Research Article *Open Access*

Journal of CardioVascular Insights

DOI: *doi.org/10.63721/26JCVI0121*

Associations between Asthma and Pulmonary Arterial Hypertension: Insights from the National Inpatient Sample 2016-2020

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Citation: *Omar Khayat MD, Steven Zhou MD, Jerry Dahan Wu, Sara El Yazghi Ezzaher, Kaiyu Jia, et al. (2026) Associations between Asthma And Pulmonary Arterial Hypertension: Insights From The National Inpatient Sample 2016-2020, J of Card Vas Insights 2(2), 01-07. WMJ/JCVI-121*

Abstract

Background: *Asthma and Pulmonary Arterial Hypertension (PAH) share pathological mechanisms, including chronic inflammation, smooth muscle hyperplasia, and the activation of the nuclear factor of activated T cells (NFAT) pathway. However, the clinical correlation between the two diseases is understudied.*

Methods: *We conducted a retrospective cross-sectional study utilizing the Nationwide Inpatient Sample database from 2016 to 2020, which included adults aged ≥18 years. Using ICD-10 codes, PAH and asthma were identified. Secondary pulmonary hypertension (PH) and comorbidities known to be associated with PH were excluded. Logistic regression estimated adjusted odds ratios for PAH, controlling for age, sex, race, chronic kidney disease (CKD), diabetes, hypertension, dyslipidemia, and smoking.*

Results: *Among 18,767,441 hospitalizations, 1,496 had PAH. Patients with PAH were older (mean age: 60.4 vs 52.4 years) and more often female (73.2% vs 61.6%). Asthma prevalence was higher in PAH (9.1% vs 6.7%). Adjusted analysis revealed that asthma was associated with PAH (aOR 1.47, 95% CI 1.23-1.76, $p < 0.001$). Other factors significantly associated with PAH included female sex, older age, Black, Hispanic, and Asian/Pacific Islander race, diabetes, and dyslipidemia.*

Conclusion: *Asthma was associated with 47% higher odds of PAH. Findings support a potential shared NFAT-mediated mechanism. Prospective studies are needed to clarify temporality and assess whether asthma therapies influence PAH risk.*

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Submitted: 23.04.2026 **Accepted**: 29.04.2026 **Published**: 05.04.2026

Introduction

Asthma and pulmonary hypertension (PH) are typically thought of as two distinct disorders that can significantly impact respiratory function and overall health. While asthma is characterized by chronic airway inflammation and reversible bronchoconstriction, pulmonary hypertension involves elevated pressure in the pulmonary arteries, often leading to right heart failure if untreated [1,2].

Emerging evidence suggests that asthma and primary pulmonary arterial hypertension (PAH) may share a common pathogenic mechanism involving the calcineurin-NFAT signaling pathway, which promotes both airway and vascular remodeling. Vasoactive intestinal peptide (VIP), a natural inhibitor of this pathway, has been shown in animal models to reverse features of both asthma and PAH when administered [3]. The absence of VIP leads to activation of calcineurin–NFAT signaling and to the development of inflammation and remodeling in both the airways and pulmonary vasculature [3].

Understanding this connection is crucial, as coexisting PAH can worsen clinical outcomes in asthmatic patients and may require different therapeutic approaches. There is already evidence to suggest that asthma is associated with increased cardiovascular diseases, including coronary artery disease (CAD), peripheral artery disease (PAD), and pulmonary embolism [4-6]. In fact, evidence suggests that treatments for respiratory pathologies, including beta-2 agonists, are associated with improvements in pulmonary vascular function and cardiac hemodynamics with exercise in patients with heart failure with preserved ejection fraction [6,7].

While the theoretical pathophysiology linking asthma to PAH exists, there is limited literature characterizing this association in large clinical populations. This study utilizes a nationwide cohort to investigate whether asthma is independently associated with PAH.

Methods

Data Source and Study Design We conducted a retrospective cross-sectional analysis using the National Inpatient Sample (NIS) database from **2016 to 2020**. The NIS is the largest all-payer inpatient care database in the United States, developed by the Healthcare Cost and Utilization Project (HCUP). It contains data on more than 7 million hospital stays annually, weighted to estimate more than 35 million hospitalizations nationally. Because the NIS uses de-identified data, this study was deemed exempt from Institutional Review Board (IRB) review.

Study Population We included all adult patients (aged ≥18 years) hospitalized during the study period. The study population was stratified into two cohorts based on the presence of PAH.

- **PAH Cohort (Cases):** Defined by the presence of the ICD-10-CM diagnosis code **I27.0** (Primary pulmonary hypertension).
- **Control Cohort:** Defined as all hospitalized adult patients without a diagnosis of PAH.
- To strictly isolate the association between asthma and primary pulmonary vascular remodeling, we rigorously excluded patients with known causes of pulmonary hypertension. Exclusions were categorized according to the 2022 ESC/ERS Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension clinical classification [8]. We excluded patients with any of the following conditions:
- **Group 1 (Associated Forms):** Connective tissue diseases, HIV, Portal hypertension, Congenital heart disease, Systemic Sclerosis, and Schistosomiasis.
- **Group 2 (Left Heart Disease):** Heart failure (preserved or reduced ejection fraction) and Valvular heart disease, Congenital heart disease, Congenital malformations of the Great Arteries and Veins
- **Group 3 (Lung Diseases):** COPD, Restrictive lung disease, Obstructive sleep apnea, and Hypoventilation syndromes.
- **Group 4 (Pulmonary Artery Obstructions):** Chronic thromboembolic pulmonary hypertension (CTEPH).
- **Group 5 (Unclear/Multifactorial):** Hematologic disorders (Sickle cell disease), Systemic disorders (Sarcoidosis, Lupus), and others (Mediastinal disease, Lung cancer/Metastasis).

The primary exposure of interest was a diagnosis of Asthma (ICD-10-CM J45.x). Covariates extracted for adjustment included age, sex, race, chronic kidney disease (CKD), diabetes mellitus, dyslipidemia, hypertension, and smoking status. Data were

analyzed using IBM SPSS Statistics. We used Pearson Chi-square tests for categorical variables and multivariable logistic regression to determine the independent association between asthma and PAH, reporting adjusted Odds Ratios (aOR) with 95% Confidence Intervals (CI). (Supplemental table)

Supplemental Table: ICD-10 Codes Used As Exclusion Criteria

Clinical Condition / Description	ICD-10-CM Codes
Human Immunodeficiency Virus	B20
Portal Hypertension	K766
Schistosomiasis	B65, B65.0, B65.1, B65.2, B65.8, B65.9
Systemic Sclerosis (Scleroderma)	M34, M34.0, M34.2, M34.8, M34.81, M34.89, M34.9
Mixed Connective Tissue Disease	M35.9
Sarcoidosis of Lung	D86.0
Left Heart Failure	I50.1, I50.20–I50.23, I50.30–I50.33, I50.4, I50.40–I50.43, I50.8, I50.82–I50.84, I50.89, I50.9
Valvular Heart Diseases	I05.0–I05.2, I05.9, I06.0–I06.2, I06.8, I34.0, I34.2, I35.0–I35.2
COPD / Emphysema	J43.1, J43.2, J43.8, J43.9, J44.x (J44.0, J44.1, J44.8, J44.81, J44.89, J44.9)
Sleep Apnea	G47.3, G47.30–G47.37, G47.39
Obesity Hypoventilation Syndrome	E66.2
Chronic Thromboembolic pulmonary hypertension	I27.24
Secondary Pulmonary Hypertension	I27.2, I27.20, I27.21, I27.22, I27.23, I27.24, I27.29
Mediastinitis	J98.5, J98.51, J98.59
Metastasis of the Lung	C78.0, C78.00–C78.02, C78.1, C78.2
Congenital Heart Disease	All codes starting with Q20, Q21, Q22, Q23, Q24
Congenital Malformation (Great Arteries)	All codes starting with Q25
Congenital Malformation (Great Veins)	All codes starting with Q26
Lung Cancer	All codes starting with C34
Sickle Cell Disease	All codes starting with D57
Cirrhosis of Liver	All codes starting with K74
Systemic Lupus Erythematosus	M32.1, M32.10–M32.15, M32.19, M32.8, M32.9
Chronic Kidney Disease (Stage 3+)	N18.3, N18.30–N18.32, N18.4, N18.5, N18.6
Interstitial Lung Disease	J84.01–J84.09, J84.10, J84.111–J84.113, J84.115–J84.117, J84.170, J84.178, J84.2, J84.81–J84.848, J84.89, J84.9
Pulmonary Hypertension	I27.0, I27.20, I27.21, I27.22, I27.23, I27.29
Dyslipidemia / Hyperlipidemia	E78.0, E78.00, E78.01, E78.1, E78.2, E78.3, E78.4, E78.41, E78.49, E78.5, E78.6
Essential Hypertension	I10

Tobacco Use / Dependence	Codes starting with F17.2; Z72.0, Z87.891, Z77.22
Diabetes Mellitus (Types 1, 2, & Other)	All codes starting with E10, E11, E13
Atopic Conditions	All codes starting with L20; H10.10–H10.13, J30.1, J30.2, J30.5, J30.8, J30.81, J30.89, J30.9

All patient data obtained in the NIS is deidentified and this study does not require Institutional Review Board approval.

Results

Our sample included 18767441 patients, of which pulmonary artery hypertension was present in 1496 individuals. Within the PAH population, 73.2% of individuals were female, and 9.1% were found to have a concurrent diagnosis of asthma. Majorities of both the pulmonary artery hypertension group and the null group were white (62.8% and 64.0%, respectively), with the remaining distributions (Table 1).

Table 1: Univariate Analysis of Patient Characteristics Stratified by Primary Pulmonary Arterial Hypertension (PAH) Status

Variable	No PAH (N=18,765,945)	PAH (N=1,496)	Univariate OR (95% CI)	P-value
Age (years), Mean ± SD	52.35 ± 20.8	60.44 ± 19.9	—	<0.001*
Female Sex, n (%)	11,553,034 (61.6%)	1,095 (73.2%)	1.70 (1.52 – 1.91)	< 0.001
Asthma, n (%)	1,264,611 (6.7%)	136 (9.1%)	1.38 (1.16 – 1.65)	< 0.001
Race, n (%)				0.121
White	11,625,482 (64.0%)	900 (62.8%)	Reference	
Black	2,725,677 (15.0%)	219 (15.3%)	1.03 (0.89 – 1.19)**	
Hispanic	2,448,960 (13.5%)	187 (13.1%)	0.97 (0.83 – 1.13)**	
Asian/Pacific Islander	602,060 (3.3%)	65 (4.5%)	1.39 (1.08 – 1.79)**	
Native American	127,466 (0.7%)	14 (1.0%)	1.41 (0.82 – 2.41)**	
Other	627,708 (3.5%)	47 (3.3%)	0.96 (0.71 – 1.29)**	
Comorbidities, n (%)				
CKD (III-V/ ESRD)	1,276,248 (6.8%)	229 (15.3%)	2.48 (2.15 – 2.85)	< 0.001
Diabetes Mellitus	3,817,616 (20.3%)	379 (25.3%)	1.33 (1.18 – 1.49)	< 0.001
Dyslipidemia	4,740,288 (25.3%)	495 (33.1%)	1.46 (1.31 – 1.63)	< 0.001
Hypertension	6,432,508 (34.3%)	302 (20.2%)	0.49 (0.43 – 0.55)	< 0.001
Smoking History	5,627,696 (30.0%)	414 (27.7%)	0.89 (0.80 – 1.00)	0.051

Abbreviations: PAH: Pulmonary Artery Hypertension; PAH: Primary Pulmonary Arterial Hypertension; CKD: Chronic Kidney Disease; COPD: Chronic Obstructive Pulmonary Disease; aOR: Adjusted Odds Ratio; CI: Confidence Interval

Of the sample population, 7.9% of patients with PAH had concurrent asthma. This was significantly higher than the 6.8% of patients without PAH who had a concurrent asthma diagnosis (p-value<0.001). After perfor-

ming a multivariate regression to adjust for the potential confounders listed in the methods section, the odds ratio was determined to be 1.47. (Table 2)

Table 2: Multivariable Logistic Regression Analysis of Factors Associated with Primary Pulmonary Arterial Hypertension (PAH)

Variable	Adjusted OR (aOR)	95% Confidence Interval	P-value
Asthma	1.47	(1.23 – 1.76)	< 0.001
Age (per year)	1.03	(1.02 – 1.03)	< 0.001
Female Sex	1.9	(1.69 – 2.14)	< 0.001
Race			0.003
White	Reference	—	—
Black	1.23	(1.05 – 1.42)	0.009
Hispanic	1.19	(1.01 – 1.40)	0.037
Asian/Pacific Islander	1.46	(1.13 – 1.88)	0.003
Native American	1.69	(1.00 – 2.87)	0.052
Other	1.13	(0.84 – 1.51)	0.422
CKD (III-V/ESRD)	1.07	(0.91 – 1.26)	0.441
Diabetes Mellitus	1.15	(1.01 – 1.31)	0.039
Dyslipidemia	1.29	(1.13 – 1.46)	< 0.001
Hypertension	0.3	(0.26 – 0.34)	< 0.001
Smoking History	1.07	(0.95 – 1.21)	0.254

Abbreviations: aOR: Adjusted Odds Ratio; CI: Confidence Interval; CKD: Chronic Kidney Disease; ESRD: End-Stage Renal Disease; PAH: Primary Pulmonary Arterial Hypertension

Discussion

In this large, nationally representative inpatient cohort, we found that patients with pulmonary artery hypertension (PAH) had significantly higher odds of having a diagnosis of asthma compared with patients without PAH, even after adjustment for key cardiometabolic comorbidities. Specifically, amongst patients with PAH, we noted a 47% increase in the odds of having concurrent asthma. These findings provide population-level clinical evidence supporting a potential link between asthma and pulmonary vascular disease.

Several biologically plausible mechanisms may explain this association. Chronic airway inflammation in asthma is characterized by persistent immune activation, cytokine release, and airway remodeling, processes that may extend beyond the bronchial tree to involve the pulmonary vasculature. Experimental models have demonstrated that dysregulation of the calcineurin–NFAT signaling pathway promotes both airway smooth muscle hypertrophy and pulmonary vascular remodeling, leading to phenotypes consistent with asthma and PAH. Vasoactive intestinal peptide (VIP), an endogenous inhibitor of this pathway, has been shown to reverse features of both diseases in animal models, further supporting a shared molecular axis [3].

Our findings align with broader epidemiologic evidence demonstrating increased cardiovascular risk among patients with asthma, including higher rates of coronary artery disease, peripheral arterial disease, and venous thromboembolism. The present study extends this association to pulmonary vascular disease specifically, reinforcing the concept that asthma may

represent an inflammatory condition with important cardiovascular consequences. Notably, β_2-adrenergic agonists, commonly used in asthma management, have been shown to improve pulmonary vascular reserve and cardiac hemodynamics in patients with heart failure with preserved ejection fraction, suggesting that airway-directed therapies may exert secondary effects on pulmonary vascular function [7].

Demographically, patients with PAH in our cohort were older and more likely to be female, findings that are consistent with known epidemiologic patterns of pulmonary arterial hypertension [9]. According to the Global Burden of Disease Study in 2021, prevalence increased progressively with age, peaking amongst the 75-79 year age cohort [10]. Racial and ethnic differences were modest but notable, with higher adjusted odds of PAH among Black, Hispanic, and Asian/Pacific Islander patients compared with white patients. Such patterns have been noted in other studies, particularly for the Black population [11]. There is also well-documented evidence of racial differences in asthma, being more common amongst Black and Hispanic populations [12, 13], which may suggest that observed racial differences in PAH may be, at least in part, mediated by the higher prevalence of asthma in these populations. Disparities may also reflect a combination of genetic susceptibility, environmental exposures, access to care, or differences in disease recognition and coding practices.

Interestingly, traditional cardiovascular risk factors demonstrated heterogeneous associations. Diabetes and dyslipidemia were independently associated with PAH, whereas hypertension was inversely associated. These findings may reflect residual confounding or selection bias related to exclusion of left-sided heart failure and valvular disease, conditions commonly linked with systemic hypertension. For diabetes in particular, there are studies showing a significant association between hyperglycemia and both pulmonary arterial remodeling and group 1 pulmonary hypertension [14]. Despite its well-documented association with PAH, primary hypertension was observed at lower frequency amongst the pulmonary arterial hypertension cohort [15, 16]. This interaction, however, should be interpreted cautiously due to our study's aggressive exclusion criteria as we excluded many of the downstream effects of hypertension that would predispose patients to developing pulmonary hypertension. Additionally, smoking was not independently associated with PH in the adjusted model, which may reflect the exclusion of COPD and emphysema, thereby limiting smoking-related pulmonary vascular pathology in the study population.

This study has several important limitations. First, its retrospective, cross-sectional design precludes causal inference, and temporality between asthma and PH cannot be established. Second, reliance on ICD-10 codes introduces the potential for misclassification and underdiagnosis, particularly for milder asthma or early-stage PH. Additionally, we were unable to stratify asthma by severity, duration, phenotype, or treatment exposure, factors that may significantly influence pulmonary vascular risk [17]. Other important mechanistic variables - such as pulmonary function testing, echocardiographic parameters, right heart catheterization data, IgE levels, and inflammatory biomarkers - were unavailable in the NIS database. Finally, the inpatient nature of the dataset may limit generalizability to ambulatory populations.

Despite these limitations, the strengths of this study include its large sample size, national representativeness, and rigorous exclusion of alternative causes of secondary pulmonary hypertension, allowing for a more focused examination of the asthma - PAH relationship. Our findings underscore the importance of considering pulmonary vascular disease in patients with asthma, particularly older women and individuals with metabolic comorbidities.

Future studies should aim to establish temporal relationships through longitudinal designs and to explore whether asthma severity, duration, or specific phenotypes confer differential risk for PH. Additionally, mechanistic studies evaluating inflammatory signaling pathways, immune mediators, and the impact of asthma-directed therapies on pulmonary vascular remodeling are warranted. Improved understanding of this relationship may open avenues for earlier identification and targeted intervention in high-risk patients, ultimately improving cardiopulmonary outcomes.

Conclusion

Patients with pulmonary hypertension were found to have 47% higher odds of having a history of asthma compared to those without pulmonary hypertension. These findings support the hypothesis that asthma may contribute to the development of pulmonary hypertension. While the mechanism behind this association is unclear, potential reasons based on current literature include chronic inflammation, IgE-mediated immune responses, and activation of the calcineurin-NFAT signaling pathway. Recognizing asthma as a potential risk factor for pulmonary hypertension may have important implications for early identification, monitoring, and targeted management of high-risk patients.

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