Brief report

Association between orchiectomy and asthma: Insights from 2 population-based cohorts

Battoul Fakhry, MD,[a] Celine Chedraoui, MD,[a] Joelle Sleiman, MD,[a] Amy Attaway, MD,[a] Hyun Jo Kim, MS,[b] and Joe G. Zein, MD, PhD[c] *Cleveland, Ohio, and Scottsdale, Ariz*

Background: Orchiectomy, which results in hypogonadism, may increase the risk of asthma due to androgen deficiency.
Objectives: We aimed to investigate the association between orchiectomy and asthma risk.
Methods: Men aged 18 years or older between 1999 and 2016 were identified from the national real-world database IBM-Explorys. We used multivariable logistic regression adjusted for age and body mass index to determine the risk of asthma among individuals who had and had not undergone orchiectomy. To reproduce our findings, we selected men aged 18 years or older with or without a history of orchiectomy who were enrolled in the globally federated TriNetX database as of May 2024.
Results: In the IBM-Explorys database, the orchiectomy group had a 2-fold increase in the odds of having asthma (adjusted odds ratio = 2.03 [95% CI = 1.91-2.16]; $P < .001$). Similarly, in the TriNetX database, the risk of asthma was higher in the orchiectomy group than in the nonorchiectomy group (adjusted odds ratio =1.61 [95% CI = 1.42-1.82]; $P < .001$).
Conclusion: Patients who have undergone an orchiectomy are at increased risk of developing asthma. More research is needed to determine the mechanisms underlying the relationship between asthma diagnosis and orchiectomy. (J Allergy Clin Immunol Global 2025;4:100443.)

Key words: *Asthma, orchiectomy, prevalence*

Abbreviations used
aOR: Adjusted odds ratio
AR: Androgen receptor
BMI: Body mass index
DHEA-S: Dehydroepiandrosterone sulfate
FVC: Forced vital capacity
ICD: International Classification of Diseases
SNOMED: Systematized Nomenclature of Medicine

INTRODUCTION

Asthma prevalence and severity are greater in prepubescent boys and older men than in young adults, suggesting a modulatory role of male sex hormones in asthma pathogenesis.[1] Androgens inhibit airway smooth muscle hypertrophy and hyperplasia, type 2 airway inflammation, and group 2 innate lymphoid cells, all of which contribute to asthma.[2] Higher androgen levels correlate with better lung function in both young asthmatic individuals and the general population, whereas low testosterone levels are common in patients with moderate-to-severe asthma.[2] However, few studies have investigated asthma in individuals with primary hypogonadism (ie, low serum testosterone level and high luteinizing hormone level).[3] Orchiectomy, the surgical removal of 1 or both testes, is a primary treatment for testicular neoplasms or metastatic diseases. Postorchiectomy primary hypogonadism affects around 20% of individuals with testicular cancer after the procedure, regardless of chemotherapy.[4] Individuals who have undergone orchiectomy may therefore be prone to development of the syndrome of androgen deficiency of aging males, which could deprive individuals of the bronchorelaxing action of testosterone and its metabolites (5α- and 5β-dihydrotestosterone) and possibly increase their risk of asthma.[5] Here, we have aimed to determine the risk of asthma in individuals who underwent orchiectomy in 2 population-based real-world databases: IBM-Explorys and TriNetX.

We utilized the validated multicentric research platform IBM-Explorys (IBM, Cleveland, Ohio) to assess a retrospective cohort of adult men (aged ≥18 years) between 1999 and 2016, with or without a surgical history of orchiectomy (SNOMED [Systematized Nomenclature of Medicine] identifier 386633000). Explorys aggregates deidentified electronic health records from both inpatient and outpatient settings across 39 health care organizations in the United States.[6] We used multivariable logistic regression models to assess the risk of asthma (SNOMED identifier 195967001) in individuals who underwent orchiectomy, as adjusted for age and body mass index (BMI).

To reproduce our findings, we used data from TriNetX on men aged 18 years or older who were enrolled as of May 2024 and did or did not have a history of orchiectomy. TriNetX is the largest global federated electronic health record database, comprising more than 120 health care organizations across 29 countries, and it has been extensively validated by numerous published studies.[7] The data set used in the analysis reflects all available data until the extraction date of May 2024. To determine the risk of asthma

From [a]the Lerner Research Institute and Respiratory Institute, Cleveland Clinic; [b]the Department of Systems Biology and Bioinformatics, Case Western Reserve University, Cleveland; and [c]the Department of Medicine, Mayo Clinic, Scottsdale.

Received for publication July 30, 2024; revised December 9, 2024; accepted for publication December 27, 2024.
Available online February 18, 2025.

Corresponding author: Joe Zein, MD, PhD, Medicine, Mayo Clinic Arizona, 13400 E Shea Blvd, Scottsdale, AZ 85259. E-mail: Zein.Joe@mayo.edu.

2772-8293

https://doi.org/10.1016/j.jacig.2025.100443

TABLE I. Clinical characteristics among individuals with asthma stratified by their history of orchiectomy in Explorys and TriNetX

Data set	Explorys		TriNetX	
Category	Orchiectomy (n = 8,920)	Nonorchiectomy (n = 21,903,503)	Orchiectomy (n = 22,508)	Nonorchiectomy (n = 42,074,338)
Asthma, no. (%)	1,110 (12.4)	1,205,780 (5.5)	2,008 (8.9)	1,692,977 (4.0)
Age (y), mean (SD)	—	—	44.9 (19.8)	47.6 (20.4)
Age ≥ 65 y, no. (%)	530 (47.8)	505,340 (41.9)		
Weight category, no. (%)*				
Normal	340 (30.6)	528,220 (43.8)	—	—
Overweight	520 (46.9)	418,720 (34.7)	—	—
Obese	250 (22.5)	258,840 (21.5)	247 (12)	42,376 (8.0)
Outcomes: Risk of asthma				
Unadjusted OR	2.66 (95% CI = 2.50-2.83)		1.54 (95% CI = 1.41-1.69)	
aOR	2.03 (95% CI = 1.91-2.16)		1.61 (95% CI = 1.42-1.82)	

For asthma frequency, percentages are calculated on the basis of total population of the respective group (orchiectomy or nonorchiectomy). For age and weight categories, percentages are calculated on the basis of the population within each subgroup (orchiectomy with asthma or nonorchiectomy with asthma).
OR, Odds ratio.
*Weight category is stratified into normal weight for a BMI of 18.5 to 24.9 kg/m^2, overweight for a BMI of 25 to 29.9 kg/m^2, or obese for a BMI greater than 30 kg/m^2.

(International Classification of Diseases [ICD], 10th Revision, Clinical Modification [ICD-10-CM] identifier J45.xx), we used a 1:1 propensity score matching method without replacement while controlling for age and obesity.

RESULTS AND DISCUSSION

Of the 21,912,423 adult men in Explorys, 8,920 (0.04%) had a history of orchiectomy. The prevalence of asthma was significantly higher in the orchiectomy group than in the controls (12.4% vs 5.5% [$P < .001$]; see Table I). This disparity remains evident even when the data are stratified by age group and BMI categories (Fig 1). After age and BMI had been accounted for, orchiectomy was associated with a 2-fold increase in the odds of development of asthma (adjusted odds ratio [aOR] = 2.03 [95% CI = 1.91-2.16]; $P < .001$). Among those individuals who underwent orchiectomy, asthma was more likely to occur in those aged 65 or older (aOR = 1.12 [95% CI = 1.11-1.12]; $P < .001$) and those with a BMI of 30 or higher (aOR = 2.86 [95% CI = 2.85-2.88]; $P < .001$) (Fig 2).

Of the 42,096,846 individuals in TriNetX who met the inclusion criteria, 22,508 (0.05%) carried a history of orchiectomy. Asthma was diagnosed in 2,008 individuals with a history of orchiectomy (8.9%) and 1,692,977 individuals (4.0%) without a history of orchiectomy. After adjustment for age, race, and obesity, the risk of asthma was higher in the orchiectomy than in the nonorchiectomy group (aOR =1.61 [95% CI = 1.42-1.82]; $P < .001$) (Table I). Subgroup analysis of the individuals with a history of orchiectomy in the setting of testicular cancer showed increased odds of asthma versus in those patients who had undergone orchiectomy without a history of testicular cancer (aOR = 1.18 [95% CI = 1.03-1.34]; n =7,251).

To our knowledge, the incidence of asthma among individuals who have undergone orchiectomy has not been reported previously. Our analysis of real-world data from both Explorys and TriNetX revealed a prevalence of asthma of about 9% in the orchiectomy group. Furthermore, we observed a 1.6-fold increase in likelihood of asthma among individuals with a history of orchiectomy and an absolute difference of more than 5% in prevalence versus in their counterparts.

Previous studies have shown that level of free testosterone is inversely associated with asthma and correlates with better lung function.[2] The negative impact of hypogonadism on the respiratory system after orchiectomy, particularly with regard to asthma, is poorly understood. Androgen deficiency resulting from this procedure may contribute to asthma symptoms, as other forms of hypogonadism such as Klinefelter syndrome, transient medical castration, and androgen receptor deficiency have been linked to increased levels of inflammatory cells and biomarkers involved in chronic airway inflammation.[3,6] Notably, testosterone treatment in patients with asthma and Klinefelter syndrome may reverse inflammatory status and improve asthma control.[3] In fact, a significant improvement in asthma control was reported in patients with Klinefelter syndrome and moderate-to-severe asthma who were receiving 70 mg of nebulized dehydroepiandrosterone sulfate (DHEA-S) versus in those receiving placebo.[8] In a pilot study, we also found that over-the-counter DHEA-S improved FEV_1 value by 51 mL in women with serum DHEA-S levels less than 200 μg/dL.[9] The beneficial effect of androgen was also demonstrated with testosterone supplementation.[10] Testosterone was shown to have direct bronchorelaxing and bronchoprotective properties in animal models of asthma.[5] A large study by the UK Biobank reported that among 256,419 adults aged 40 to 69 years, those with elevated free testosterone levels (regardless of whether they were men or women) had a lower risk of asthma.[2] Moreover, higher levels of testosterone in men were positively correlated with ratio of FEV_1 value to and forced vital capacity (FEV_1/FVC).[2] In a study conducted on Puerto Rican youth aged 6 to 20 years, increased ratio of free testosterone to estradiol was associated with improved FEV_1/FVC values in both sexes and higher FEV_1 values in males. It was only in females with asthma that this increased ratio was linked to a decrease in eosinophil count. Testosterone alone did not show any significant effect on lung function or eosinophil count.[11] In contrast, in another cross-sectional study (the National Health and Nutrition Examination Survey [NHANES]), serum testosterone was inversely linked with odds of current asthma in both sexes. Particularly in men, every 1-unit increase in $\log^2$ testosterone level reduced the odds of asthma development by 11%. In addition, increased testosterone level was significantly associated with increases in FEV_1 value but not in levels of eosinophils or fractional

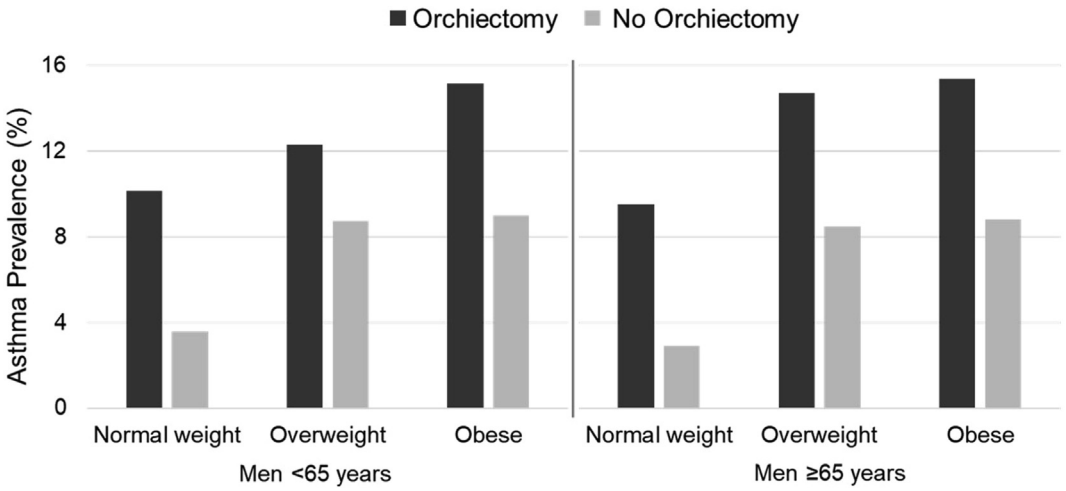

FIG 1. Bar plot of the prevalence of asthma in men from Explorys with and without a history of orchiectomy in different age and BMI subgroups. The prevalence of asthma was higher in individuals with a history of orchiectomy than in those without a history of orchiectomy irrespective of age and weight categories.

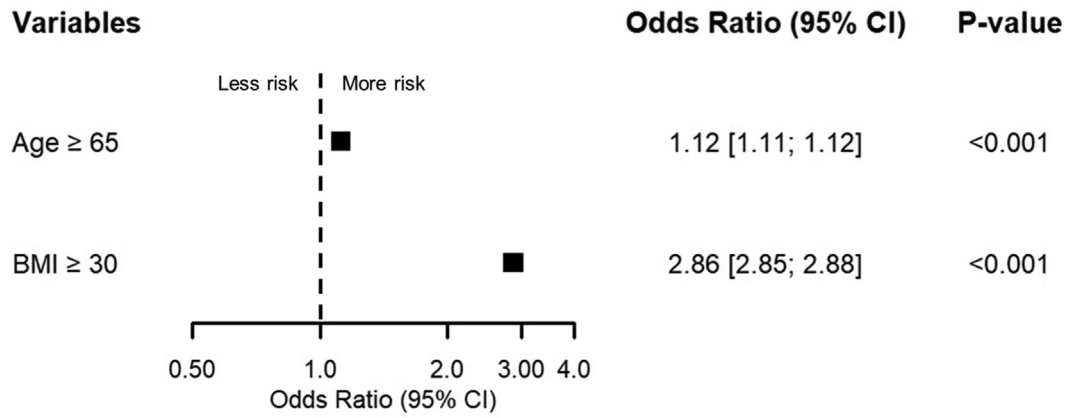

FIG 2. Forest plot showing the likelihood of asthma according to age and BMI in the orchiectomy group from the Explorys cohort. Individuals who underwent orchiectomy had higher odds of asthma if they were aged 65 years or older and had a BMI of 30 or higher.

exhaled nitric oxide.[12] Bronchial epithelial cell data from the Severe Asthma Research Program (SARP) showed that androgen receptor (AR) gene expression positively correlated with FEV_1 and FEV_1/FVC values, as well as with Asthma Quality of Life Questionnaire score and negatively linked with fractional exhaled nitric oxide level. There was also an observed reduction in ARs in patients with asthma treated with oral corticosteroids.[13] In this same study, Zein et al found that FEV_1 percent predicted was positively associated with levels of DHEA-S and testosterone in men with severe asthma.[13] In another analysis of IBM Explorys conducted by Gaston et al, patients with phenotypic evidence of AR deficiency (ie, androgen insensitivity syndrome) had a higher risk of asthma.[6] In addition, patients with a history of orchiectomy are at higher risk of metabolic syndrome, a condition that is commonly reported in patients with asthma.[4] Our findings suggest a 2-fold increased risk of asthma in obese patients with a history of orchiectomy. Previous studies have shown that decreased testosterone levels are linked with increased adiposity and adipokine dysregulation, such as increased leptin and decreased adiponectin levels. These inflammatory mediators can enhance airway remodeling and hyperresponsiveness, which are hallmarks of asthma.[14,15]

A major limitation of our study is that patients may have received care outside the Explorys and TriNetX networks, leading to incomplete medical records. Moreover, our findings may be biased because billing codes (SNOMED in Explorys and ICD-10-CM and ICD-10 Procedure Coding System [ICD-10-PC] in TriNetX) were used to diagnose asthma without confirmatory spirometry. Another limitation is that we did not evaluate the effect of orchiectomy duration or age at orchiectomy on the odds of asthma. Of note, because of the cross-sectional nature of our analysis, it is not possible to establish causality or demonstrate the temporal relationship between orchiectomy and asthma. Despite these limitations, this is, to our knowledge, the first study to explore the prevalence of asthma among patients with a history of orchiectomy using real-world data. Our findings are widely applicable, as Explorys and TriNetX are representative of national and international populations, respectively. Additionally, our results in Exlporys were validated and confirmed by the TriNetX cohort.

Future studies should explore the potential impact of orchiectomy or altered testosterone levels on lung function and eosinophilic inflammation. Such research could provide valuable insights into the effect of androgen on eosinophilic airway inflammation. More studies are needed to distinguish between unilateral and bilateral orchiectomy, as well as to explore how disease-specific contexts interact with orchiectomy so as to understand their different modulatory effect on asthma. Given the complexity of asthma pathogenesis, orchiectomy affects asthma risk through a combination of hormonal, metabolic, and immunologic pathways.[5,14,16] Further mechanistic research is crucial to investigate the relative contribution of androgen depletion and other mediators on asthma. On the basis of our findings, we propose use of targeted screening questions during asthma consultation regarding orchiectomy status and androgen-related conditions in male patients with asthma alongside preoperative patient education through educational materials or by health care providers (eg, primary care physicians, allergists, immunologists, pulmonologists, surgeons) on the potential impact of orchiectomy on respiratory health to promote informed personalized care. Hence, it is important to establish a specific threshold below which the risk of asthma development increases, which could guide these interventions.

In conclusion, individuals with orchiectomy appear to have greater odds of having asthma. More research is warranted to understand the complex relationship between asthma and orchiectomy, as well as the underlying mechanisms driving their coexistence.

DISCLOSURE STATEMENT

Supported by the National Heart Lung and Blood Institute, National Institutes of Health (grant R01 HL161674 [to principal investigator J.G.Z.]).

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

REFERENCES

1. Zein JG, Dweik RA, Comhair SA, Bleecker ER, Moore WC, Peters SP, et al. Asthma is more severe in older adults. PLoS One 2015;10:e0133490.
2. Han YY, Yan Q, Yang G, Chen W, Forno E, Celedon JC. Serum-free testosterone and asthma, asthma hospitalisations and lung function in British adults. Thorax 2020;75:849-54.
3. Ladias S, Katsenos S. Klinefelter syndrome and bronchial asthma: is there any relationship between the low testosterone levels and asthma exacerbations? Lung India 2018;35:368.
4. Kirby M. Testicular cancer: low testosterone and the metabolic syndrome. Trends Urol Mens Health 2020;11:12-7.
5. Montaño LM, Espinoza J, Flores-Soto E, Chávez J, Perusquía M. Androgens are bronchoactive drugs that act by relaxing airway smooth muscle and preventing bronchospasm. J Endocrinol 2014;222:1-13.
6. Gaston B, Marozkina N, Newcomb DC, Sharifi N, Zein J. Asthma risk among individuals with androgen receptor deficiency. JAMA Pediatr 2021;175:743.
7. Palchuk MB, London JW, Perez-Rey D, Drebert ZJ, Winer-Jones JP, Thompson CN, et al. A global federated real-world data and analytics platform for research. JAMIA Open 2023;6:ooad035.
8. Canguven O, Albayrak S. Do low testosterone levels contribute to the pathogenesis of asthma? Med Hypotheses 2011;76:585-8.
9. Marozkina N, Zein J, DeBoer MD, Logan L, Veri L, Ross K, et al. Dehydroepiandrosterone supplementation may benefit women with asthma who have low androgen levels: a pilot study. Pulm Ther 2019;5:213-20.
10. Wulfsohn NL, Politzer WM, Henrico JS. Testosterone therapy in bronchial asthma. S Afr Med J 1964;38:170-2.
11. Han YY, Forno E, Witchel SF, Manni ML, Acosta-Pérez E, Canino G, et al. Testosterone-to-estradiol ratio and lung function in a prospective study of Puerto Rican youth. Ann Allergy Asthma Immunol 2021;127:236-42.e1.
12. Bulkhi AA, Shepard KV, Casale TB, Cardet JC. Elevated testosterone is associated with decreased likelihood of current asthma regardless of sex. J Allergy Clin Immunol Pract 2020;8:3029-35.e4.
13. Zein JG, McManus JM, Sharifi N, Erzurum SC, Marozkina N, Lahm T, et al. Benefits of airway androgen receptor expression in human asthma. Am J Respir Crit Care Med 2021;204:285-93.
14. Tang Fui M, Dupuis P, Grossmann M. Lowered testosterone in male obesity: mechanisms, morbidity and management. Asian J Androl 2014;16:223.
15. Behre HM, Simoni M, Nieschlag E. Strong association between serum levels of leptin and testosterone in men. Clin Endocrinol (Oxf) 1997;47:237-40.
16. Cephus JY, Stier MT, Fuseini H, Yung JA, Toki S, Bloodworth MH, et al. Testosterone attenuates group 2 innate lymphoid cell-mediated airway inflammation. Cell Rep 2017;21:2487-99.