brief Report and Review of the Literature. Cardiology in Review. 2006 Sep;14(5):223–6. [PubMed: 16924162]
24. Rantala A, Jaakkola JJK, Jaakkola MS. Respiratory Infections Precede Adult-Onset Asthma. Hartl D, editor. PLoS ONE. 2011 Dec 21;6(12):e27912. [PubMed: 22205932]
25. Di Marco F, Santus P, Centanni S. Anxiety and depression in asthma. Current Opinion in Pulmonary Medicine. 2011 Jan;17(1):39–44. [PubMed: 20975562]
26. Yousif A, Dault R, Courteau M, Blais L, Cloutier AM, Lacasse A, et al. The validity of diagnostic algorithms to identify asthma patients in healthcare administrative databases: a systematic literature review. Journal of Asthma. 2022 Jan 2;59(1):152–68.

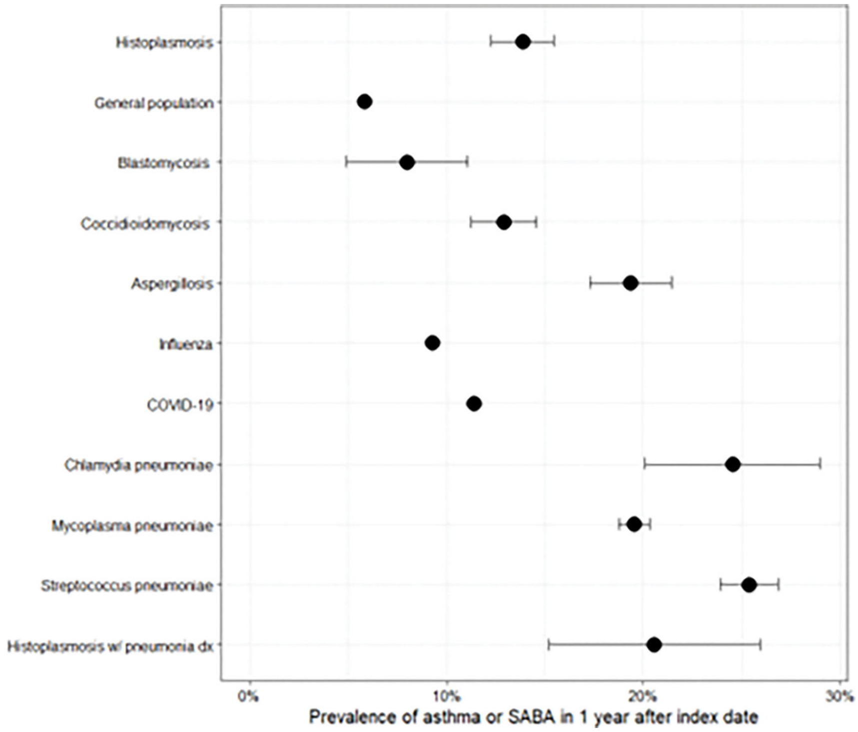

Figure 1. Proportion of patients with a new asthma diagnosis code or short acting beta agonist (SABA) prescription in one year after index date of histoplasmosis and other comparison cohorts. Abbreviations: dx = diagnosis

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 1.

Characteristics of patients with histoplasmosis with and without a new asthma diagnosis code or short-acting β2 agonist (SABA) prescription after histoplasmosis diagnosis, 2018 to 2023

	Total		Asthma/SABA		No asthma/SABA		
	n=1,819	%	n=252	%	n=1,567	%	p-value
Sex							0.489
Male	903	49.6%	120	47.6%	783	50.0%	
Female	916	50.4%	132	52.4%	784	50.0%	
Median age (interquartile range)	57.0	(43.0–68.0)	56.0	(44.5–66.0)	57.0	(43.0–68.0)	0.922
Age group in years							0.745
<18	99	5.4%	12	4.8%	87	5.6%	
18 to 44	384	21.1%	51	20.2%	333	21.3%	
45 to 64	824	45.3%	122	48.4%	702	44.8%	
≥65	512	28.1%	67	26.6%	445	28.4%	
US census region of primary beneficiary's residence (n=1,773)							0.373
Northeast	91	5.1%	17	6.9%	74	4.8%	
Midwest	905	51.0%	116	47.3%	789	51.6%	
South	672	37.9%	95	38.8%	577	37.8%	
West	105	5.9%	17	6.9%	88	5.8%	
Urban/rural classification (n=1,373)							0.080
Non-rural	956	69.6%	139	75.1%	817	68.8%	
Rural	417	30.4%	46	24.9%	371	31.2%	
Season of index date							0.680
Winter	463	25.5%	57	22.6%	406	25.9%	
Spring	481	26.4%	66	26.2%	415	26.5%	
Summer	435	23.9%	64	25.4%	371	23.7%	
Fall	440	24.2%	65	25.8%	375	23.9%	
Provider type(s) on index date *							
Acute care hospital	617	33.9%	101	40.1%	516	32.9%	0.026
Allergy/immunology	8	0.4%	2	0.8%	6	0.4%	0.306
Family practice or internal medicine	565	31.1%	85	33.7%	480	30.6%	0.324
Infectious disease	138	7.6%	15	6.0%	123	7.8%	0.291
Laboratory	146	8.0%	23	9.1%	123	7.8%	0.488
Other	758	41.7%	97	38.5%	661	42.2%	0.270
Pulmonary disease	188	10.3%	39	15.5%	149	9.5%	0.004
Radiology	188	10.3%	33	13.1%	155	9.9%	0.121
Unknown	106	5.8%	6	2.4%	100	6.4%	0.012
Histoplasmosis form on index date *							
Pulmonary	503	27.7%	89	35.3%	414	26.4%	0.003

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

	Total		Asthma/SABA		No asthma/SABA		
	n=1,819	%	n=252	%	n=1,567	%	p-value
Disseminated	67	3.7%	7	2.8%	60	3.8%	0.411
Other or unspecified	1,319	72.5%	166	65.9%	1,153	73.6%	0.011
Hospitalized on the index date	247	13.6%	48	19.0%	199	12.7%	0.006
Symptoms and clinical findings [*,†]							
Systemic							
Fever	204	11.2%	31	12.3%	173	11.0%	0.556
Chills, without fever	10	0.5%	1	0.4%	9	0.6%	1.000
Generalized hyperhidrosis	26	1.4%	4	1.6%	22	1.4%	0.775
Sepsis	96	5.3%	18	7.1%	78	5.0%	0.153
Fatigue or malaise	202	11.1%	36	14.3%	166	10.6%	0.083
Myalgia	37	2.0%	4	1.6%	33	2.1%	0.588
Nausea or vomiting	137	7.5%	20	7.9%	117	7.5%	0.793
Pulmonary							
Cough	280	15.4%	47	18.7%	233	14.9%	0.123
Dyspnea	340	18.7%	70	27.8%	270	17.2%	<0.001
Wheezing	18	1.0%	7	2.8%	11	0.7%	0.007
Chest pain	256	14.1%	46	18.3%	210	13.4%	0.040
Hypoxemia	57	3.1%	18	7.1%	39	2.5%	<0.001
Acute respiratory failure	18	1.0%	7	2.8%	11	0.7%	0.007
Solitary pulmonary nodule	369	20.3%	51	20.2%	318	20.3%	0.984
Other nonspecific abnormal finding of lung field	517	28.4%	79	31.3%	438	28.0%	0.267
Pleural effusion	124	6.8%	27	10.7%	97	6.2%	0.008
Diseases of mediastinum	33	1.8%	4	1.6%	29	1.9%	1.000
Pulmonary fibrosis	147	8.1%	22	8.7%	125	8.0%	0.684
Hemoptysis	33	1.8%	4	1.6%	29	1.9%	1.000
Upper respiratory							
Acute pharyngitis, unspecified	61	3.4%	8	3.2%	53	3.4%	0.865
Nasal congestion and postnasal drip	29	1.6%	4	1.6%	25	1.6%	1.000
Other signs and symptoms							
Erythema nodosum	3	0.2%	1	0.4%	2	0.1%	0.361
Other erythematous conditions	13	0.7%	0	0.0%	13	0.8%	0.236
Enlarged lymph nodes	293	16.1%	35	13.9%	258	16.5%	0.302
Headache	90	4.9%	18	7.1%	72	4.6%	0.083
Low back pain	124	6.8%	19	7.5%	105	6.7%	0.624
Abdominal pain	248	13.6%	38	15.1%	210	13.4%	0.471
Pain in joint	185	10.2%	32	12.7%	152	9.7%	0.153
Rash and other nonspecific skin eruption	43	2.4%	7	2.8%	36	2.3%	0.641
Lymphedema/lymphangitis	38	2.1%	8	3.2%	30	1.9%	0.194

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

	Total		**Asthma/SABA**		**No asthma/SABA**		
	n=1,819	**%**	**n=252**	**%**	**n=1,567**	**%**	**p-value**
Acute pericarditis	4	0.2%	2	0.8%	2	0.1%	0.095
Other diagnoses [*,†]							
Acute nasopharyngitis or acute upper respiratory infections of multiple and unspecified sites	61	3.4%	12	4.8%	49	3.1%	0.181
Acute sinusitis	76	4.2%	12	4.8%	64	4.1%	0.618
Allergic contact dermatitis	6	0.3%	1	0.4%	5	0.3%	0.592
Allergic rhinitis	85	4.7%	18	7.1%	67	4.3%	0.045
Anxiety disorder	189	10.4%	36	14.3%	153	9.8%	0.029
Atopic dermatitis	15	0.8%	4	1.6%	11	0.7%	0.143
Bronchitis or unspecified lower acute respiratory infection	56	3.1%	10	4.0%	46	2.9%	0.378
Cancer	230	12.6%	32	12.7%	198	12.6%	0.978
Chronic obstructive pulmonary disease (COPD) or other chronic lower respiratory disease	167	9.2%	41	16.3%	126	8.0%	<0.001
Chronic sinusitis	32	1.8%	8	3.2%	24	1.5%	0.072
Conjunctivitis	17	0.9%	3	1.2%	14	0.9%	0.720
COVID-19[‡]	41	4.5%	12	8.8%	29	3.7%	0.009
Depression	165	9.1%	34	13.5%	131	8.4%	0.009
Diabetes	317	17.4%	44	17.5%	273	17.4%	0.988
Fibromyalgia	23	1.3%	4	1.6%	19	1.2%	0.548
Food allergy	10	0.5%	1	0.4%	9	0.6%	1.000
HIV	33	1.8%	4	1.6%	29	1.9%	1.000
Hypersensitivity pneumonitis	1	0.1%	0	0.0%	1	0.1%	1.000
Hypertension	653	35.9%	100	39.7%	553	35.3%	0.177
Hypothyroidism	168	9.2%	15	6.0%	153	9.8%	0.052
Immune-mediated inflammatory disease	146	8.0%	21	8.3%	125	8.0%	0.847
Influenza	27	1.5%	5	2.0%	22	1.4%	0.409
Overweight and obesity	228	12.5%	39	15.5%	189	12.1%	0.129
Pneumonia	219	12.0%	45	17.9%	174	11.1%	0.002
Viral pneumonia	15	0.8%	10	4.0%	5	0.3%	<0.001
Bacterial pneumonia	34	1.9%	6	2.4%	28	1.8%	0.458
Organism unspecified	199	10.9%	40	15.9%	159	10.1%	0.007
Smoking (current or past)	240	13.2%	39	15.5%	201	12.8%	0.249
Solid organ or hematopoietic stem cell transplantation	46	2.5%	9	3.6%	37	2.4%	0.256
Vitamin D deficiency	121	6.7%	11	4.4%	110	7.0%	0.117
Eosinophilia on in the year after index date	9	0.5%	2	0.8%	7	0.4%	0.361
Testing on or in the year after index date							
Chest CT	612	33.6%	111	44.0%	501	32.0%	<0.001
Spirometry	227	12.5%	83	32.9%	144	9.2%	<0.001

	Total		Asthma/SABA		No asthma/SABA		
	n=1,819	**%**	**n=252**	**%**	**n=1,567**	**%**	**p-value**
Nitric oxide expired gas determination	10	0.5%	5	2.0%	5	0.3%	0.007
Outpatient prescription medications							
Antifungals[§]	374	20.6%	50	19.8%	324	20.7%	0.761
Fluconazole	89	4.9%	16	6.3%	72	4.6%	0.248
Isavuconazole	5	0.3%	2	0.8%	3	0.2%	0.144
Itraconazole	270	14.8%	30	11.9%	240	15.3%	0.158
Posaconazole	11	0.6%	0	0.0%	11	0.7%	0.380
Voriconazole	22	1.2%	2	0.8%	20	1.3%	0.758
Biologic drug[¶]	4	0.2%	1	0.4%	3	0.2%	0.450

[*] Non-mutually exclusive categories

[†] In the 90 days before or on the index date

[‡] For patients with index date on or after January 1, 2020 (n=910)

[§] In the 7 days before to 6 months after the index date

[¶] Benralizumab, Dupilumab, Mepolizumab, Omalizumab, or Reslizumab in the year after index date

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 2.

Summary of proposed mechanisms for airway hyperresponsiveness following histoplasmosis

Mechanism	Description
Chronic inflammation and remodeling	Persistent immune activation leads to structural airway changes
Th2 immune skewing	Predisposes to eosinophilic airway inflammation
Microbiome disruption	Alters immune regulation and allergen tolerance
Epithelial barrier dysfunction	Enhances allergen and irritant exposure
Fungal persistence	Prolonged antigen exposure may drive chronic inflammation
Genetic factors	Shared risk factors for both asthma and fungal infection susceptibility