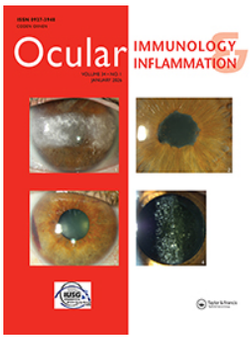

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ORIGINAL ARTICLE

Smoking and Risk of Uveitis: A Systematic Review and Meta-Analysis

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ABSTRACT

Purpose: Uveitis is a relatively common eye condition that can lead to substantial symptoms and visual impairment. Identifying modifiable risk factors is essential for effective prevention and management. This systematic review and meta-analysis aimed to assess the causal role of smoking in uveitis by summarizing existing evidence on its impact on pathogenesis, disease progression, and treatment outcomes.

Methods: A comprehensive search was conducted in Ovid MEDLINE and Embase in December 2024. Studies were eligible if they included an ophthalmologist-confirmed diagnosis of uveitis and reported on smoking exposure. Exclusion criteria were pediatric populations, case reports/series, interventional studies, and studies involving patients with systemic disease to minimize confounding. The review followed PRISMA guidelines and a pre-registered PROSPERO protocol (CRD42025641517). Risk of bias was assessed using Joanna Briggs Institute tools. Data were extracted by one reviewer and verified by another. Meta-analyses were performed using RevMan, with heterogeneity evaluated by I^2. Certainty of evidence was assessed using GRADE methodology.

Results: Of 892 articles screened, seven met inclusion criteria: four retrospective case-control studies, one retrospective cohort study, and two cross-sectional studies. The pooled odds ratio (OR) for the association between smoking and uveitis was 1.97 (95% CI, 1.71–2.27) across 1557 individuals with uveitis and 4293 controls. The effect was statistically significant ($Z = 9.42$; $p < 0.00001$). Former smokers also had an increased risk (OR 1.23), and smokers showed a tendency toward more complications.

Conclusion: Smoking is a significant and modifiable risk factor for uveitis. These findings support the integration of smoking cessation into clinical management and prevention strategies.

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(e-)cigarettes; nicotine; smoking; uveitis; vaping

Uveitis is an inflammatory eye condition affecting the uveal tract—including the iris, ciliary body, and choroid—that can lead to significant visual impairment even if treated adequately. This heterogeneous condition is typically classified into infectious, autoimmune, and idiopathic causes.[1,2] Uveitis is categorized based on the primary anatomical location of inflammation, with anterior uveitis accounting for 50% to 90% of all cases.[3] Population-based estimates of uveitis epidemiology vary considerably due to differences in methodologies, definitions of uveitis, and geographical regions.[4] Uveitis is frequently observed in association with systemic inflammatory diseases, such as sarcoidosis, ankylosing spondyloarthritis, and Behçet's disease.[5–10] While genetic predisposition and immune dysregulation are well-established contributors to its pathogenesis, environmental, occupational, and lifestyle factors are increasingly recognized as relevant influences.[11–14]

One such potentially modifiable risk factor is smoking, although the strength and direction of this association remain uncertain.[15] Tobacco smoke contains thousands of harmful compounds that can affect nearly every organ in the body. Smoking is a well-established risk factor for several inflammatory diseases and is linked to conditions such as chronic obstructive pulmonary disease (COPD), cancer, and cardiovascular disease.[16] Moreover, observational studies and Mendelian randomization analyses have demonstrated an association between smoking and an increased risk of various ophthalmologic conditions, including age-related macular degeneration (AMD) and cataract.[17–20] While the exact mechanisms underlying these detrimental effects remain incompletely understood, oxidative stress and immune dysregulation are thought to play key roles. In ophthalmology, oxidative stress is involved in the pathogenesis of several eye diseases, such as senile cataract, AMD, uveitis, retinopathy of prematurity, and keratitis.[21–23] More recently, it was reported that electronic cigarettes users also have an increased risk of new-onset uveitis, and other ocular symptoms.[24] In inflammatory eye diseases, oxidized protein levels appear to increase in parallel with the degree of inflammatory activity. Emerging evidence suggests that these mechanisms may also contribute to the development and severity of complications of uveitis. Potential underlying processes include

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immune system dysregulation, increased systemic inflammation, and endothelial dysfunction, all of which may influence both the onset and severity of the disease.[25] However, a comprehensive, systematic evaluation of the association between smoking and uveitis is currently lacking.

In this meta-analysis, we systematically assessed the available literature and quantified the effect of smoking on the risk of uveitis. By doing so, we aim to provide a clearer understanding of the role of tobacco smoke in the pathogenesis of this ocular condition and its implications for prevention and clinical management.

Methods

We registered the review prospectively on PROSPERO (CRD42025641517) and reported it following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[26]

Eligibility criteria

We included studies that examined smoking as a risk factor for the development of uveitis in patients without systemic disease. To be eligible, uveitis had to be the primary outcome of the study, and had to be determined by an ophthalmologist. One study describing self-reported uveitis was excluded. We excluded studies without an English abstract or full text availability, as well as those involving children or animals.

Search strategies

A systematic literature search was conducted by one of the authors (SK) using Ovid MEDLINE on December 9, 2024. The search strategy combined free-text terms and Medical Subject Headings (MeSH) to maximize sensitivity and comprehensiveness. Details of the complete search strategy are provided in eTable S1 in the Supplement.

We also manually reviewed the reference lists of all included studies ("snowballing") and used the "similar articles" and "cited by" features in PubMed to identify additional relevant publications. On December 29, 2024, the search was extended to include Embase.

Study selection

Two researchers (SK and MD) independently reviewed the titles and abstracts to determine which reports should be retrieved, and also assessed them independently. In case of disagreement between the reviewers, consensus was reached through discussion. Discrepancies between reviewers were resolved through consultation with a third reviewer (RE).

Data extraction and risk of bias assessment

One investigator (SK) extracted all relevant study characteristics, methods, and results from each included study, and organized the information into a table for analysis. An independent investigator (MD) verified all extracted data. We resolved discrepancies during data extraction by discussion or consultation with a third investigator (RE) where needed. Articles were included if they described smoking as a risk factor or cause of uveitis, without restrictions on the time frame between exposure and the development of uveitis. To reduce potential confounding by systemic inflammatory diseases and their treatments, which may be independently associated with both smoking and uveitis, studies involving patients with systemic inflammatory conditions were excluded. Specifically, we excluded studies involving systemic inflammatory diseases such as Behçet's disease, sarcoidosis, and ankylosing spondylitis. Patients with non-inflammatory systemic conditions, including diabetes mellitus and hypertension, were not excluded. In contrast, we included studies on presumed ocular histoplasmosis syndrome (POHS), as these were classified under posterior uveitis in the original reports and specifically investigated smoking as a risk factor for this phenotype. Moreover, POHS occurs only in the eye, in contrast to the excluded systemic disorders.

The following data were collected and summarized in tables from each report: author(s), study type, sample size, age and sex of the population studied, country of study, type of uveitis, and outcomes. Items from the Joanna Briggs Institute (JBI) Checklist for case control studies and cohort studies[27] were used by both reviewers (SK and MD) independently to assess the risk of bias. In case of disagreement between the reviewers, consensus was once again reached through discussion or consulting a third reviewer (RE).

Evaluation of heterogeneity and data synthesis

We used RevMan[28] to analyze the included studies and generate a forest plot, calculating the cumulative OR and its 95% confidence intervals (CIs). We investigated clinical heterogeneity by assessing diversity in population (e.g., age, and sex distribution) and uveitis characteristics. The methodological heterogeneity was assessed by evaluating the risk of bias. Statistical heterogeneity was determined by calculating the contribution of heterogeneity to the total variability across the studies (I^2). If asymmetry was detected, we examined the characteristics of the included studies to assess whether the asymmetry was attributable to publication bias or other factors. Comparative studies were visually represented using a forest plot. A meta-analysis with a random-effects model was applied.

Certainty assessment

The certainty of the evidence was assessed by two reviewers (SK and MD) using the five Grading of Recommendations Assessment, Development and Evaluation (GRADE) considerations. The overall certainty was categorized as very low, low, moderate, or high.[29]

Results

Study selection

A total of 1103 records were identified by the systematic database search. Of these, 211 were excluded, namely 70

duplicates, 107 animal studies, and 34 without an English-language abstract. The remaining 892 records were screened based on titles and abstracts. After initial screening, 53 articles were selected for full-text review. The most common reasons for exclusion during screening were lack of relevance to the predefined outcome ($n = 17$), studies restricted to patients with systemic inflammatory diseases[30–39] ($n = 10$), and other studies ineligible for various reasons ($n = 19$; eTable S2 in the Supplement). Full-text evaluation showed that seven studies met the inclusion criteria and were retained for qualitative synthesis. A detailed overview of the study selection process is provided in the PRISMA flow diagram[40] in Figure 1.

Characteristics of included studies

Four of the included studies were retrospective case-control studies.[15,41–43] One included study was a retrospective cohort study,[24] and two were observational cross-sectional studies.[44,45] Among the studies that specified the type of uveitis, posterior uveitis—most commonly presenting as presumed ocular histoplasmosis syndrome (POHS)[42,43] —and anterior uveitis[15,24,41,44] were most frequently reported. Most studies reported a higher prevalence of female participants.[15,24,42–44] The mean age of participants ranged from 36 years in the study by Chheda et al.[42] to 63 years in the study by Yuen et al.[41] Key characteristics of the included studies are summarized in Table 1.[15,24,41–45]

Risk of bias assessment and certainty of evidence

The risk of bias assessment is presented in eTables S3–S5 in the Supplement. Reporting bias was evaluated using the JBI Checklist and was determined to be low overall.

Certainty of evidence was assessed using the GRADE approach, with the use of GRADEpro software. The certainty of evidence was rated as high. Details of the GRADE assessment are provided in eTable S6 in the Supplement.

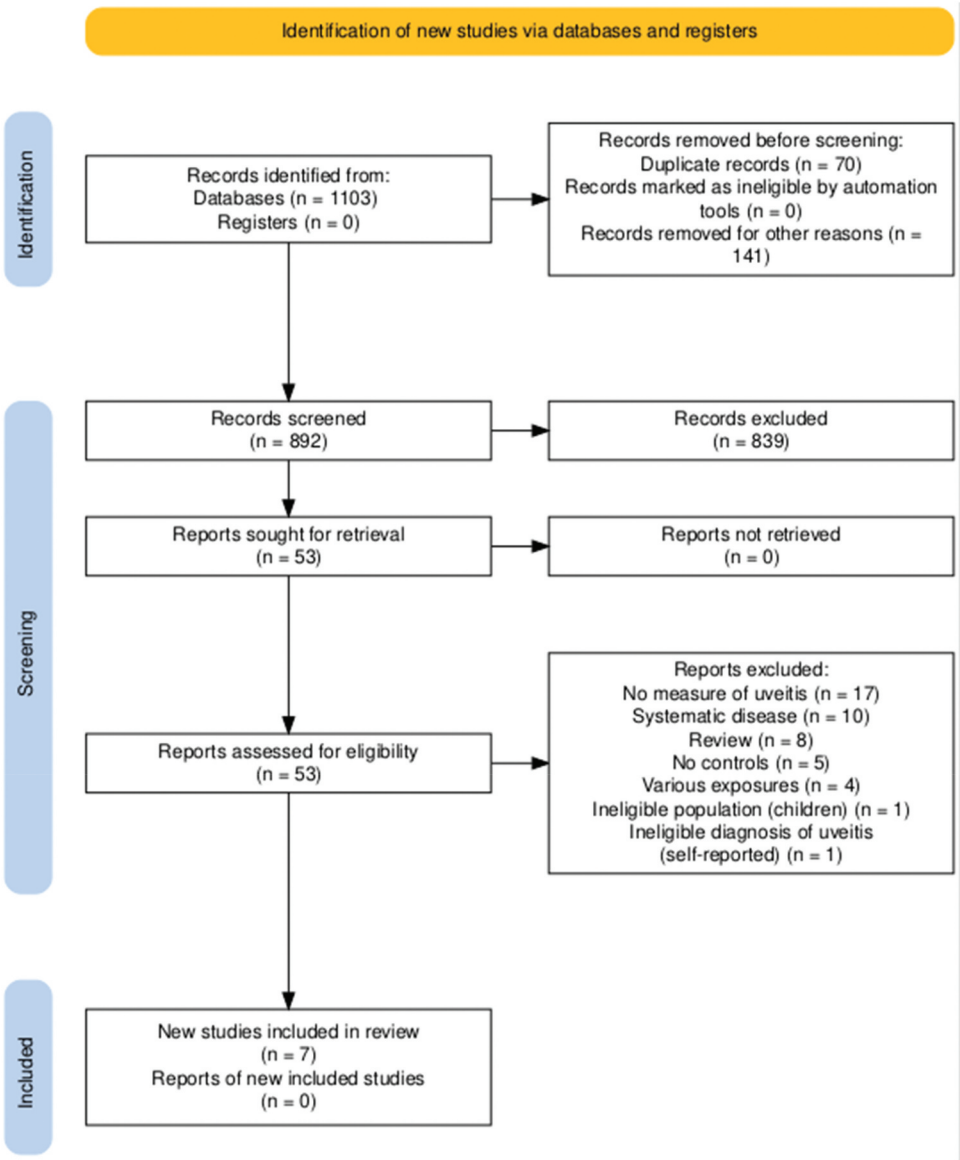

Figure 1. PRISMA flow diagram.

Table 1. Characteristics of included studies.[15,24,41–44]

Source, year	Study type	Country	Period of data collection	Population	Type of uveitis, A, B, C, D	Age, y; mean ± SD	Sex Female, n (%)
Yuen et al., 2015[41]	Retrospective, population-based, case-control study	USA	2006–2007 (2 y)	Total=1150			
				100 uveitis	A=86, B=3, C=11, D=0	50; NR	48 (48)
				528 other ophthalmic	NA	63; NR	287 (54)
				522 healthy controls	NA	53; NR	294 (56)
Chheda etal., 2012[42]	Retrospective, case-control study	USA	2000–2010 (10 y)	Total=568			
				142 POHS patients with CNV	A=0, B=0, C=142, D=0	39±7.1	81 (57)
				426 controls	NA	36±9.1	239 (56)
Richey etal., 2022[43]	Retrospective pair-matched case–control study	USA	2013–2019 (7 y)	Total=3004			
				751 POHS patients	A=0, B=0, C=751, D=0	61; NR	380 (63)
				2253 controls	NA	61; NR	1140 (63)
Lin et al., 2010[15]	Retrospective, case-control study	USA	2002–2009 (8 y)	Total=1128			
				564 uveitis patients*	A=331, B=57, C=24, D=133, Other=49	45±18.5	349 (61)
				564 controls	NA	54±18.7	340 (60)
Hsu et al., 2024[24]	Retrospective, cohort study	China	2019–2023 (4 y)	838 650 patients from TriNetX database			
				419 325 e-cigarette users	Total=2035 A=1944, B=22, C=127, D=28	51±16.1	203 994 (49)
				419 325 nonusers (controls)	Total=751 A=701, B=17, C=53, D=17	52±16.3	201 653 (48)
Roesel et al., 2011[44]	Cross-sectional study	Germany	Unknown	350 patients with noninfectious uveitis	A=151, B=79, C=49, D=71	44±14.8	214 (61)
Thorne et al., 2008[45]	Cross-sectional study	USA	1984–2006 (22 y)	208 patients (363 affected eyes)	A=0, B=208, C=0, D=0	37; NR (6–76)#	138 (66)

Abbreviations: A, anterior; B, intermediate; C, posterior; CVN, choroidal neovascularization; D, panuveitis; NA, not applicable; NR, not reported; POHS, presumed ocular histoplasmosis syndrome; *31 at more than 1 anatomical location; #range in parentheses.

Meta-analysis findings of risk of uveitis in current smokers

A total of four retrospective studies were included in the meta-analysis,[15,41–43] comprising 1557 individuals with uveitis and 4293 controls. Individual studies consistently demonstrated a positive association, with ORs ranging from 1.78 (95% CI, 1.37–2.31; Lin et al.[15] to 3.07 (95% CI, 2.06–4.58; Chheda et al.).[42] The study by Richey et al.[43] contributed the largest weight to the overall estimate (50.8%). These results are graphically presented in Figure 2. The pooled analysis yielded a cumulative OR of 1.97 (95% CI, 1.71–2.27), indicating a statistically significant association between cigarette smoking and an increased risk of uveitis (Figure 2). The overall test for effect was highly significant ($Z = 9.42$; $p < 0.00001$). Heterogeneity across the included studies was moderate, with an I^2 value of 46% ($\chi^2 = 5.55$; $df = 3$; $p = 0.14$), suggesting some variability in effect estimates that may reflect differences in study populations or methodologies.

When the study by Hsu et al.[24] on e-cigarette use and the risk of uveitis was incorporated, the cumulative OR increased accordingly to 2.53 (95% CI, 2.35–2.71). The overall test for effect was highly significant ($Z = 25.30$; $p < 0.0005$), and the heterogeneity was high (I^2 value of 80%).

Meta-analysis findings of risk of uveitis in past smokers

A total of three retrospective studies were included in the meta-analysis,[15,41,43] comprising 1415 individuals with uveitis and 3867 controls. Individual studies had ORs ranging from 0.58 (95% CI, 0.34–0.99; Yuen et al.[41] to 1.54 (95% CI, 1.13–2.10; Lin et al.).[15] The study by Richey et al.[43] contributed the largest weight to the overall estimate (50.8%). These results are graphically presented in Figure 3. The pooled analysis yielded a cumulative OR of 1.23 (95% CI, 1.05–1.44), indicating a statistically significant association between past cigarette

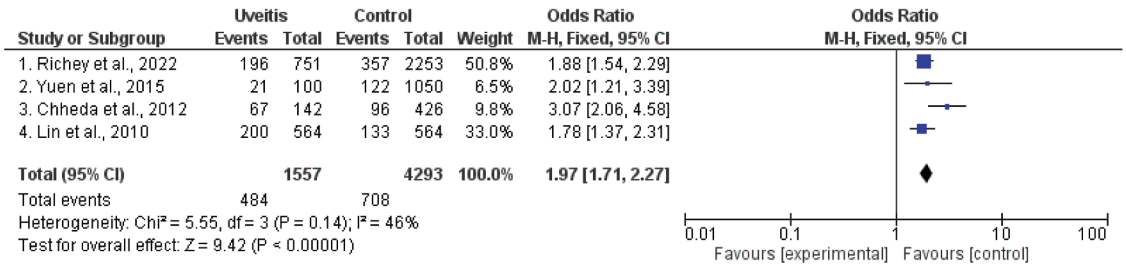

Figure 2. Association between cigarette smoking and risk of uveitis: meta-analysis of four retrospective studies.[15,41–43] Forest plot showing the pooled odds ratio (OR) and 95% confidence interval (CI) for the association between cigarette smoking and uveitis across four retrospective studies.

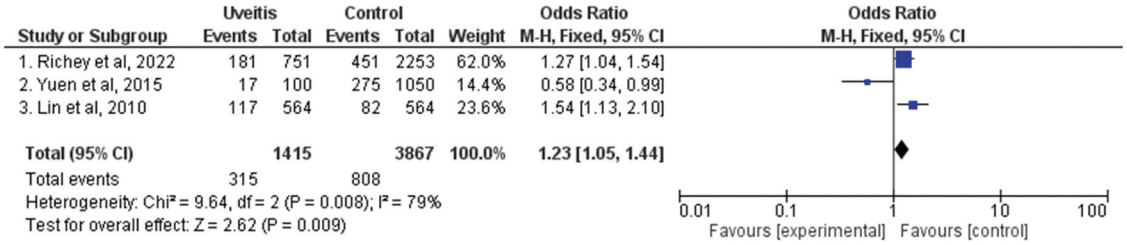

Figure 3. Association between past cigarette smoking and risk of uveitis: meta-analysis of three retrospective studies.[15,41,43] Forest plot showing the pooled odds ratio (OR) and 95% confidence interval (CI) for the association between past smoking and uveitis across three retrospective studies.

smoking and an increased risk of uveitis. The overall test for effect was highly significant ($Z = 2.62$; $p < 0.009$).

Heterogeneity across the included studies was high, with an I^2 value of 79% ($\chi^2 = 9.64$; $df = 2$; $p = 0.009$), suggesting some variability in effect estimates that may reflect differences in study populations or methodologies.

Findings of risk of complications of uveitis in smokers

A total of four studies reported on smoking and the risk of complications in uveitis patients.[15,43–45] Two of these studies could not be included in the meta-analysis due to their lack of necessary data.[15,45] Attempts to contact the authors to obtain this information were unsuccessful. Consequently, two studies[43,44] remained, which was insufficient to conduct a meta-analysis. Thorne et al.[45] investigated smoking as a risk factor for cystoid macular edema (CME) in patients with intermediate uveitis. In a cohort of 280 patients, actively smoking at presentation was associated with a significantly increased risk of developing CME compared with never smoking (OR 3.90; 95% CI, 1.43–10.66). Lin et al.[15] examined cigarette smoking as a risk factor for uveitis in 564 uveitis patients. Smoking was associated with an increased risk of intermediate uveitis (OR 2.7; 95% CI, 1.4–5.6), and the risk further increased regarding intermediate uveitis with CME (OR 8.4; 95% CI, 2.5–28.8). Similarly, the OR of panuveitis was higher among smokers (OR 3.9; 95% CI, 2.4–6.1), and even more pronounced regarding panuveitis complicated by CME (OR 8.0; 95% CI, 3.3–19.5). The pooled OR of the remaining two studies was 1.30 (95% CI, 0.96–1.76); therefore, a statistically significant association could not be demonstrated. However, the trend suggests a potentially increased risk of complications among smokers.

Discussion

This systematic review and meta-analysis demonstrated that cigarette smoking is a significant risk factor for the development of uveitis and may also serve as a prognostic factor associated with a more severe disease course among individuals with uveitis. The pooled analysis of four retrospective studies yielded an OR of 1.97 (95% CI, 1.71–2.27), indicating a nearly two-fold increased risk of uveitis among smokers. Importantly, this elevated risk persisted even among former smokers, highlighting the long-lasting impact of tobacco-induced tissue damage. Emerging data further imply a substantially increased risk of ocular pathology in e-cigarette users, including uveitis, raising concerns as vaping prevalence continues to rise.[24,25]

The eye is particularly susceptible to oxidative stress due to its high metabolic activity and constant exposure to light, which can contribute to the development of uveitis.[22,46] Mechanistically, smoking generates substantial oxidative stress by disrupting the balance between reactive oxygen species (ROS) and antioxidant defenses.[47] This redox imbalance activates pro-inflammatory pathways such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and mitogen-activated protein kinase (MAPK), leading to the upregulation of cytokines including tumor necrosis factor alpha (TNF-α), interleukin (IL)-1β, and IL-6, central mediators of immune dysregulation in uveitis.[22,48] Furthermore, tobacco-derived ROS cause direct cellular injury and mitochondrial dysfunction, impairing ocular tissue repair.[46,49,50] Vaporized e-cigarette liquids, containing reactive aldehydes and fine particulate matter, similarly compromise epithelial barriers and induce ROS production.[51,52] Preclinical models confirm that e-cigarette exposure activates inflammatory cascades comparable to those triggered by combustible tobacco products.[52] These converging mechanisms suggest that both traditional smoking and vaping represent modifiable contributors to the pathogenesis and progression of uveitis.

The clinical implications of these findings are profound. Data from Hsu et al. demonstrated that e-cigarette use conferred a hazard ratio (HR) of 2.53 (95% CI, 2.33–2.76) for incident uveitis.[24] This elevated risk was consistent across all age groups and remained stable over a four-year follow-up, emphasizing that vaping, like cigarette smoking, cannot be considered benign. Additionally, a large cross-sectional study of 4351 US youths revealed that dual users of cigarettes and e-cigarettes reported significantly more severe ocular symptoms—including dryness, burning, redness, blurred vision, and headaches—compared to non-users.[53] Preclinical data corroborate these findings, demonstrating that e-cigarette exposure disrupts tear film stability, induces oxidative damage, and elicits inflammatory responses in ocular tissues.[51] Notably, dual use appears to exert additive detrimental effects.[24,53] As vaping rates rise, particularly among adolescents and young adults, ophthalmologists should systematically inquire about all forms of nicotine exposure when evaluating patients with ocular inflammation.[24,53]

Beyond disease risk, smoking appears to impair therapeutic efficacy in uveitis.[16] Elevated TNF-α levels among smokers may diminish responses to anti-TNF agents such as infliximab and adalimumab.[54–56] Similarly, smoking-induced oxidative

stress and altered cytochrome P450 enzyme activity can accelerate corticosteroid metabolism,[57] leading to reduced drug bioavailability and efficacy.[58] These mechanisms mirror findings in other inflammatory diseases, such as rheumatoid arthritis and Crohn's disease, where smoking consistently predicts poorer responses to biological therapy.[55,56] Although direct clinical studies in uveitis remain limited, the convergence of mechanistic and epidemiological evidence underscores the need to assess and address smoking and vaping behaviors prior to initiating therapy. Integrating formal cessation protocols into clinical practice may optimize treatment outcomes and disease control.

Given the central role of oxidative stress and inflammation in uveitis,[46] smoking cessation must be recognized as an essential component of management. Although intervention studies specific to uveitis are lacking, extrapolation from other chronic inflammatory conditions strongly supports benefits. Quitting smoking reduces oxidative burden, lowers pro-inflammatory cytokine levels, and enhances therapeutic responses. Routine assessment of smoking and vaping behaviors, combined with active cessation counseling, should become standard practice in uveitis management.

Moreover, complementary strategies aimed at mitigating oxidative stress may offer additional therapeutic benefit.[59–61] Preclinical studies suggest that antioxidants such as vitamin C, vitamin E, and N-acetylcysteine bolster endogenous defenses, suppress cytokine-mediated inflammation, and protect ocular tissues from ROS-induced damage.[62] Quercetin, a naturally occurring flavonoid, has shown potential in counteracting cigarette smoke–induced oxidative injury as well as inflammatory damage by activating the Nrf2 pathway.[63–66] Although clinical trials are warranted, dietary or pharmacological antioxidant supplementation represents a promising adjunctive approach in uveitis care. Lifestyle interventions—including antioxidant-rich diets and stress reduction—may further help preserve ocular tissue integrity and prevent disease progression.

Limitations

There are a number of limitations to this study. First, the total number of included studies was modest. Still, the consistency of the effect estimates across the studies enhances the robustness of the association observed. However, some heterogeneity in study design, population characteristics, and outcome definitions was present, potentially contributing to variability in the results. Second, although some studies evaluated outcomes relevant to this meta-analysis and reported ORs, they did not provide sufficient data for inclusion in the quantitative synthesis, and attempts to contact the corresponding authors for clarification were unsuccessful. Third, we excluded studies that included patients with systemic inflammatory diseases to minimize confounding and better isolate the specific effect of smoking on uveitis. This decision was based on the recognition that many systemic diseases associated with uveitis are themselves more prevalent among smokers, and often require immunosuppressive treatments that can independently influence both the development and progression of uveitis. Including such patients would therefore introduce substantial confounding, making it difficult to distinguish the independent contribution of smoking. While this strategy improves internal validity, it may limit the generalizability of our findings to broader patient populations with systemic comorbidities. Future studies should consider stratified analyses or advanced causal inference approaches to disentangle these complex interactions.

Fourth, smoking exposure—including duration, intensity, pack-years, and cessation status—was not consistently reported across studies. Some studies also grouped current and former smokers into a single "ever smoker" category, potentially introducing misclassification bias and attenuating observed associations. Moreover, some heterogeneity in study design, population characteristics, and outcome definitions—including variation in how uveitis was defined—may have contributed to variability in our findings.

Conclusions

This systematic review and meta-analysis identified cigarette smoking as a significant and modifiable risk factor for uveitis, influencing both disease onset and progression. In addition, cigarette smoking likely impairs the efficacy of key uveitis therapies, including corticosteroids and biological agents. While evidence regarding e-cigarette use is currently limited, emerging cohort data and mechanistic studies suggest that vaping may similarly increase the risk of ocular inflammatory diseases. Given the rising prevalence of e-cigarette use, particularly among younger populations, further research is warranted to confirm and characterize these associations. Comprehensive uveitis management should therefore incorporate systematic assessment of both traditional and e-cigarette use, active cessation support, and adjunctive strategies targeting oxidative stress and immune dysregulation. Ophthalmologists, as frontline providers managing ocular inflammatory diseases, are uniquely positioned to identify nicotine exposure and intervene at an early stage. Addressing nicotine exposure may represent an underappreciated avenue to improve long-term outcomes in patients with uveitis.

Author contributions

CRediT: **Sanela Kuč MD:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing; **Marjolein Drent MD, PhD:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing; **Roel Erckens MD, PhD:** Conceptualization, Investigation, Methodology, Supervision, Validation, Visualization, Writing – review & editing; **Steven Ronsmans MD, PhD:** Conceptualization, Writing – review & editing; **Petal A. Wijnen PhD:** Conceptualization, Data curation, Formal analysis, Methodology, Software, Writing – review & editing; **Marlies Gijs PhD:** Writing – review & editing; **Carroll A. B. Webers MD, PhD:** Supervision, Writing – review & editing.

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No potential conflict of interest was reported by the author(s).

Data availability statement

Explanation for why data not available: Data will be shared on a case-by-case basis and upon reasonable request.

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References

1. Wu X, Tao M, Zhu L, Zhang T, Zhang M. Pathogenesis and current therapies for non-infectious uveitis. *Clin Exp Med*. 2023;23(4):1089–1106. doi: 10.1007/s10238-022-00954-6.
2. Asghar MA, Tang S, Wong LP, Yang P, Zhao Q. Infectious uveitis: a comprehensive systematic review of emerging trends and molecular pathogenesis using network analysis. *J Ophthal Inflamm Infect*. 2024;14(1):60. doi: 10.1186/s12348-024-00444-8.
3. Thorne JE, Suhler E, Skup M, et al. Prevalence of noninfectious uveitis in the United States: a claims-based analysis. *JAMA Ophthalmol*. 2016;134(11):1237–1245. doi: 10.1001/jamaophthalmol.2016.3229.
4. Garcia-Aparicio A, Garcia de Yebenes MJ, Oton T, Munoz-Fernandez S. Prevalence and incidence of uveitis: a systematic review and meta-analysis. *Ophthalmic Epidemiol*. 2021;28(6):461–468. doi: 10.1080/09286586.2021.1882506.
5. El Jammal T, Loria O, Jamilloux Y, Gerfaud-Valentin M, Kodjikian L, Seve P. Uveitis as an open window to systemic inflammatory diseases. *J Clin Med*. 2021;10(2):281. doi: 10.3390/jcm10020281.
6. Joukainen E, Antonen J, Leinonen S. Risk factors for uveitis in a Finnish sarcoid population. *Acta Ophthalmol*. 2025;103(1):16–22. doi: 10.1111/aos.16738.
7. Leinonen S. Ocular sarcoidosis, to screen or not to screen? *Front Med (Lausanne)*. 2024;11:1348435. doi: 10.3389/fmed.2024.1348435.
8. Liba T, Gorenshtein A, Leibovitch L, Gepstein R, Machinski E, Segal O. Epidemiological characterization of uveitis in Japan: a systematic review. *Ocul Immunol Inflamm*. 2025;33(7):1086–1095. doi: 10.1080/09273948.2025.2452193.
9. Lin H, Zhang J, Liang C, et al. Differences in the prevalence of uveitis between Crohn's disease and ulcerative colitis: a systematic review and meta-analysis. *Acta Ophthalmol*. 2024;102(4):e485–e492. doi: 10.1111/aos.15793.
10. Rademacher J, Mullner H, Diekhoff T, et al. Keep an eye on the back: spondyloarthritis in patients with acute anterior uveitis. *Arthritis Rheumatol*. 2023;75(2):210–219. doi: 10.1002/art.42315.
11. Bai YC, Wang CY, Lin CL, Lai JN, Wei JC. Association between air pollution and the risk of uveitis: a nationwide, population-based cohort study. *Front Immunol*. 2021;12:613893. doi: 10.3389/fimmu.2021.613893.
12. Biju Mark J, Smit DP, E R R Sr. Intermediate uveitis: an updated review of the differential diagnosis and relevant special investigations. *Ocul Immunol Inflamm*. 2025;33(4):522–534. doi: 10.1080/09273948.2025.2450473.
13. Jacquot R, Seve P, Jackson TL, Wang T, Duclos A, Stanescu-Segall D. Diagnosis, classification, and assessment of the underlying etiology of uveitis by artificial intelligence: a systematic review. *J Clin Med*. 2023;12(11):3746. doi: 10.3390/jcm12113746.
14. Bosello F, Vanzo A, Zaffalon C, et al. Obesity, body fat distribution and eye diseases. *Eat Weight Disord*. 2024;29(1):33. doi: 10.1007/s40519-024-01662-8.
15. Lin P, Loh AR, Margolis TP, Acharya NR. Cigarette smoking as a risk factor for uveitis. *Ophthalmology*. 2010;117(3):585–590. doi: 10.1016/j.ophtha.2009.08.011.
16. Larsson SC, Burgess S. Appraising the causal role of smoking in multiple diseases: a systematic review and meta-analysis of Mendelian randomization studies. *EBioMedicine*. 2022;82:104154. doi: 10.1016/j.ebiom.2022.104154.
17. Colijn JM, Meester-Smoor M, Verzijden T, et al. Genetic risk, lifestyle, and age-related macular degeneration in Europe: the EYE-RISK consortium. *Ophthalmology*. 2021;128(7):1039–1049. doi: 10.1016/j.ophtha.2020.11.024.
18. Tseng YT, Huang ST, Wang CH, Wang LY, Kuo YC. Association of smoking cessation patterns and untreated smoking with glaucoma, cataract, and macular degeneration: a population-based retrospective study. *Sci Rep*. 2024;14(1):14788. doi: 10.1038/s41598-024-65813-8.
19. Kralova JS, Kolar P, Kapounova Z, Vesely P, Brazdova ZD. Lifestyle factors associated with age-related macular degeneration: case-control study. *Eur J Ophthalmol*. 2024;34(5):1548–1554. doi: 10.1177/11206721241229310.
20. Nordstrom M, Zetterberg M, Toren K, Schioler L, Holm M. The more smoking the more cataract: a study on smoking, snus use and cataract in a Swedish population. *Acta Ophthalmol*. 2025;103(1):77–84. doi: 10.1111/aos.16770.
21. Dogru M, Kojima T, Simsek C, Tsubota K. Potential role of oxidative stress in ocular surface inflammation and dry eye disease. *Invest Ophthalmol Vis Sci*. 2018;59(14):DES163–DES168. doi: 10.1167/iovs.17-23402.
22. Dammak A, Pastrana C, Martin-Gil A, et al. Oxidative stress in the anterior ocular diseases: diagnostic and treatment. *Biomedicines*. 2023;11(2):292. doi: 10.3390/biomedicines11020292.
23. Mitchell P, Wang JJ, Smith W, Leeder SR. Smoking and the 5-year incidence of age-related maculopathy: The Blue Mountains Eye Study. *Arch Ophthalmol*. 2002;120(10):1357–1363. doi: 10.1001/archopht.120.10.1357.
24. Hsu AY, Wang YH, Hsia NY, et al. Risk of uveitis among e-cigarette users: a multi-institutional TriNetX study. *Ophthalmology*. 2025;132(3):370–373. doi: 10.1016/j.ophtha.2024.11.008.
25. Wang TW, Gentzke AS, Neff LJ, et al. Characteristics of e-cigarette use behaviors among US youth, 2020. *JAMA Netw Open*. 2021;4(6):e2111336. doi: 10.1001/jamanetworkopen.2021.11336.
26. Page MJ, McKenzie JE, Bossuyt PM, et al. The prisma 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi: 10.1136/bmj.n71.
27. Barker TH, Stone JC, Sears K, et al. Revising the JBI quantitative critical appraisal tools to improve their applicability: an overview of methods and the development process. *JBI Evid Synth*. 2023;21(3):478–493. doi: 10.11124/JBIES-22-00125.
28. Cochrane. RevMan. https://subscribe.cochrane.org/info. Accessed February, 2025.
29. Group GW. *GradePro GDT*. https://www.gradepro.org/. Accessed March, 2025.
30. Siasos G, Paraskevopoulos T, Gialafos E, et al. Vascular function and ocular involvement in sarcoidosis. *Microvasc Res*. 2015;100:54–58. doi: 10.1016/j.mvr.2015.03.008.
31. Jones GT, Ratz T, Dean LE, Macfarlane GJ, Atzeni F. Disease severity in never smokers, ex-smokers, and current smokers with axial spondyloarthritis: results from the Scotland registry for ankylosing spondylitis. *Arthritis Care Res (Hoboken)*. 2017;69(9):1407–1413. doi: 10.1002/acr.23157.
32. Marsh K, Mac Gearailt C, O'Shea F, Fitzgerald G. In axial spondyloarthritis current smoking is associated with lower prevalence of uveitis and peripheral arthritis in males, but not females. *Joint Bone Spine*. 2024;91(5):105746. doi: 10.1016/j.jbspin.2024.105746.
33. Yaşar Bilge N, Kalyoncu U, Atagündüz P, et al. Uveitis-related factors in patients with spondyloarthritis: TReasure real-life results. *Am J Ophthalmol*. 2021;228:58–64. doi: 10.1016/j.ajo.2021.03.026 .
34. Zhao S, Jones GT, Macfarlane GJ, et al. Associations between smoking and extra-axial manifestations and disease severity in axial spondyloarthritis: results from the BSR Biologics Register for Ankylosing Spondylitis (BSRBR-AS). *Rheumatol (Oxford)*. 2019;58(5):811–819. doi: 10.1093/rheumatology/key371.
35. Zhao SS, Macfarlane GJ, Jones GT, et al. Smoking does not protect patients with axial spondyloarthritis from attacks of uveitis. *Ann*

Rheum Dis. 2019;78(9):1287–1288. doi: 10.1136/annrheumdis-2019-215348.
36. Costa E, Almeida D, Cerqueira M, Costa JR, Ribeiro AR, Sousa-Neves J. Smoking as associated factor for spondyloarthritis related uveitis: results from a single centre cross-sectional study. *Acta Reumatol Port*. 2020;45(4):265–269.
37. Torgutalp M, Eroğlu D, Sezer S, et al. Patient characteristics in Behçet's syndrome and their associations with major organ involvement: a single-centre experience of 2118 cases. *Scand J Rheumatol*. 2022;51(1):50–58. doi: 10.1080/03009742.2021.1904622.
38. Malek Mahdavi A, Khabbazi A, Yaaghoobian B, et al. Cigarette smoking and risk of Behcet's disease: a propensity score matching analysis. *Mod Rheumatol*. 2019;29(4):633–639. doi: 10.1080/14397595.2018.1493065.
39. Derakhshan MH, Dean L, Jones GT, Siebert S, Gaffney K. Predictors of extra-articular manifestations in axial spondyloarthritis and their influence on TNF-inhibitor prescribing patterns: results from the British Society for Rheumatology Biologics Register in ankylosing spondylitis. *RMD Open*. 2020;6(2):e001206. doi: 10.1136/rmdopen-2020-001206.
40. Haddaway NR, Page MJ, Pritchard CC, McGuinness LA. Prisma2020: an R package and shiny app for producing PRISMA 2020-compliant flow diagrams, with interactivity for optimised digital transparency and open synthesis. *Campbell Syst Rev*. 2022;18(2):e1230. doi: 10.1002/cl2.1230.
41. Yuen BG, Tham VM, Browne EN, et al. Association between smoking and uveitis: results from the Pacific Ocular Inflammation Study. *Ophthalmology*. 2015;122(6):1257–1261. doi: 10.1016/j.ophtha.2015.02.034.
42. Chheda LV, Ferketich AK, Carroll CP, Moyer PD, Kurz DE, Kurz PA. Smoking as a risk factor for choroidal neovascularization secondary to presumed ocular histoplasmosis syndrome. *Ophthalmology*. 2012;119(2):333–338. doi: 10.1016/j.ophtha.2011.08.003.
43. Richey BF, Obrock RS, Gee ZM, Lu DY, Jacobsen G, Richards SC. Smoking, rural residence and diabetes as risk factors for presumed ocular histoplasmosis syndrome. *Retina*. 2022;42(2):369–374. doi: 10.1097/IAE.0000000000003322.
44. Roesel M, Ruttig A, Schumacher C, Heinz C, Heiligenhaus A. Smoking complicates the course of non-infectious uveitis. *Graefes Arch Clin Exp Ophthalmol*. 2011;249(6):903–907. doi: 10.1007/s00417-010-1597-1.
45. Thorne JE, Daniel E, Jabs DA, Kedhar SR, Peters GB, Dunn JP. Smoking as a risk factor for cystoid macular edema complicating intermediate uveitis. *Am J Ophthalmol*. 2008;145(5):841–846. doi: 10.1016/j.ajo.2007.12.032.
46. Bohm EW, Buonfiglio F, Voigt AM, et al. Oxidative stress in the eye and its role in the pathophysiology of ocular diseases. *Redox Biol*. 2023;68:102967. doi: 10.1016/j.redox.2023.102967.
47. Seo YS, Park JM, Kim JH, Lee MY. Cigarette smoke-induced reactive oxygen species formation: a concise review. *Antioxid (Basel)*. 2023;12(9):1732. doi: 10.3390/antiox12091732.
48. Moustardas P, Aberdam D, Lagali N. Mapk pathways in ocular pathophysiology: potential therapeutic drugs and challenges. *Cells*. 2023;12(4):617. doi: 10.3390/cells12040617.
49. Jomova K, Raptova R, Alomar SY, et al. Reactive oxygen species, toxicity, oxidative stress, and antioxidants: chronic diseases and aging. *Arch Toxicol*. 2023;97(10):2499–2574. doi: 10.1007/s00204-023-03562-9.
50. Miglio F, Naroo S, Zeri F, Tavazzi S, Ponzini E. The effect of active smoking, passive smoking, and e-cigarettes on the tear film: an updated comprehensive review. *Exp Eye Res*. 2021;210:108691. doi: 10.1016/j.exer.2021.108691.
51. Auschwitz E, Almeda J, Andl CD. Mechanisms of e-cigarette vape-induced epithelial cell damage. *Cells*. 2023;12(21):2552. doi: 10.3390/cells12212552.
52. Prasad KN, Bondy SC. Electronic cigarette aerosol increases the risk of organ dysfunction by enhancing oxidative stress and inflammation. *Drug Chem Toxicol*. 2022;45(6):2561–2567. doi: 10.1080/01480545.2021.1972680.
53. Nguyen AX, Gaiha SM, Chung S, Halpern-Felsher B, Wu AY. Ocular symptoms in adolescents and young adults with electronic cigarette, cigarette, and dual use. *JAMA Ophthalmol*. 2023;141(10):937–946. doi: 10.1001/jamaophthalmol.2023.3852.
54. Lee S, Kuenzig ME, Ricciuto A, et al. Smoking may reduce the effectiveness of anti-TNF therapies to induce clinical response and remission in Crohn's disease: a systematic review and meta-analysis. *J Crohns Colitis*. 2021;15(1):74–87. doi: 10.1093/ecco-jcc/jjaa139.
55. Alizadeh M, Ali O, Cross RK. Assessing progression of biologic therapies based on smoking status in patients with Crohn's disease. *Inflamm Bowel Dis*. 2024;30(5):788–794. doi: 10.1093/ibd/izad131.
56. Soderlin MK, Petersson IF, Geborek P. The effect of smoking on response and drug survival in rheumatoid arthritis patients treated with their first anti-TNF drug. *Scand J Rheumatol*. 2012;41(1):1–9. doi: 10.3109/03009742.2011.599073.
57. Ryu CS, Choi YJ, Nam HS, et al. Short-term regulation of the hepatic activities of cytochrome P450 and glutathione S-transferase by nose-only cigarette smoke exposure in mice. *Food Chem Toxicol*. 2019;125:182–189. doi: 10.1016/j.fct.2018.12.035.
58. Chaudhuri R, Livingston E, McMahon AD, Thomson L, Borland W, Thomson NC. Cigarette smoking impairs the therapeutic response to oral corticosteroids in chronic asthma. *Am J Respir Crit Care Med*. 2003;168(11):1308–1311. doi: 10.1164/rccm.200304-503OC.
59. Kulbay M, Wu KY, Nirwal GK, Belanger P, Tran SD. The role of reactive oxygen species in age-related macular degeneration: a comprehensive review of antioxidant therapies. *Biomedicines*. 2024;12(7):1579. doi: 10.3390/biomedicines12071579.
60. Shu DY, Chaudhary S, Cho KS, et al. Role of oxidative stress in ocular diseases: a balancing act. *Metabolites*. 2023;13(2):187. doi: 10.3390/metabo13020187.
61. Yadav UC, Kalariya NM, Ramana KV. Emerging role of antioxidants in the protection of uveitis complications. *Curr Med Chem*. 2011;18(6):931–942. doi: 10.2174/092986711794927694.
62. Polyak E, Ostrovsky J, Peng M, et al. N-acetylcysteine and vitamin E rescue animal longevity and cellular oxidative stress in pre-clinical models of mitochondrial complex I disease. *Mol Genet Metab*. 2018;123(4):449–462. doi: 10.1016/j.ymgme.2018.02.013.
63. Zhao L, Wang H, Du X. The therapeutic use of quercetin in ophthalmology: recent applications. *Biomed Pharmacother*. 2021;137:111371. doi: 10.1016/j.biopha.2021.111371.
64. Ding K, Jiang W, Zhan W, et al. The therapeutic potential of quercetin for cigarette smoking-induced chronic obstructive pulmonary disease: a narrative review. *Ther Adv Respir Dis*. 2023;17:17534666231170800. doi: 10.1177/17534666231170800.
65. Boots AW, Drent M, Swennen EL, Moonen HJ, Bast A, Haenen GR. Antioxidant status associated with inflammation in sarcoidosis: a potential role for antioxidants. *Respir Med*. 2009;103(3):364–372. doi: 10.1016/j.rmed.2008.10.007.
66. Veith C, Drent M, Bast A, van Schooten FJ, Boots AW. The disturbed redox-balance in pulmonary fibrosis is modulated by the plant flavonoid quercetin. *Toxicol Appl Pharmacol*. 2017;336:40–48. doi: 10.1016/j.taap.2017.10.001.