

Incidence and Prevalence of Idiopathic Orbital Inflammatory Syndrome: A Retrospective Analysis

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Abstract

Background

Idiopathic orbital inflammatory syndrome (IOIS) is characterized by orbital inflammation that can lead to pain, restricted eye movement, and vision loss. Current IOIS research has been limited by small cohorts and case studies. To address this gap, we used a large, international, deidentified database to evaluate the annual and 11-year incidence and prevalence of idiopathic orbital inflammatory syndrome (IOIS) among adults and characterize the associated demographic and clinical features of IOIS patients.

Methods

In this retrospective cohort trend study, we used ICD-10 codes to analyze the annual and 11-year incidence and prevalence of IOIS between 2013 and 2023 in subjects ≥ 18 years old in the TriNetX database. Characteristics collected included age, sex, race, ethnicity, prescribed immunosuppressive agents, associated systemic diseases, and ocular complications.

Results

IOIS was diagnosed in 5,102 subjects, predominantly female (63.35%), White (62.59%), and non-Hispanic or Latino (71.7%), with a mean age of 51.4 ± 18.4 years. The cumulative 11-year incidence was 0.82 per 100,000 persons; prevalence was 3.86 per 100,000 persons. Both rates rose over the study period, with a decline in 2020–2021. After stratification by age and race, rates were highest among subjects aged 40–79 years and Native American individuals. Prednisone was the most prescribed immunosuppressive agent (29.76%). Diplopia was the most frequent ocular complication (12.86%). Rheumatoid arthritis was the most common associated systemic disease (7.74%).

Conclusions

IOIS patients within the TriNetX database had similar demographics and immunosuppressant medication use as previous studies on IOIS but showed a decreased incidence.

Introduction

Idiopathic orbital inflammatory syndrome (IOIS) or orbital pseudotumor, was first described by Birch-Hirschfeld in 1905.¹ It is the third most common orbital disease and accounts for 6–16% of orbital lesions and 10% of orbital tumors.² IOIS most often occurs in middle-aged adults with a female predominance of up to 66% of cases.^{3–5} Clinically, IOIS can cause pain, diplopia, proptosis, and eye movement limitations. Inadequate or delayed treatment can lead to vision loss and the spread of

inflammation to surrounding structures, including the optic nerve. This increases the risk of developing secondary complications, including glaucoma, exposure keratitis, and corneal ulceration.^{5,6} While the pathophysiology of IOIS remains undetermined, T-cell dysregulation leading to the activation of the innate immune system and IgG4-driven immune responses are hypothesized to result in continued inflammation.^{7–9}

The diagnosis of IOIS involves a combination of imaging, histopathologic, and clinical findings. Neuroimaging, with either MRI or CT scans, shows a diffuse, contrast-enhanced orbital lesion or extraocular muscle enlargement. Orbital biopsy can rule out alternative diagnoses and provide tissue for pathologic analysis, which shows lymphoplasmacytic infiltrate and the absence of granulomatous inflammation, vasculitis, or necrosis. Plasma cell staining can also be performed to exclude IgG4-related disease.¹⁰ For IOIS to be differentiated from IgG4-related disease, the ratio of IgG4-positive to total IgG-positive plasma cells should be $\leq 40\%$ or there should be ≤ 30 IgG4-positive plasma cells per high powered field.¹⁰ In cases of myositic IOIS, a response to corticosteroids within 48 hours of administration is also a clinical consideration for diagnosis.¹⁰ It is also important to note that for certain subtypes of IOIS, especially those involving the lacrimal gland, surgical intervention undertaken for diagnostic purposes may also have a therapeutic benefit. In these cases, obtaining a large biopsy and/or performing debulking of the lacrimal gland has been reported to achieve disease control in up to 80% of subjects, with only 8% subsequently requiring additional immunosuppressive therapy.¹¹ However, systemic immunosuppression remains the cornerstone of treatment for most cases of IOIS. Current first-line treatment for IOIS involves corticosteroids, which have been found to be an effective monotherapy in nearly 40% of subjects.¹² Due to the systemic side-effects associated with long-term corticosteroid use, non-corticosteroid immunosuppressant agents, including anti-metabolites and biologics, have been used and have shown efficacy in treating IOIS.^{13,14}

Current IOIS research is limited by small, single-center, retrospective cohorts and case studies, with no studies to date exceeding 80 subjects.^{15–17} These methodological limitations have resulted in inconsistent findings, driven by variability in diagnostic criteria and study populations. In particular, diagnostic criteria differ in whether corticosteroid response and tissue biopsy are required to confirm the diagnosis.¹⁰ Additionally, due to the lack of large-scale studies on IOIS, there are limited data on the incidence, prevalence, and racial demographics of the disease. This study addressed these limitations by utilizing a large-scale, deidentified database to analyze the annual and 11-year cumulative incidence and prevalence of IOIS. Secondary outcomes included analysis of associated systemic diseases, immunosuppressive medication use, and ocular complications.

Methods

This was a retrospective cohort trend study using the TriNetX Global Collaborative Network from January 1, 2013 to December 31, 2023. The database contains medical records of over 100 million subjects from 162 healthcare organizations. The data were collected in January 2026. Subjects included

in the study were 18 years of age or older and identified as having IOIS using the International Classification for Diseases, 10th Edition (ICD-10) code H05.1. The primary outcome was the yearly and 11-year cumulative incidence and prevalence of IOIS. Demographics collected included sex, age, ethnicity, and race.

Secondary outcomes included the rate of ocular complications within the IOIS cohort using ICD-10 codes: diplopia (H53.2), proptosis (H05.20, H05.24, H05.25); blindness and low vision (H54). Ocular complications were included only if they occurred on the same day or after the IOIS diagnosis.

Systemic inflammatory diseases occurring with a diagnosis of IOIS were also evaluated using ICD-10 codes: ankylosing spondylitis (M45), rheumatoid arthritis (M05, M06), sarcoidosis (D86), Sjogren syndrome (M35.0), Crohn disease (K50), ulcerative colitis (K51), systemic lupus erythematosus (M32), Behcet disease (M35.2), scleroderma (M34), granulomatosis with polyangiitis (M31.7), and eosinophilic granulomatosis with polyangiitis (M30.1).

Immunosuppressive medications prescribed for the management of IOIS were analyzed using RxNorm and Healthcare Common Procedure Coding System (HCPCS) codes. Medications were included only if they were prescribed at or after the IOIS diagnosis. The medications evaluated were prednisone (8640), oral prednisolone (J7510), methotrexate (6851), azathioprine (1256), mycophenolate (265323, 7145, 68149, J7517, J7518), tacrolimus (42316), oral cyclosporine (3008, J7502, J7515), cyclophosphamide (3002), chlorambucil (2346), adalimumab (327361), infliximab (191831), tocilizumab (612865), anakinra (72435), golimumab (819300), certolizumab pegol (709271), and rituximab (121191).

All statistical tests to calculate the incidences and prevalences were performed using software on the TriNetX platform. Incidence and prevalence rates were reported as cases per 100,000 persons. The data were de-identified per Section § 164.514(a) of the HIPAA Privacy Rule. The process by which the data were de-identified is attested to through a formal determination by a qualified expert as defined in Section § 164.514(b)(1) of the HIPAA Privacy Rule. This formal determination by a qualified expert was refreshed on December 2020. Given the deidentified and aggregated data within the database, the Drexel University College of Medicine Internal Review Board deemed this study exempt and it followed the tenets of the Declaration of Helsinki.

Results

Of the 153,231,486 subjects within the database, 5,102 (0.0033%) subjects were diagnosed with IOIS. The average age was 51.4 years (SD 18.4) and the cohort was predominantly female (n = 3,232; 63.35%), White (n = 3193; 62.6%), and non-Hispanic or Latino (n = 3658; 71.7%). Full demographic information can be found in Table 1.

From 2013–2023, the cumulative incidence of IOIS diagnosis was 0.82 per 100,000 persons and the cumulative prevalence of IOIS diagnosis was 3.86 per 100,000 persons. The yearly incidence and prevalence of IOIS increased throughout the time period, except for a decrease in the incidence in 2020

and 2021 (Figs. 1 and 2). When stratified by age, the highest incidence and prevalence was found in those 40–59 and 60–79 (Table 2). When stratified by race, the Native American cohort had the highest cumulative incidence and prevalence rates at 4.33 per 100,000 persons and 7.26 per 100,000 persons, respectively (Table 2).

Prednisone (n = 923; 29.76%) was the most prescribed immunosuppressive medication followed by the antimetabolites, including methotrexate (n = 408; 8.32%) (Supplementary Table 1). Diplopia was the most common ocular complication (n = 656; 12.86%) followed by proptosis (n = 599; 11.74%), and low vision and blindness (n = 506; 9.92%) (Supplementary Table 2). The most associated systemic diagnosis was rheumatoid arthritis (n = 395; 7.74%) followed by sarcoidosis (n = 214; 4.19%), and Sjögren syndrome (n = 207; 4.06%) (Supplementary Table 3).

Discussion

The results of this large, retrospective cohort study largely align with the current literature on the demographic and clinical characteristics IOIS, while providing novel population-level data on disease incidence, prevalence, racial distribution, systemic associations, and treatment patterns. Although no population-based studies have been conducted on IOIS, a 10-year study conducted in Olmsted County, Minnesota in 2022 reported an incidence of orbital masses of 142.67 per 100,000 persons.¹⁸ IOIS is a common etiology of orbital lesions with 11% of masses in a 30-year-long 2002 Wills Eye Hospital study attributed to IOIS.¹⁹ Furthermore, a 20-year study at Newcastle Eye Center conducted in 2019 in the United Kingdom found that 31.3% of biopsies of orbital mass lesions were due to IOIS.²⁰ These studies suggest a more frequent occurrence of IOIS than the incidence found in our study. However, the duration of each study varied and largely had longer time periods compared to our study. Additionally, all were conducted at tertiary referral centers, which may have patient populations with more severe orbital pathologies. Overall, this retrospective cohort study demonstrated an increasing incidence and prevalence of IOIS throughout the study period. The cause of this increasing incidence and prevalence of IOIS is likely manifold as it reflects the progressive clarification and standardization of IOIS diagnostic criteria as well as the improved recognition of the disease in clinical practice. Differentiation of IOIS from IgG4-related ophthalmic disease is a factor in the increase in IOIS diagnoses since 2013.¹⁰ Additionally, analysis of orbital biopsies has improved due to the increased implementation of high-throughput assays and comprehensive molecular characterization of biopsy samples.²¹ The dip in incidence in 2020 and 2021 can be attributed to the SARS-CoV-2 pandemic, which resulted in a decrease in ophthalmology clinic visits due to clinic closures and lockdown restrictions.^{22–26}

The peak incidence and prevalence of IOIS in our study at ages 40–79 aligns with previous case series and population-based studies, supporting the concept that IOIS primarily affects adults rather than pediatric populations.²⁷ A retrospective study of 172 subjects with IOIS at the Massachusetts Eye and Ear Infirmary reported a mean age of 46 years and a study of 111 subjects at a tertiary referral center in Germany found a mean age of 49.5 years.^{4,28} The Massachusetts Eye and Ear Infirmary study also had a

female predominance (66%), which aligns with our cohort, which was 63.35% female.⁴ While our age and sex-related findings mirror the existing literature, we identified a new demographic finding that Native Americans had a higher incidence and prevalence of IOIS. Claims database analyses and scoping reviews have found that Native Americans have increased rates of both intraocular and orbital diseases, although the incidence of IOIS was not specifically assessed.^{29,30} However, the prevalence of autoimmune diseases associated with IOIS, particularly Sjogren syndrome, rheumatoid arthritis, systemic lupus erythematosus, and inflammatory myopathies, are higher in Native Americans compared to other racial groups.^{31–33} These findings demonstrate the importance of considering demographic variations in disease epidemiology and suggest that population-specific characteristics increase the incidence of IOIS development.

Analysis of systemic autoimmune and inflammatory comorbidities revealed that rheumatoid arthritis, sarcoidosis, and Sjögren syndrome demonstrated the highest systemic associations with IOIS. Many of these conditions are included in the differential diagnosis of IOIS due to overlapping clinical presentation and radiographic features.^{4,34} IOIS is widely considered an immune-mediated inflammatory disorder characterized by lymphoplasmacytic infiltration, cytokine-driven tissue edema, and, in some cases, fibrosis within the orbit.^{2,3,35,36} This inflammatory profile parallels key pathogenic mechanisms seen in both rheumatoid arthritis and Sjögren syndrome with B- and T-cell dysregulation and chronic cytokine activation.^{3,37–39} Overlapping immune pathways, including Th1- and Th17-mediated responses, B-cell activation, and elevated pro-inflammatory cytokines (e.g., TNF- α , IL-6) with soft tissue compartments rich in orbital fibroblasts may promote the development of orbital inflammation in genetically susceptible individuals.^{7,40,41} Collectively, these data suggest that IOIS may share pathogenic mechanisms and represent an extra-articular manifestation of these systemic autoimmune diseases versus existing as entirely isolated orbital process.

Systemic corticosteroids remain the first-line therapy for IOIS due to their rapid efficacy in controlling inflammation and are often used as monotherapy rendering this class the most frequently prescribed treatment.¹² However, high rates of recurrence and long-term side effects of corticosteroids require use of anti-metabolite or biologic agents, which have a delayed onset of up to 6 months for full efficacy.⁴² Antimetabolites are the most commonly used non-corticosteroid immunosuppressive agents, while tumor necrosis α (TNF) inhibitors or other biologic agents are only prescribed in refractory cases.^{9,14,43,44} Rituximab, a CD20 inhibitor, is particularly effective in cases associated with vasculitides and the myositis and dacryoadenitis subtypes of IOIS.^{28,45} Collectively, the broad spectrum of medications prescribed after initial corticosteroid therapy reflects the lack of standardized treatment protocols for IOIS and the differential efficacy based on the associated autoimmune disorder or IOIS subtype.

Diplopia was the most common ocular complication, which reinforces the role of extraocular muscle inflammation and motility restriction in IOIS pathophysiology.⁴⁶ Involvement of one or more extraocular muscles leads to edema, muscular enlargement, and fibrosis resulting in impaired ocular alignment and binocular diplopia. Prior case studies have similarly identified diplopia as one of the most frequent

presenting symptoms, particularly in the myositic subtype of IOIS.⁴⁷ The observed 9.92% incidence of low vision and blindness falls within the lower end of the range reported in the literature.⁴⁸ In the 2007 Sydney Eye Hospital case series, 5 subjects (21%) presented with decreased vision.⁴⁹ Additionally, a 2009 case series from the National Taiwan University Hospital evaluated 9 subjects with idiopathic sclerosing orbital inflammation, which is a subtype of IOIS, and found that 8 subjects (89%) presented with reduced visual acuity.⁵⁰ A case series of sclerosing IOIS at Vancouver General Hospital reported that 3 subjects (19%) progressed to blindness.⁵¹ Rates of low vision and blindness in these studies tend to be higher due to the aggressive and fibrotic nature of idiopathic sclerosing orbital inflammation. The lower rate of our cohort likely reflects the larger number of subjects with IOIS in the TriNetX database compared to case series. In addition, the database represents a more globally representative study population that includes all IOIS subtypes. Regardless of subtype, vision loss in IOIS is thought to occur when inflammatory expansion within the confined orbital space leads to compressive optic neuropathy or when inflammation directly involves the optic nerve sheath.^{46,52,53} Rates of proptosis were found to be less common than reported by past case studies on IOIS subjects. In the 2007 case series from Sydney Eye Hospital, proptosis was reported in 15 subjects (63%).⁴⁹ Additionally, a 2012 cross-literature review of cases of idiopathic sclerosing orbital inflammation found that 73% of cases presented with proptosis.⁵⁴ This discrepancy may be due to the TriNetX database relying on billing diagnostic codes rather than free-text clinical documentation. Additionally, an important difference lies in the study populations examined. Previous IOIS studies assessing proptosis were conducted with smaller patient cohorts at academic sites specializing in orbital masses and pathology, while the TriNetX database draws from a larger number of patients from a diverse range of clinical settings.

Although a large, international dataset enabled assessment of the incidence and prevalence of a rare condition, there are limitations to this study. The retrospective design of this study relies on accurate diagnostic coding, which reflects variability in diagnostic criteria prior to recent standardization. Additionally, the deidentified and aggregated nature of the TriNetX data prevented individual chart review and prevented assessment of the treatment indication for which a medication was prescribed. Pathology and imaging study results also were unavailable to confirm an IOIS diagnosis, the disease severity, or involvement of associated ocular structures.

In summary, this large-scale, retrospective study provides important insights into the incidence and prevalence of IOIS, which has increased since 2013. Prospective, multicenter studies are needed to assess the accuracy of newer diagnostic criteria, evaluate the efficacy of immunosuppressive treatments, and characterize the disease burden across all ethnic groups. Specifically, better phenotypic characterization of IgG4-related and non-IgG4-related IOIS could improve diagnostic accuracy and guide clinical management. Determining treatment efficacy could help establish standardized treatment protocols that can assist clinicians in managing IOIS in patients. Additionally, the cause of disproportionate rates of IOIS in Native Americans found in this study warrants further investigation to determine what underlies this increased susceptibility.

Declarations

Competing Interests Statement:

The authors report there are no competing interests to declare.

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Author Contribution Statement

RA was responsible for design of the study, acquisition and analysis of data, drafting the manuscript, and revision of the manuscript. WD was responsible for revision of the manuscript. MB was responsible for design of the study, revision of the manuscript, and final approval of the manuscript to be published.

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Tables

Table 1 and 2 are available in the Supplementary Files section.

Figures

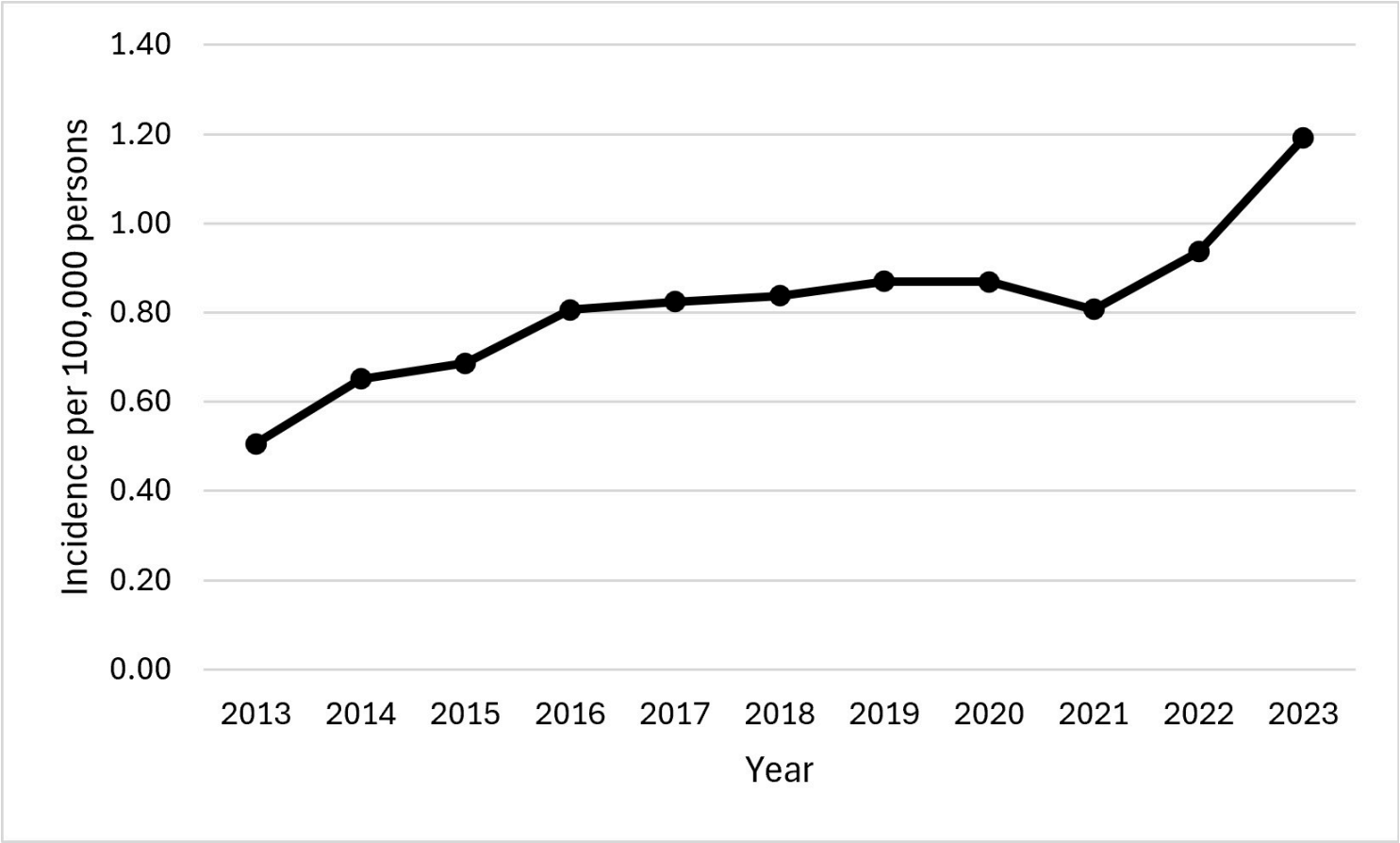


Figure 1

Incidence of Idiopathic Orbital Inflammatory Syndrome from 2013 to 2023 in the TriNetX Global Collaborative Network

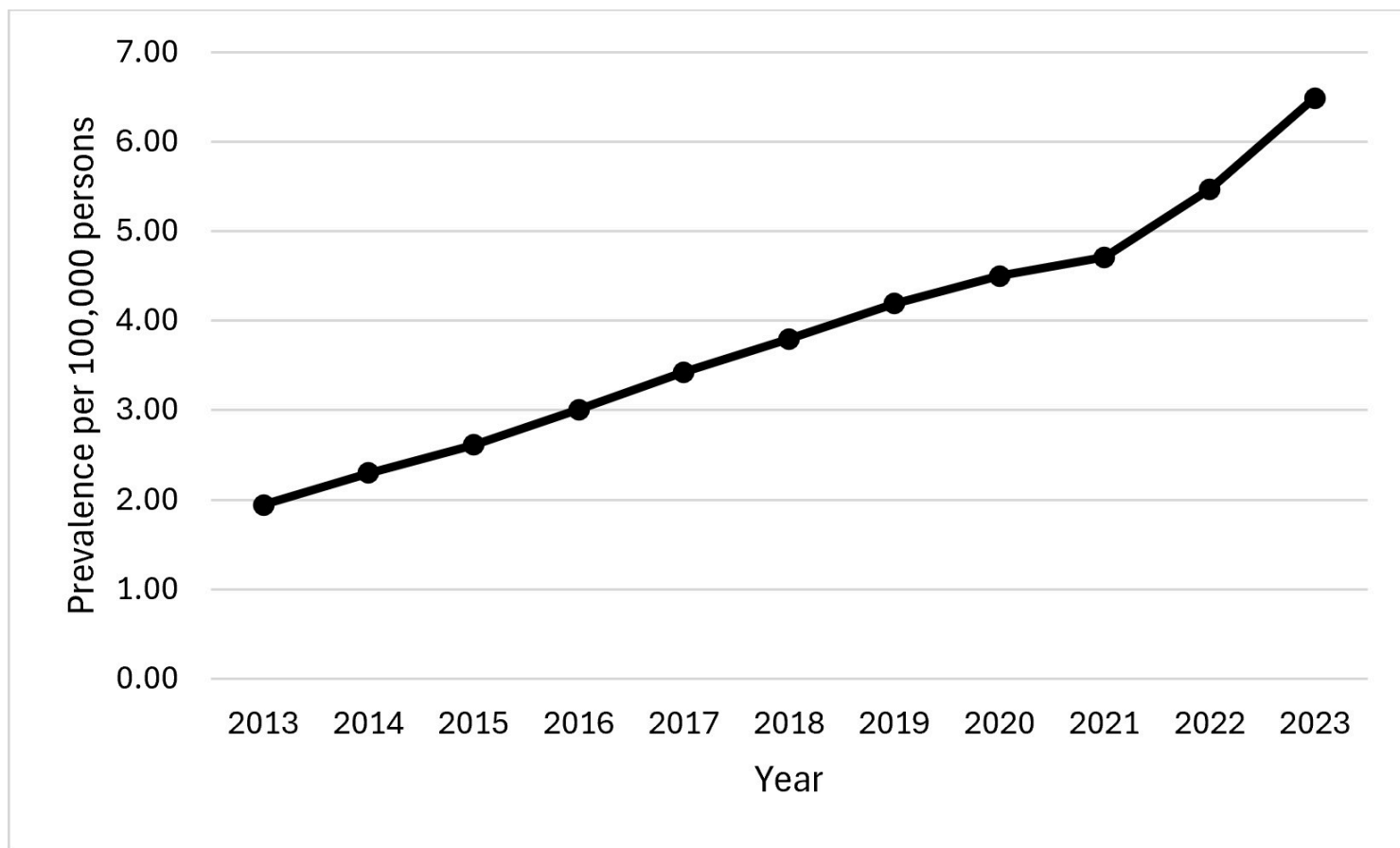


Figure 2

Prevalence of Idiopathic Orbital Inflammatory Syndrome from 2013 to 2023 in the TriNetX Global Collaborative Network

Supplementary Files

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