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Risk of Developing Pediatric Uveitis Among Patients With Early-Onset Atopic Dermatitis

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IMPORTANCE The relationship between atopic dermatitis (AD) and pediatric uveitis may be underexplored, warranting large-scale, multicenter studies.

OBJECTIVE To evaluate the risk of pediatric uveitis among children with early-onset AD compared with a matched control population.

DESIGN, SETTING, AND PARTICIPANTS This cohort study used aggregated electronic health records of US patients with early-onset AD and matched controls from January 1, 2004, through December 14, 2024, sourced from health care organizations in the collaborative research network TriNetX. Patients with early-onset AD and matched controls without AD were included in the analysis; those with uveitis prior to AD diagnosis were excluded. Propensity score matching was applied to balance baseline characteristics. The analyses were conducted on December 14, 2024.

EXPOSURE *International Classification of Diseases, 10th Revision* (*ICD-10*) diagnosis code for AD.

MAIN OUTCOMES AND MEASURES The primary outcome was the hazard ratio (HR) for developing pediatric uveitis in the AD cohort compared with the matched controls. Cox proportional hazards models were applied to assess the risk.

RESULTS A total of 114 889 patients were identified in the AD cohort (mean [SD] follow-up, 6.0 [3.3] years; mean [SD] age, 0.5 [0.7] years; 64 817 male [56.4%]) and the control cohort (mean [SD] follow-up, 6.6 [3.7] years; mean [SD] age, 0.6 [0.8] years; 65 377 male [56.9%]) after matching. The AD cohort demonstrated a higher risk of developing pediatric uveitis compared with controls (94 [0.08%] vs 58 [0.05%]; HR, 1.92 [95% CI, 1.38-2.66]). Sensitivity analyses among patients without dupilumab use (89 of 113 284 [0.08%] vs 59 of 113 284 [0.05%]; HR, 1.77 [95% CI, 1.27-2.46]) and those without autoimmune conditions (80 of 114 425 [0.07%] vs 61 of 114 425 [0.05%]; HR, 1.52 [95% CI, 1.09-2.12]) similarly indicated an increased risk in the AD cohort. Additionally, patients with severe AD had a higher risk of developing pediatric uveitis compared with those with nonsevere AD (12 of 3004 [0.40%] vs 97 of 126 482 [0.08%]; HR, 3.64 [95% CI, 2.00-6.66]).

CONCLUSIONS AND RELEVANCE This cohort study of children with early-onset AD found an elevated risk of pediatric uveitis compared with matched controls, independent of autoimmune conditions or dupilumab use. These findings support the potential need to consider ophthalmologic monitoring in children with early-onset AD to try to detect and subsequently manage uveitis if it develops.

Supplemental content

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Atopic dermatitis (AD) is a chronic inflammatory skin disorder affecting 5% to 20% of children globally.[1,2] Most cases of AD are early onset, developing in infancy, with 45% of patients developing symptoms by 6 months of age and 60% by 12 months.[3] It is associated with a range of ophthalmic complications, including blepharitis, keratoconjunctivitis, keratoconus, glaucoma, cataracts, retinal detachment, and uveitis.[4] Although uveitis is rare and often asymptomatic in the pediatric population,[5] it can become chronic and lead to ocular damage, potentially resulting in cataracts, glaucoma, and amblyopia.[5,6] Despite its potential severity, uveitis in the context of AD has been reported in only a few case studies,[7-12] with some attributing its occurrence to the use of dupilumab,[7,10-12] a treatment for AD. Furthermore, to our knowledge, only 1 single-center case-control study has investigated the association between atopy and uveitis, in a primarily adult population.[13] To address the apparent underexplored association between early-onset AD and pediatric uveitis, we used TriNetX, a multicenter electronic medical record database, to assess uveitis risk in children with early-onset AD vs matched controls.

Key Points

Question Is the risk of pediatric uveitis increased in children with early-onset atopic dermatitis (AD) compared with a matched control population?

Findings In this cohort study of 114 889 patients with early-onset AD, an elevated risk of pediatric uveitis was observed compared with 114 889 propensity-score–matched controls without AD. This increased risk was independent of autoimmune conditions or dupilumab use.

Meaning These findings support the potential need to consider ophthalmologic monitoring in children with early-onset AD to try to detect and subsequently manage uveitis if it develops.

Methods

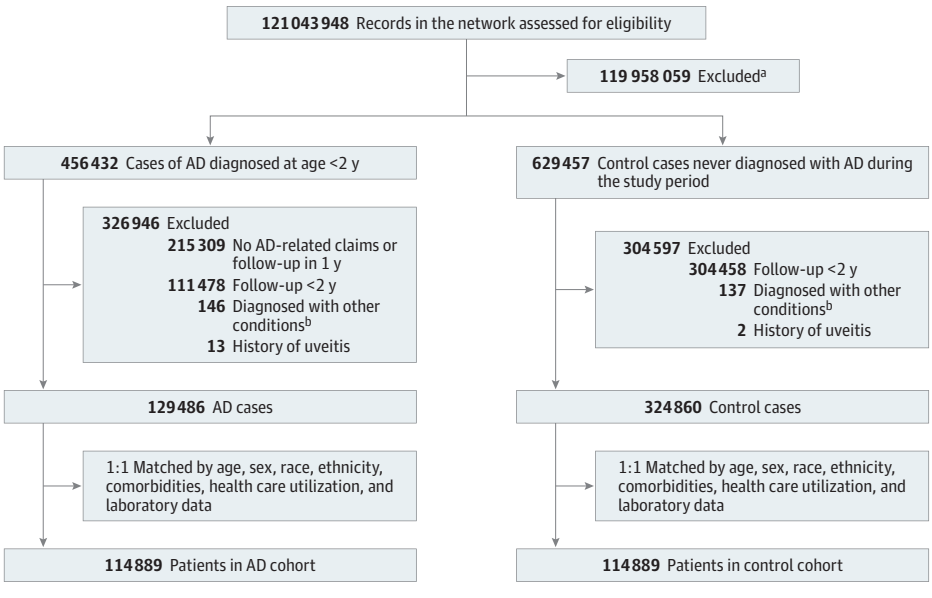
Study Population

This study used data from the TriNetX Research Network. The analyses were conducted on December 14, 2024. We focused on the US Collaborative Network, comprising 69 health care organizations across all 50 individual states in the US with 121 043 948 patients. This study was approved by the institutional review board of the Chi Mei Medical Center and conducted under the principles of the Declaration of Helsinki.[14] The necessity for obtaining informed consent was exempted given that the study was based exclusively on aggregated data and statistical summaries derived from deidentified information. No protected health information was accessed, and no study-specific interventions were conducted in this retrospective analysis.

Study Design

This retrospective cohort study was conducted over a 20-year period, starting on January 1, 2004, and concluding on December 14, 2024. The inclusion criteria encompassed all incident cases of early-onset AD, defined as those initially diagnosed with AD before the age of 2 years (**Figure 1**). This age definition of early-onset AD has been used in previous studies.[15,16] To identify these cases, the L20 diagnostic code from the *International Classification of Diseases, 10th Revision* (*ICD-10*) was used. Among the identified individuals, we included only those who had at least 1 AD-related follow-up claim within a year of the index date and who had received at least 1 of the following treatments: oral antihistamines, topical corticosteroids, or topical calcineurin inhibitors (drug list available in eTable 1 in Supplement 1). Furthermore, only those with a minimum follow-up period of 2 years after the index date were included. The index date was

Figure 1. Flowchart of the Selection of Study Participants



AD indicates atopic dermatitis.

[a]For more details on definition of exclusions prior to separation into the AD and control cohorts, please refer to the Methods section and the eMethods in Supplement 1.

[b]History of ophthalmia nodosa, viral hepatitis, human immunodeficiency virus, tuberculosis, and syphilis before the index date.

defined as the date of the earliest AD diagnosis claim. To reduce confounding, we applied exclusion criteria, which eliminated patients with a history of ophthalmia nodosa, viral hepatitis, human immunodeficiency virus, tuberculosis, and syphilis prior to the index date. Patients diagnosed with uveitis before the index date were also excluded. After applying these criteria, a cohort of 129 486 patients diagnosed with AD was established for analysis.

Baseline characteristics, such as age at the event, race, ethnicity, and sex, were documented and presumably self-reported. Race and ethnicity data were included as potential covariates and were reported by the health care institutions collaborating with the TriNetX platform. Additionally, assessments of comorbidities, medical utilization settings, and laboratory data were performed to identify potential confounders in the association between AD and the subsequent risk of uveitis. These factors were determined based on historical diagnoses and medical records prior to the index date. Comorbidities of interest included common atopic conditions such as asthma and allergic rhinitis. Specific autoimmune conditions, including enteropathic arthropathies, juvenile arthritis, Crohn disease, ulcerative colitis, celiac disease, systemic lupus erythematosus (SLE), Sjögren syndrome, systemic sclerosis, Behçet disease, dermatomyositis, and sarcoidosis, were also included (relevant *ICD-10* codes in eTable 2 in Supplement 1). Medical utilization settings, including ambulatory, emergency, and inpatient encounters, were analyzed, as well as laboratory tests such as leukocyte count and C-reactive protein levels.

A control group was established consisting of patients who had never been diagnosed with AD between January 1, 2004, and December 14, 2024. The index date for the control group was determined from a randomized date between January 1, 2004, and December 14, 2024, based on their first health care encounter. Only patients who were younger than 2 years of age on the index date and had a minimum follow-up period of 2 years after the index date were included. The same exclusion criteria applied to the AD cohort were also applied to the control group, and patients with a history of uveitis before the index date were excluded. Based on these criteria, 324 860 patients were included in the control group. This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline, ensuring compliance with reporting standards.

Main Outcomes

The primary outcome of the study was the incidence of pediatric uveitis (detailed *ICD-10* codes available in eTable 3 in Supplement 1). Additionally, specific uveitis subtypes, including iridocyclitis (H20) and chorioretinal inflammation (H30), were separately analyzed. Patients were followed up for a maximum duration of 16 years from the index date, with uveitis onset occurring prior to 18 years of age. The incidence of pediatric uveitis prior to propensity score matching (PSM) is presented in eTable 4 in Supplement 1.

Statistical Analyses

Statistical analyses were performed using the built-in statistical functions of the TriNetX network. Baseline characteristics of the AD and control groups were presented as mean measures for continuous variables, or counts with percentages for categorical variables.

PSM was used to balance baseline characteristics including age, sex, race, ethnicity, the aforementioned comorbidities, medical utilization settings, and laboratory data between the AD and control cohorts.[17] A logistic regression model was used to estimate propensity scores, optimizing the variables between the 2 cohorts. Nearest-neighbor greedy matching with a caliper width of 0.1 pooled SDs was applied, ensuring that the maximum allowable difference in propensity scores between the AD and control participants in each matched pair was minimized, leading to less biased estimates compared with other matching algorithms.[18] Standardized mean differences (SMDs) were used to assess the balance of these variables between the AD and control cohorts. An SMD greater than 0.1 indicated a difference between the 2 groups.[19] Detailed information on the definition of the control group and its matching process with the AD cohort is provided in the eMethods in Supplement 1.

Cox proportional hazards models were applied to compare the risk of outcomes after PSM, with results reported as hazard ratios (HRs) and 95% CIs. The proportional hazards assumption was tested using Schoenfeld residuals. All the results derived from the Cox proportional hazards models in our study conform to the proportional hazards assumption. Additionally, Kaplan-Meier survival analysis with a log-rank test was performed to assess the cumulative incidence of pediatric uveitis. All *P* values were 2-sided and not adjusted for multiple analyses, with a threshold for significance $P < .05$.

AD Severity Analysis

To investigate the association of AD severity on the risk of developing pediatric uveitis, we conducted a subanalysis within the unmatched AD cohort. Standard indices for assessing AD severity, such as the SCORing Atopic Dermatitis Index, Eczema Area and Severity Index, and Investigator's Global Assessment Index,[20,21] rely on clinical observations and patient-reported outcomes, including symptoms like itching and sleep disturbance, which were not available in our database. Consequently, we categorized AD severity based on the prescribed medications in accordance with AD treatment guidelines.[20,22,23] This method of classification is consistent with approaches used in previous studies.[24-26]

Specifically, patients in the AD group who, within 1 year after the index date, received any of the following treatments were classified as having severe AD: (1) at least 1 treatment with omalizumab, dupilumab, tralokinumab, abrocitinib, baricitinib, upadacitinib, intravenous immunoglobulin, interferon gamma, or rituximab, and/or (2) cyclosporine, azathioprine, mycophenolate mofetil, methotrexate, or systemic corticosteroids for more than 2 weeks (detailed drug codes available in eTable 2 in Supplement 1). Patients who did not meet these criteria were categorized as having nonsevere AD. Based on these criteria, 3004 patients were included in the severe AD group, while 126 482 patients were included in the nonsevere AD group. The risk of developing pediatric uveitis was then compared between the severe and nonsevere AD groups.

Table 1. Baseline Characteristics of AD Cohort and Control Before and After PSM

Characteristics	Before PSM, No (%)			After PSM, No (%)		
	AD cohort (n = 129 486)	Control cohort (n = 324 860)	SMD	AD cohort (n = 114 889)	Control cohort (n = 114 889)	SMD
Age at index, mean (SD), y	0.6 (0.7)	0.3 (0.6)	0.35	0.5 (0.7)	0.6 (0.8)	0.07
Sex						
Female	54 955 (42.4)	159 248 (49.0)	0.13	50 057 (43.6)	49 501 (43.1)	0.01
Male	73 770 (57.0)	165 601 (51.0)	0.12	64 817 (56.4)	65 377 (56.9)	0.01
Unknown	761 (0.6)	11 (<0.1)	0.11	15 (0.1)	11 (0.1)	0.003
Race						
American Indian or Alaska Native	563 (0.4)	1193 (0.4)	0.01	498 (0.4)	548 (0.5)	0.01
Asian	8166 (6.3)	10 388 (3.2)	0.15	7128 (6.2)	7689 (6.7)	0.02
Black or African American	39 027 (30.1)	65 513 (20.2)	0.23	32 415 (28.2)	31 209 (27.2)	0.02
Native Hawaiian or other Pacific Islander	539 (0.4)	2118 (0.7)	0.03	533 (0.5)	649 (0.6)	0.01
White	51 906 (40.1)	200 129 (61.6)	0.44	49 546 (43.1)	51 129 (44.5)	0.03
Other[a]	11 791 (9.1)	18 854 (5.8)	0.13	10 207 (8.9)	9577 (8.3)	0.02
Unknown	17 494 (13.5)	26 665 (8.2)	0.17	14 562 (12.7)	14 088 (12.3)	0.01
Ethnicity						
Hispanic or Latino	25 012 (19.3)	57 928 (17.8)	0.04	22 679 (19.7)	23 429 (20.4)	0.02
Not Hispanic or Latino	86 044 (66.5)	243 199 (74.9)	0.19	78 251 (68.1)	78 833 (68.6)	0.01
Unknown	18 430 (14.2)	23 733 (7.3)	0.23	13 959 (12.1)	12 627 (11.0)	0.04
Comorbidities						
Asthma	6987 (5.4)	3272 (1.0)	0.25	3353 (2.9)	3171 (2.8)	0.01
Enteropathic arthropathies	0	0	NA	0	0	NA
Juvenile arthritis	10 (<0.1)	10 (<0.1)	0.01	10 (<0.1)	10 (<0.1)	<0.001
Crohn disease	10 (<0.1)	10 (<0.1)	0.01	0	10 (<0.1)	0.01
Ulcerative colitis	21 (<0.1)	10 (<0.1)	0.01	10 (<0.1)	10 (<0.1)	<0.001
Celiac disease	17 (<0.1)	14 (<0.1)	0.01	11 (<0.1)	11 (<0.1)	<0.001
Systemic lupus erythematosus	10 (<0.1)	10 (<0.1)	0.01	10 (<0.1)	10 (<0.1)	<0.001
Sjögren syndrome	0	0	NA	0	0	NA
Systemic sclerosis	10 (<0.1)	0	0.01	10 (<0.1)	0	0.01
Behçet disease	0	0	NA	0	0	NA
Dermatopolymyositis	10 (<0.1)	0	0.01	10 (<0.1)	0	0.01
Allergic rhinitis	7471 (5.8)	2517 (0.8)	0.28	2939 (2.6)	2512 (2.2)	0.02
Sarcoidosis	10 (<0.1)	0	0.01	10 (<0.1)	0	0.01
Medical utilization						
Ambulatory	109 910 (84.9)	231 461 (71.2)	0.33	95 823 (83.4)	96 007 (83.6)	0.004
Emergency	27 883 (21.5)	23 418 (7.2)	0.42	18 366 (16.0)	19 507 (17.0)	0.03
Inpatient encounter	9326 (7.2)	10 369 (3.2)	0.18	6498 (5.7)	6262 (5.5)	0.01
Laboratory results, mean (SD)						
C-reactive protein level in serum, plasma or blood, mg/dL	2.25 (3.58)	2.14 (3.30)	0.03	2.15 (3.38)	2.34 (3.44)	0.06
Leukocyte count in blood, No./uL	10 800 (4560)	9900 (4000)	0.03	10 700 (3580)	9800 (4000)	0.03

Abbreviations: AD, atopic dermatitis; NA, not applicable; PSM, propensity score matching; SMD, standardized mean difference.

SI conversion factors: To convert C-reactive protein level to milligrams per liter, multiply by 10; leukocyte count to × 10^9 per liter, multiply by 0.001.

[a] Includes multiracial.

Sensitivity Analysis

To isolate the association of AD with the risk of developing pediatric uveitis, 2 separate sensitivity analyses were conducted. The first sensitivity analysis excluded patients from both the AD and control cohorts who had used dupilumab at any point during the study period. The second sensitivity analysis excluded patients from both cohorts who had a diagnostic claim for any of the previously mentioned autoimmune conditions at any time during the study period.

After applying these exclusions, PSM with 1:1 matching was performed, balancing age, sex, race, ethnicity, remaining comorbidities, medical utilization settings, and laboratory data. The risk of developing pediatric uveitis was then compared between the remaining patients in both cohorts.

Results

Baseline Demographic and Clinical Characteristics

A total of 114 889 patients were included in both the AD (mean [SD] age, 0.5 [0.7] years; 64 817 male [56.4%]; 32 415 Black [28.2%], 22 679 Hispanic [19.7%], and 49 546 White [43.1%]) and control cohorts (mean [SD] age, 0.6 [0.8] years; 65 377 male (56.9%); 31 209 Black [27.2%], 23 429 Hispanic [20.4%], and

Table 2. Result of Primary Analysis and AD Severity Analysis

Uveitis type	Patients who developed uveitis, No. (%)		HR (95% CI)
	AD cohort (n = 114 889)[a]	Control cohort (n = 114 889)[b]	
All uveitis	94 (0.08)	58 (0.05)	1.92 (1.38-2.66)
Iridocyclitis	86 (0.08)	49 (0.04)	2.09 (1.47-2.98)
Chorioretinal inflammation	11 (0.01)	≤10 (≤0.01)[c]	1.23 (0.52-2.91)
Severe vs nonsevere AD			
All uveitis			
Severe AD[d]	12 (0.40)	NA	3.64 (2.00-6.66)
Nonsevere AD[e]	97 (0.08)	NA	
Iridocyclitis			
Severe AD[d]	11 (0.37)	NA	3.65 (1.94-6.85)
Nonsevere AD[e]	88 (0.07)	NA	
Chorioretinal inflammation			
Severe AD[d]	≤10 (≤0.33)[c]	NA	5.87 (1.29-26.68)
Nonsevere AD[e]	11 (0.01)	NA	

Abbreviations: AD, atopic dermatitis; HR, hazard ratio.

[a] Mean (SD) follow-up duration of the AD cohort, 6.0 (3.3) years.

[b] Mean (SD) follow-up duration of the control cohort, 6.6 (3.7) years.

[c] If the patient's count was between 1 and 10, the result was reported as ≤10 due to the limitations of the TriNetX platform, which prevents the inclusion of raw patient numbers. HRs were calculated using the true event counts within the TriNetX platform.

[d] 3004 patients included in the severe AD subcohort. Mean (SD) follow-up duration of the severe AD cohort, 7.7 (3.7) years.

[e] 126 482 patients included in the nonsevere AD subcohort. Mean (SD) follow-up duration of the nonsevere AD cohort, 6.0 (3.3) years.

51 129 White [44.5%]) after PSM (**Table 1**). Mean (SD) follow-up was 6.0 (3.3) years for the AD cohort, and 6.6 (3.7) years for the control cohort. Post-PSM, all variables achieved balance with SMD below 0.1.

Main Outcomes

The AD group had a higher risk of developing pediatric uveitis compared with controls (94 [0.08%] vs 58 [0.05%]; HR, 1.92 [95% CI, 1.38-2.66]; $P < .001$) (**Table 2**; **Figure 2**A). The risk of iridocyclitis was also elevated in the AD group (86 [0.08%] vs 49 [0.04%]; HR, 2.09 [95% CI, 1.47-2.98]).

Severity Analysis

In severity analysis, the severe AD cohort had a higher risk of pediatric uveitis (12 of 3004 [0.40%] vs 97 of 126 482 [0.08%]; HR, 3.64 [95% CI, 2.00-6.66]; $P < .001$) (Table 2; Figure 2B). Additionally, the risks of iridocyclitis and chorioretinal inflammation were elevated in the severe AD group.

Sensitivity Analysis

Following PSM, all SMDs were below 0.1, indicating balanced cohorts (eTable 5 in Supplement 1). After excluding patients with dupilumab use (leaving a total of 113 284 patients), the AD cohort continued to demonstrate a higher risk of pediatric uveitis (89 [0.08%] vs 59 [0.05%]; HR, 1.77 [95% CI, 1.27-2.46]), as well as an elevated risk of iridocyclitis (80 [0.07%] vs 51 [0.05%]; HR, 1.84 [95% CI, 1.29-2.62]) (**Table 3**).

Post-PSM, all SMDs were below 0.1 (eTable 6 in Supplement 1). Excluding patients with autoimmune conditions (leaving a total of 114 425 patients), the AD cohort still exhibited a higher risk of pediatric uveitis (80 [0.07%] vs 61 [0.05%]; HR, 1.52 [95% CI, 1.09-2.12]), along with an increased risk of iridocyclitis (71 [0.06%] vs 51 [0.05%]; HR, 1.62 [95% CI, 1.13-2.33]) (Table 3).

Discussion

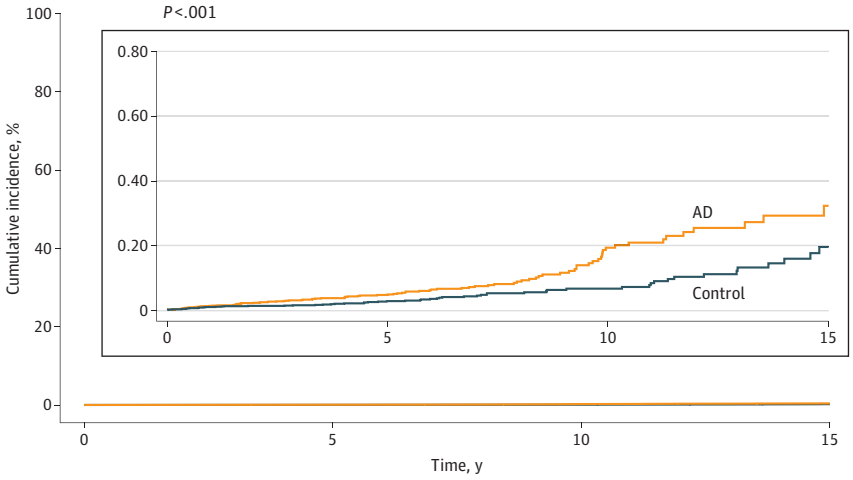
In this retrospective cohort study, we found an increased risk of pediatric uveitis in patients with early-onset AD compared with matched controls (0.08% vs 0.05%), independent of dupilumab use (0.08% vs 0.05%) or autoimmune conditions (0.07% vs 0.05%). Additionally, patients with severe AD exhibited a markedly higher risk of pediatric uveitis than those with nonsevere AD, indicating a correlation between AD severity and uveitis risk (0.40% vs 0.08%).

Uveitis associated with AD has been infrequently discussed, with only a limited number of case reports documenting this relationship.[7-10] Nevertheless, the sequelae of uveitis can be severe, with some patients developing bilateral cataracts[9] or even amblyopia.[8] However, following the introduction of dupilumab for AD treatment, recent case reports have focused predominantly on dupilumab-associated uveitis.[7,10-12] These cases of uveitis in patients with AD treated with dupilumab can be complicated by serous retinal detachment (RD), cystoid macular edema, or secondary glaucoma, with an aqueous humor inflammatory cytokine profile resembling that of noninfectious uveitis.[7,11,12] Studies have suggested that the underlying mechanism of dupilumab-associated uveitis may involve the upregulation of interferon γ and the Th1 immune response, resulting from the inhibition of interleukin 4 and interleukin 13 signaling by dupilumab.[7,11] Notably, these cases of uveitis typically resolve after discontinuation of dupilumab and/or treatment with local or systemic corticosteroids.[7,10-12]

Although large-scale studies on dupilumab and uveitis risk are lacking, we conducted a sensitivity analysis excluding dupilumab users. The analysis showed that early-onset patients with AD still had an elevated risk of pediatric uveitis, indicating the risk is independent of dupilumab use.

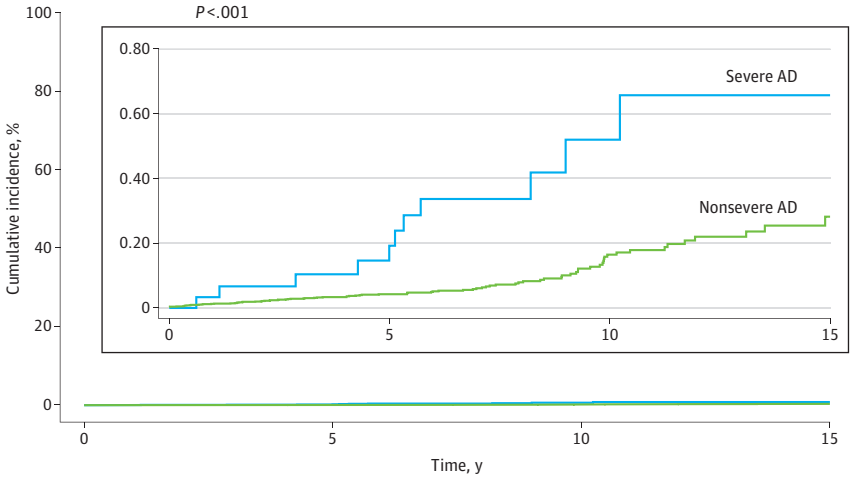
Figure 2. Kaplan-Meier Curves for Cumulative Incidence of Pediatric Uveitis Overall and by AD Severity

A Cumulative incidence of pediatric uveitis in the AD and control groups



No. at risk				
AD	114889	60563	14006	3257
Control	114889	68084	20708	4903
No. at events				
AD	0	50	84	93
Control	0	29	45	58

B Cumulative incidence of pediatric uveitis in the AD and control groups



No. at risk				
Severe AD	3004	2191	767	156
Nonsevere AD	126482	66778	15551	3601
No. at events				
Severe AD	0	≤10[a]	11	12
Nonsevere AD	0	53	87	96

A, The hazard ratio (HR) was 1.92 (95% CI, 1.38-2.66). B, HR was 3.64 (95% CI, 2.00-6.66). HRs were calculated using the true event counts within the TriNetX platform. AD indicates atopic dermatitis.

[a]If the patient's count is between 1 and 10, the result is reported as ≤10 due to the limitations of the TriNetX platform, which prevents the inclusion of raw patient numbers.

Despite aforementioned case reports suggesting a potential association between uveitis and AD, only 1 large-scale study has explored this link.[13] Grajewski et al[13] conducted a single-center case-control study examining allergies and atopy in uveitis patients compared with controls, finding no association between AD and uveitis. In contrast, our study identified an elevated risk of pediatric uveitis in patients with early-onset AD. Several factors may explain this discrepancy. Our study used strict criteria, including patients diagnosed with AD before age 2 years, with follow-up visits and treatments, enhancing diagnostic precision. We classified AD severity based on prescribed medications, adhering to established guidelines. Grajewski and colleagues' reliance on questionnaires may have introduced recall bias, lacking details on AD onset and severity. Furthermore, our study focused on pediatric uveitis, likely influenced by distinct risk factors compared to Grajewski and colleagues' predominantly adult cohort (mean age, 45 years). Finally, our multicenter cohort offered broader generalizability than their single-center study.

Besides investigating the association of AD on pediatric uveitis risk, we assessed how AD severity may affect this risk. Previous studies have demonstrated the role of AD severity in the development and prognosis of various ocular diseases. Jeon et al[25] found severe pediatric AD increases the risk of cataracts and the need for cataract surgery. Choi et al[24]

Table 3. Result of Sensitivity Analyses

Uveitis type	Patients who developed uveitis, No. (%)		HR (95% CI)
	AD cohort without dupilumab use (n = 113 284)[a]	Control cohort without dupilumab use (n = 113 284)[b]	
All uveitis	89 (0.08)	59 (0.05)	1.77 (1.27-2.46)
Iridocyclitis	80 (0.07)	51 (0.05)	1.84 (1.29-2.62)
Chorioretinal inflammation	11 (0.01)	≤10 (≤0.01)[c]	1.82 (0.70-4.70)
Without autoimmune conditions[d]			
All uveitis	80 (0.07)	61 (0.05)	1.52 (1.09-2.12)
Iridocyclitis	71 (0.06)	51 (0.05)	1.62 (1.13-2.33)
Chorioretinal inflammation	11 (0.01)	≤10 (≤0.01)[c]	1.53 (0.61-3.82)

Abbreviations: AD, atopic dermatitis; HR, hazard ratio.

[a] Mean (SD) follow-up duration of the AD cohort without dupilumab use, 6.0 (3.3) years.

[b] Mean (SD) follow-up duration of the control cohort without dupilumab use, 6.6 (3.7) years.

[c] If the patient's count is between 1 and 10, the result is reported as ≤10 due to the limitations of the TriNetX platform, which prevents the inclusion of raw patient numbers. The hazard ratios were calculated using the true event counts within the TriNetX platform.

[d] 114 425 patients included in subcohort without autoimmune conditions. Mean (SD) follow-up duration: AD cohort, 6.0 (3.2) years; control cohort, 6.6 (3.7) years.

observed a biological gradient between AD severity and RD occurrence, supporting causality. Our previous research[26] revealed that glaucoma patients with severe AD had higher surgical needs, highlighting AD severity as a key factor.

Similarly, this study found that patients with severe AD have a higher risk of pediatric uveitis compared with nonsevere cases, suggesting that uveitis risk correlates with AD severity. Previous studies have identified elevated levels of inflammatory cytokines[27] and eosinophil-derived cytotoxic major basic protein (MBP)[28-30] in the aqueous humor of patients with AD. Such inflammation may subsequently lead to uveitis, particularly in the anterior segment of the eye. This may also explain why, among uveitis subtypes, only the risk of iridocyclitis remained elevated across the primary analysis (0.08% vs 0.04%), sensitivity analysis (without dupilumab use, 0.07% vs 0.05%; without autoimmune conditions, 0.06% vs 0.05%), and AD severity analysis (0.37% vs 0.07%). Long-term ocular trauma from frequent face and eyelid rubbing in patients with AD may worsen the condition by disrupting the blood-aqueous barrier.[29,31] This disruption allows more inflammatory cytokines and eosinophil-derived cytotoxic MBP to enter the aqueous humor, intensifying the inflammation.[29,31] As AD severity increases, the frequency of such ocular trauma may also rise, further compromising the blood-aqueous barrier and amplifying the inflammatory response. This mechanism may explain not only the correlation between AD severity and the increased risk of developing cataracts[25] or RD[24] but also the elevated risk of requiring glaucoma surgery[26] and the increased risk of pediatric uveitis in patients with severe AD.

Strengths and Limitations

This study's strengths include a large, nationwide cohort of 121 million patients, enhancing generalizability. To our knowledge, this was the first multicenter cohort on pediatric uveitis risk in AD, which means its unprecedented scale ensures robust conclusions. Trying to minimize confounding was attempted through closely matched controls. Sensitivity analyses, excluding patients with autoimmune conditions or dupilumab use, further supported AD's potentially isolated association on uveitis risk independent of these other risk factors, potentially increasing confidence in the study's reliability.

One concern is the potential for misclassification bias, stemming from the reliance on accurate *ICD-10* diagnosis codes for identifying outcomes and conditions, including AD. Efforts were made to mitigate this bias in the definition of AD by including only patients who had at least 1 AD-related follow-up visit and received treatment within 1 year. Including only AD patients initially diagnosed before the age of 2 years further reduce this bias, as AD onset before the age of 2 years is one of the minor diagnostic criteria for AD.[32] Reliance on *ICD-10* codes limits assessment of diagnostic details, while the study's retrospective design introduces inherent biases and data collection limitations. Although based on large multicenter cohorts, our study was not population based, potentially introducing bias and limiting generalizability to clinical settings. While retinal vasculitis, sympathetic uveitis, and panuveitis also were included as uveitis in our study, low event counts prevented statistically stable results and reliable estimates. Thus, they were not analyzed separately. Larger studies would be needed to clarify their risks in AD. Finally, as emphasized in an Invited Commentary on potential limitations of propensity score matching,[33] propensity score matching only can balance for variables used in the creation of the model, emphasizing the need for confirmation of these findings in future additional, rigorous observational studies.

Conclusions

Our multicenter cohort study demonstrates an elevated risk of pediatric uveitis in patients with early-onset AD, independent of autoimmune conditions or dupilumab use. AD severity correlated with this risk. These findings support the potential need to consider ophthalmologic monitoring in children with early-onset AD to detect and subsequently manage uveitis if it develops. These findings support an interdisciplinary approach, involving dermatology, ophthalmology, immunology, and pediatrics, that might contribute to optimized care for both AD and its associated ocular complications.

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