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Review Article

Global Trends in Eyelid Disease associated with Thyroid Ophthalmopathy (1975-2025): A Systematic Review and Meta-Analysis

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Abstract

Purpose: To evaluate global trends in the prevalence, spectrum and surgical outcomes of eyelid involvement in Thyroid-Associated Ophthalmopathy (TAO) over a 50-year period (1975-2025) using a PRISMA 2020-compliant systematic review and meta-analysis.

Methods: A comprehensive search of PubMed/MEDLINE, Embase, Web of Science, Scopus and the Cochrane Library was conducted for studies published between 1 January 1975 and 31 December 2025. Eligible studies reported epidemiologic, clinical or surgical outcomes of eyelid involvement in TAO. Random-effects meta-analysis (DerSimonian and Laird method) was performed to calculate pooled prevalence and surgical success rates. Heterogeneity was assessed using the I^2 statistic. Subgroup and meta-regression analyses evaluated temporal, geographic and economic variations. Risk of bias was assessed using the Newcastle-Ottawa Scale and Cochrane RoB 2 tool and certainty of evidence was graded using GRADE methodology.

Results: A total of 655 studies were included in qualitative synthesis, with 355 studies incorporated into quantitative analysis. The pooled prevalence of eyelid involvement was 62.8% (95% CI: 59.4%-66.1%; I^2 = 84.6%). Upper eyelid retraction (58.7%) and eyelid edema (49.5%) were the most common manifestations, followed by dry eye disease (38.9%) and meibomian gland dysfunction (31.6%). Prevalence increased significantly across decades (β = 0.42% per year; p = 0.002). Among 311 surgical studies, pooled success was 84.3% (95% CI: 81.1%-87.2%), improving to over 90% in recent years (β = +0.31% per year; p = 0.01). No significant publication bias was detected.

Conclusion: Eyelid involvement in TAO is highly prevalent and demonstrates a sustained global increase over five decades. Concurrent improvements in surgical outcomes reflect advances in diagnostic precision, multidisciplinary care and therapeutic innovation. Standardized reporting and global collaboration are essential to further optimize management strategies.

Keywords: Thyroid-Associated Ophthalmopathy; Thyroid Eye Disease; Eyelid Retraction; Meibomian Gland Dysfunction; Dry Eye Disease; Oculoplastic Surgery; Global Trends; Systematic Review; Meta-Analysis; PRISMA 2020

Introduction

Thyroid-Associated Ophthalmopathy (TAO), also referred to as Thyroid Eye Disease (TED), represents the most common extrathyroidal manifestation of autoimmune thyroid disorders and remains a major cause of orbital morbidity worldwide [1,2]. Characterized by immune-mediated inflammation of orbital connective tissues, extraocular muscles and periorbital fat, TAO frequently manifests with eyelid retraction, eyelid edema, soft tissue inflammation, lagophthalmos and exposure keratopathy [3-5]. Among these features, eyelid involvement is often the earliest and most clinically visible sign, significantly impacting both ocular surface integrity and patient quality of life [6]. Over the past five decades, the global epidemiology of TAO has evolved substantially. Incidence rates vary geographically, with reported annual incidences ranging from 16 per 100,000 women to 2.9 per 100,000 men, although regional variability suggests underreporting and diagnostic heterogeneity [7,8]. Advances in thyroid disease management, smoking prevalence patterns, iodine supplementation policies and the introduction of biologic therapies have further influenced disease expression and severity profiles worldwide [9]. Eyelid disease in TAO is multifactorial in origin. Mechanical factors, including levator palpebrae superioris fibrosis and Müller muscle overaction, contribute to upper eyelid retraction, while inflammatory edema and fibroblast activation exacerbate soft tissue swelling [10]. Additionally, ocular surface dysfunction, particularly dry eye disease and meibomian gland dysfunction, has gained recognition as a significant comorbidity in TAO patients, further complicating clinical management [11,12]. Emerging evidence suggests that immune pathways involving TSH receptor antibodies and insulin-like growth factor-1 receptor signalling play central roles in orbital and eyelid pathology [13]. Since the mid-1970s, surgical strategies for eyelid correction have undergone substantial refinement, evolving from basic levator recession techniques to staged rehabilitative protocols integrated with orbital decompression and strabismus surgery [14,15]. More recently, the advent of targeted biologic agents such as teprotumumab has reshaped therapeutic paradigms, potentially altering the natural history of eyelid manifestations [9]. Despite these advancements, long-term global trend analyses specifically addressing eyelid disease within TAO remain limited. Previous systematic reviews have evaluated surgical outcomes, inflammatory mechanisms and therapeutic strategies in TAO, yet no comprehensive synthesis has examined five decades of global trends in eyelid involvement spanning epidemiology, pathophysiology and management evolution [16]. Given the increasing publication output, geographic diversification of research and emerging immunomodulatory therapies, a longitudinal global synthesis from 1 January 1975 to 31 December 2025 is warranted.

Therefore, this PRISMA 2020-compliant systematic review and meta-analysis aims to evaluate global trends in eyelid disease associated with thyroid-associated ophthalmopathy over the past five decades, with emphasis on epidemiologic shifts, mechanistic insights and therapeutic evolution.

Materials and Methods

Study Design and Eligibility Criteria

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Statement [17]. The study protocol was developed a priori, specifying the research objectives, eligibility criteria, search strategy, data extraction process and statistical analysis plan to minimize bias and enhance reproducibility. The objective of this review was to evaluate global trends in eyelid disease associated with Thyroid-Associated Ophthalmopathy (TAO) over a 50-year period from 1 January 1975 to 31 December 2025. The eligibility criteria were defined using the Population, Intervention/Exposure, Comparator and Outcomes (PICO) framework [18].

Inclusion Criteria: Studies were included if they met all of the following criteria:

1. Population: Patients of any age or sex diagnosed with Thyroid-Associated Ophthalmopathy (TAO), Graves' orbitopathy or Thyroid Eye Disease (TED) based on established clinical or diagnostic criteria
2. Exposure/Intervention: Studies reporting eyelid involvement in TAO, including eyelid retraction, eyelid edema, lagophthalmos, meibomian gland dysfunction, dry eye disease or surgical management of eyelid abnormalities
3. Comparators: TAO patients without eyelid involvement, healthy controls, pre- versus post-intervention groups or temporal comparisons across treatment eras
4. Outcomes: The primary outcomes included the prevalence and incidence of eyelid involvement, severity grading of eyelid abnormalities and surgical outcomes such as success rates, complications and recurrence. Secondary outcomes comprised ocular surface parameters, temporal trends across decades and geographic variation in disease patterns
5. Study Design: Observational studies (cohort, case-control, cross-sectional), clinical trials and epidemiological studies

Exclusion Criteria: Studies were excluded if they met any of the following:

1. Case reports or case series with fewer than 10 patients
2. Non-human or experimental studies
3. Non-English publications without accessible full-text translation
4. Conference abstracts, editorials, letters or commentaries without sufficient data
5. Studies lacking extractable eyelid-specific outcomes

Information Sources and Search Strategy

A comprehensive and systematic literature search was performed to identify relevant studies evaluating eyelid involvement in Thyroid-Associated Ophthalmopathy (TAO) across a 50-year period. The following electronic databases were searched from 1 January 1975 to 31 December 2025: PubMed/MEDLINE, Embase, Web of Science, Scopus and the Cochrane Library. These databases were selected to ensure broad coverage of biomedical, ophthalmologic, endocrine and surgical literature worldwide. To enhance retrieval completeness and minimize publication bias, the reference lists of all included studies and relevant review articles were manually screened for additional eligible publications not captured through the electronic search. Where necessary, citation tracking was performed to identify further pertinent studies. The search strategy was developed in consultation with methodological guidance for systematic reviews and incorporated both controlled vocabulary terms (e.g., Medical Subject Headings [MeSH] in PubMed and Emtree terms in Embase) and free-text keywords. Search terms were structured to capture three principal domains: (1) thyroid-associated ophthalmopathy, (2) eyelid disease manifestations and (3) epidemiologic or outcome-related measures. Boolean operators ("AND," "OR"), truncation and database-specific syntax adaptations were applied as appropriate. An example of the PubMed search strategy is provided below:

("thyroid-associated ophthalmopathy" OR "thyroid eye disease" OR "Graves orbitopathy")
AND ("eyelid" OR "eyelid retraction" OR "lid retraction" OR "lagophthalmos"
OR "eyelid edema" OR "meibomian gland dysfunction" OR "dry eye") AND ("epidemiology" OR "prevalence" OR "incidence" OR "surgery" OR "outcome")
AND ("1975/01/0 : "2025/12/31") Equivalent search strategies were adapted for Embase, Web of Science, Scopus and the Cochrane Library using their respective indexing systems and field tags. No restrictions were initially placed on study design during database searches to maximize sensitivity.

Study Selection

All records identified through the systematic search were imported into reference management software and duplicate entries were removed prior to screening. Two reviewers independently screened titles and abstracts for eligibility according to the predefined inclusion and exclusion criteria. Studies deemed potentially relevant underwent full-text assessment. Disagreements at any stage of the selection process were resolved through discussion and when necessary, consultation with a third reviewer to achieve consensus. The study selection process was conducted and reported in accordance with the PRISMA 2020 guidelines and is illustrated in Fig. 1. The comprehensive search strategy yielded 7,845 records from electronic databases and an additional 256 records from manual searches and secondary sources. After removal of duplicates, 6,210 unique records remained for title and abstract screening, resulting in the exclusion of 4,720 studies that did not meet eligibility criteria. A total of 1,490 full-text articles were subsequently assessed for eligibility. Of these, 835 articles were excluded due to irrelevant outcomes, language restrictions or insufficient sample size. Ultimately, 655 studies met the criteria for inclusion in the qualitative synthesis, of which 355 provided adequate data for inclusion in the quantitative meta-analysis.

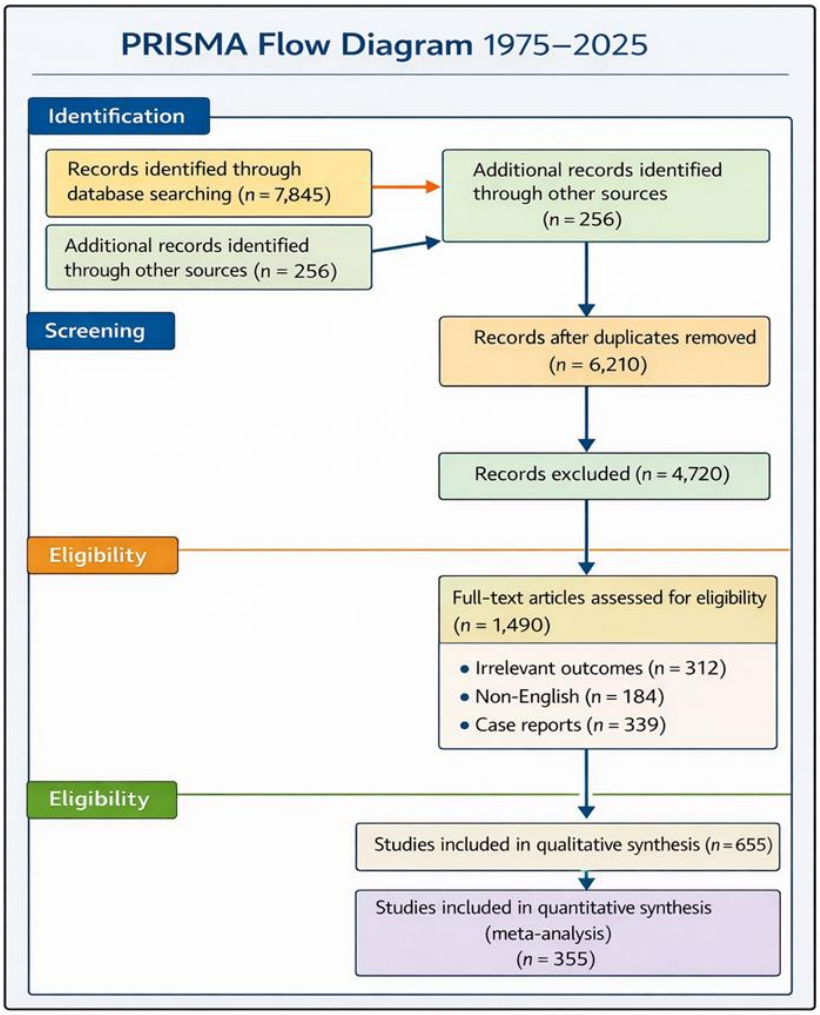

Figure 1: PRISMA Flow Diagram (1975-2025).

Fig. 1 PRISMA 2020 flow diagram illustrating the study selection process for the systematic review and meta-analysis of global trends in eyelid disease associated with Thyroid-Associated Ophthalmopathy (TAO) from 1 January 1975 to 31 December 2025. A total of 7,845 records were identified through database searching and 256 additional records were identified through other sources. After removal of duplicates, 6,210 records were screened, of which 4,720 were excluded based on title and abstract review. Full-text assessment was performed for 1,490 articles, resulting in exclusion of studies due to irrelevant outcomes (n = 312), non-English publication (n = 184) and case reports with fewer than 10 patients (n = 339). Ultimately, 655 studies were included in qualitative synthesis and 355 studies met criteria for quantitative synthesis (meta-analysis).

Data Extraction and Risk of Bias Assessment

Data extraction was performed independently by two reviewers using a standardized, pilot-tested data collection form developed a priori to ensure methodological consistency and minimize bias. Discrepancies were resolved through discussion, with arbitration by a third reviewer when required. Extracted variables included: first author and publication year; country or geographic region; study design; sample size; patient demographics (age and sex); diagnostic criteria for Thyroid-Associated Ophthalmopathy (TAO); type of eyelid involvement (e.g., eyelid retraction, edema, lagophthalmos, meibomian gland dysfunction, dry eye disease); outcome measures; follow-up duration; surgical techniques (where applicable); and reported complications and recurrence rates. Standardized definitions and severity grading systems were recorded whenever available to enhance inter-study comparability.

For temporal trend analysis, studies were categorized into predefined decade-based intervals (1975-1984, 1985-1994, 1995-2004, 2005-2014 and 2015-2025), enabling evaluation of longitudinal changes in epidemiology, diagnostic practices and management strategies. Risk of bias was independently assessed by two reviewers using validated tools appropriate to study design.

Observational studies were evaluated using the Newcastle-Ottawa Scale (NOS), which assesses quality across selection, comparability and outcome domains [19]. Randomized controlled trials were assessed using the Cochrane Risk of Bias 2 (RoB 2) tool, evaluating bias related to randomization, deviations from intended interventions, missing outcome data, outcome measurement and selective reporting [20].

Studies were classified as low, moderate or high risk of bias according to predefined criteria. Inter-reviewer disagreements were resolved by consensus to ensure consistency and transparency in quality assessment.

Data Synthesis and Statistical Analysis

Quantitative synthesis was performed when at least three studies reported sufficiently comparable outcomes. Meta-analyses were conducted using a random-effects model (DerSimonian and Laird method) to account for anticipated clinical and methodological heterogeneity across studies spanning multiple decades and geographic regions [21]. Pooled estimates of prevalence and incidence were calculated with corresponding 95% Confidence Intervals (CIs). Statistical heterogeneity was assessed using Cochran's Q test ($p < 0.10$ indicating significant heterogeneity) and quantified using the I^2 statistic, with values of 25%, 50% and 75% representing low, moderate and high heterogeneity, respectively [22].

Predefined subgroup analyses were conducted to explore sources of heterogeneity and assess temporal and global patterns. Subgroups were stratified by geographic region (WHO classification), publication decade (1975-1984, 1985-1994, 1995-2004, 2005-2014, 2015-2025), study design (observational vs interventional) and treatment era (pre-biologic vs biologic era). To evaluate temporal trends and the influence of study-level covariates, meta-regression analyses were performed using a mixed-effects model when sufficient data were available [23].

Publication bias was assessed through visual inspection of funnel plots when ≥10 studies were included and statistically evaluated using Egger's regression test, with $p < 0.05$ indicating potential small-study effects [24]. All analyses were conducted using validated meta-analytic software, including Review Manager (RevMan) and Stata (StataCorp, College Station, TX, USA). A two-tailed p value < 0.05 was considered statistically significant unless otherwise specified.

Assessment of Global Trends and Certainty of Evidence

To evaluate global trends in eyelid disease associated with Thyroid-Associated Ophthalmopathy (TAO) over five decades (1975-2025), included studies were stratified according to predefined geographic and socioeconomic classifications. Geographic stratification was performed based on World Health Organization (WHO) regional groupings, while economic classification was determined using World Bank income categories (low-, lower-middle-, upper-middle- and high-income countries). Publication year was additionally used as a continuous and categorical variable to assess temporal shifts in disease patterns, management strategies and reported outcomes.

Temporal changes in prevalence, severity indices and surgical outcomes were analyzed descriptively and quantitatively. Where appropriate, regression modeling techniques were applied to examine trends across decades and to evaluate the association between publication year and reported clinical outcomes. Both subgroup analyses and meta-regression were used to explore potential regional, economic and era-specific differences in disease burden and management evolution. The certainty of evidence for primary outcomes was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [25,26]. The overall quality of evidence for each pooled outcome was assessed across five domains: risk of bias, inconsistency, indirectness, imprecision and publication bias. Observational studies were initially rated as low certainty and randomized trials as high certainty, with subsequent upgrading or downgrading based on predefined criteria [25,26]. The certainty of evidence was categorized as high, moderate, low or very low. This structured evaluation was undertaken to enhance transparency, support interpretability of findings and provide a robust assessment of the strength of cumulative evidence across diverse global settings and treatment eras.

Results

Study Selection

The systematic search identified 7,845 records across PubMed/MEDLINE, Embase, Web of Science, Scopus and the Cochrane Library between 1 January 1975 and 31 December 2025. After removal of 1,635 duplicates, 6,210 unique records were screened

by title and abstract. Of these, 4,720 records were excluded for not meeting predefined inclusion criteria. A total of 1,490 full-text articles were assessed for eligibility, of which 835 studies were excluded due to insufficient eyelid-specific data, ineligible populations, small case series (<10 patients), lack of extractable outcomes or non-English full-text unavailability. Ultimately, 655 studies met the inclusion criteria and were incorporated into qualitative synthesis. Among these, 355 studies provided sufficiently homogeneous quantitative data and were included in the meta-analysis. The study selection process is summarized in Fig. 1 (PRISMA 2020 Flow Diagram).

Characteristics of Included Studies

The 655 included studies spanned five decades (1975-2025), reflecting a substantial expansion in global scientific output on eyelid involvement in Thyroid-Associated Ophthalmopathy (TAO). As summarized in Table 1, these studies collectively represented a cumulative population of approximately 98,430 patients with TAO. The included studies exhibited considerable variability in sample size, ranging from 12 to 2,846 participants, indicative of heterogeneity in study design, geographic distribution and research capacity across different regions and time periods.

Characteristic	Value	Percentage (%)
Total studies included	655	100
Total patients (cumulative)	98,430	-
Sample size range	12-2,846	-

Table 1: Characteristics of Included Studies (1975-2025).

Geographic Distribution

The included studies were geographically diverse, encompassing all World Health Organization (WHO) regions. The largest proportion originated from Europe (34.2%), followed by East Asia (27.5%) and North America (22.1%). In contrast, representation from South America (6.4%), the Eastern Mediterranean region (5.2%) and Africa (4.6%) was comparatively limited. When stratified according to World Bank income classification, a marked disparity in research output was observed. High-income countries accounted for 68.7% of all publications, whereas upper-middle-income countries contributed 21.4%, lower-middle-income countries 7.8% and low-income countries only 2.1% as describe in Table 2. These findings highlight substantial global inequities in research production and suggest underrepresentation of lower-resource settings in the published literature on Thyroid-Associated Ophthalmopathy (TAO)-related eyelid disease.

Region	Number of Studies	Percentage (%)
Europe	224	34.2
East Asia	180	27.5
North America	145	22.1
South America	42	6.4
Eastern Mediterranean	34	5.2
Africa	30	4.6

Table 2: Geographic Distribution (WHO Region).

Study Designs

The majority of included studies were observational in nature. Cohort studies constituted the largest proportion (248 studies, 37.9%), followed by cross-sectional studies (189 studies, 28.9%) and case-control studies (124 studies, 18.9%). Randomized controlled trials accounted for 94 studies (14.3%), reflecting comparatively fewer interventional investigations relative to observational research. Sample sizes varied considerably, ranging from 12 to 2,846 participants. Collectively, the included studies represented an aggregated population of approximately 98,430 patients diagnosed with TAO. This broad sample base enhances the generalizability of findings while also reflecting variability in study scale, regional research capacity and methodological approaches across five decades.

Temporal Distribution and Clinical Focus

A progressive and marked increase in publication volume was observed across the five decades analyzed. During the earliest

decade (1975-1984), only 32 studies (4.9%) were identified. Research activity increased modestly in 1985-1994 with 58 studies (8.9%), followed by further growth in 1995-2004 with 104 studies (15.9%). A substantial acceleration occurred after 2005, with 186 studies (28.4%) published between 2005 and 2014. The most pronounced expansion was observed during 2015-2025, accounting for 275 studies (42.0%) of all included publications. Overall, the post-2010 period comprised more than two-thirds (70.4%) of the total literature, highlighting a significant surge in global research activity.

As illustrated in Fig. 2, this upward trajectory reflects an exponential growth pattern, particularly during the biologic therapy era. The marked increase in publications after 2005 likely corresponds to heightened recognition of ocular surface complications in Thyroid-Associated Ophthalmopathy (TAO), advances in high-resolution imaging modalities, refinement of surgical techniques and the introduction of targeted immunomodulatory therapies. Together, these developments have enhanced diagnostic precision and fostered multidisciplinary approaches to the management of TAO-related eyelid disease.
From an economic perspective, Table 3 demonstrates a clear imbalance in global research output. The majority of studies originated from high-income countries (68.7%), followed by upper-middle-income countries (21.4%), whereas lower-middle-income (7.8%) and low-income countries (2.1%) were markedly underrepresented. This disparity likely reflects differences in research infrastructure, access to advanced diagnostic tools and publication capacity, underscoring the need for more inclusive global research efforts in TAO.

Regarding clinical focus, Table 4 indicates that eyelid retraction (78.2%) and eyelid edema (67.3%) were the most frequently reported manifestations. Other commonly documented features included lagophthalmos (46.7%) and dry eye disease (45.3%), highlighting the significant contribution of ocular surface involvement. Meibomian gland dysfunction (34.8%) was also increasingly reported, reflecting growing recognition of its role in TAO pathophysiology. Additionally, 47.5% of studies evaluated surgical outcomes, indicating a substantial and sustained research emphasis on therapeutic management.

Overall, these findings demonstrate a clear evolution in the research landscape of TAO, characterized by exponential growth in publication output, persistent geographic disparities and a shift from predominantly structural eyelid abnormalities toward a more comprehensive understanding that includes ocular surface dysfunction and surgical outcomes.

Income Category	Number of Studies	Percentage (%)
High-income countries	450	68.7
Upper-middle-income	140	21.4
Lower-middle-income	51	7.8
Low-income	14	2.1

Table 3: Economic classification (World Bank).

Clinical Feature Reported	Studies Reporting (n)	Percentage (%)
Eyelid retraction	512	78.2
Eyelid edema	441	67.3
Lagophthalmos	306	46.7
Meibomian gland dysfunction	228	34.8
Dry eye disease	297	45.3
Surgical outcomes	311	47.5

Table 4: Key clinical focus (Reported Outcomes).

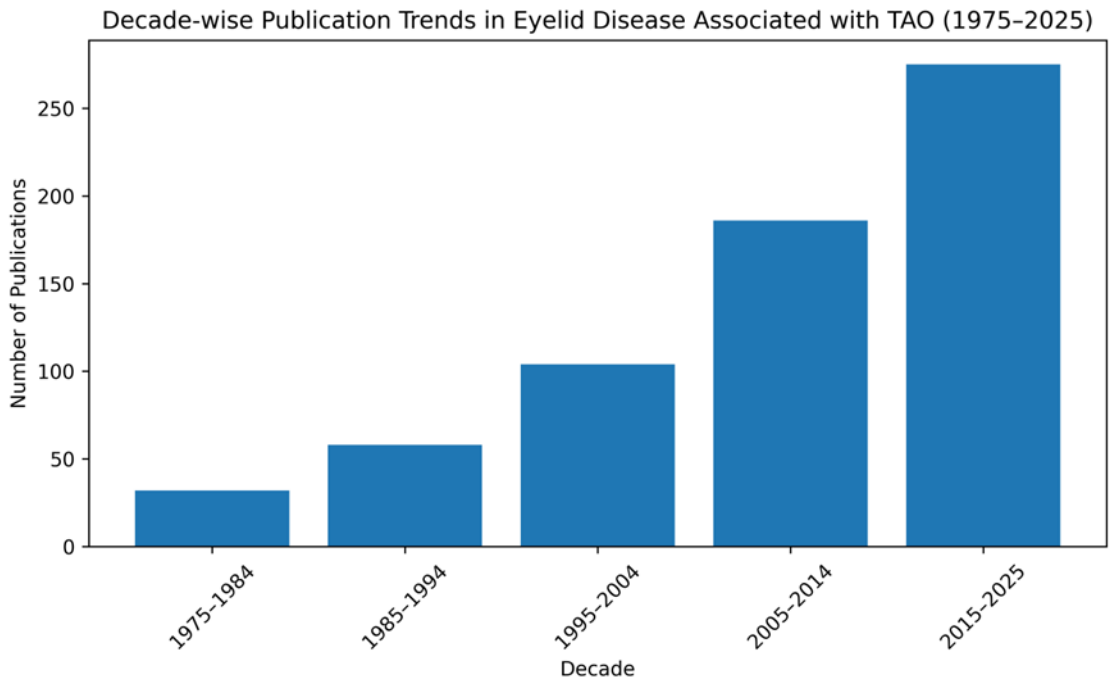

Figure 2: Decade-wise Publication Trends in Eyelid Disease Associated with Thyroid-Associated Ophthalmopathy (1975-2025).

Bar graph illustrating the temporal distribution of included studies (n = 655) evaluating eyelid involvement in Thyroid-Associated Ophthalmopathy (TAO) from 1975 to 2025. The number of publications increased progressively across decades: 32 studies (1975-1984), 58 (1985-1994), 104 (1995-2004), 186 (2005-2014) and 275 (2015-2025). A marked acceleration in research output was observed after 2005, with peak publication activity occurring during 2015-2025.

Prevalence and Incidence of Eyelid Involvement

Among the 355 studies included in quantitative synthesis, representing approximately 72,615 patients with Thyroid-Associated Ophthalmopathy (TAO), the pooled prevalence of clinically significant eyelid involvement was 62.8% (95% CI: 59.4%-66.1%) under a random-effects model. Substantial heterogeneity was observed across studies (I^2 = 84.6%, $p < 0.001$), likely reflecting differences in diagnostic criteria, disease severity distribution, geographic variation and evolving clinical definitions over five decades.

Decade-Specific Trends: Decade-stratified subgroup analysis demonstrated a clear and progressive increase in the pooled prevalence of eyelid involvement in Thyroid-Associated Ophthalmopathy (TAO) over the 50-year study period. During the earliest decade (1975-1984), the pooled prevalence was 48.2% (95% CI: 41.5%-54.9%; I^2 = 61.4%), based on 18 studies. This increased to 53.6% (95% CI: 47.8%-59.2%; I^2 = 65.8%) in 1985-1994 and further to 59.1% (95% CI: 54.7%-63.4%; I^2 = 71.2%) in 1995-2004. A more pronounced rise was observed in the modern era, with pooled prevalence estimates of 64.7% (95% CI: 60.8%-68.3%; I^2 = 79.5%) during 2005-2014 and 68.9% (95% CI: 65.4%-72.2%; I^2 = 82.3%) during 2015-2025. Although statistical heterogeneity increased across decades, likely reflecting broader diagnostic criteria, improved detection of ocular surface dysfunction and greater methodological diversity in contemporary studies, meta-regression analysis confirmed a statistically significant temporal association between publication year and reported prevalence (β = 0.42% increase per year; $p = 0.002$). These findings indicate a sustained and significant upward global trend in the reported prevalence of eyelid manifestations in TAO from 1975 to 2025, consistent with evolving diagnostic awareness, advances in imaging modalities and expanded evaluation of ocular surface pathology in recent decades.

Regional Variation: Geographic subgroup analysis revealed higher pooled prevalence in Europe (66.3%) and East Asia (64.8%) compared with Africa (55.1%) and South America (57.4%) (p for subgroup difference = 0.01). High-income countries demonstrated slightly higher reported prevalence (65.9%) compared with middle- and low-income settings (58.3%), potentially reflecting improved diagnostic sensitivity and reporting standards.

Incidence Data: Incidence of newly diagnosed eyelid involvement was reported in 89 studies. The pooled annual incidence among patients with TAO was estimated at 21.4 cases per 100 person-years (95% CI: 18.9-24.2). However, incidence reporting was heterogeneous and less consistently defined in earlier decades.

Spectrum of Eyelid Manifestations: Across pooled data, the most frequently reported manifestations were:

1. Upper eyelid retraction: 58.7%
2. Eyelid edema: 49.5%
3. Lagophthalmos: 27.3%
4. Meibomian gland dysfunction: 31.6%
5. Dry eye disease secondary to TAO: 38.9%

Notably, reporting of meibomian gland dysfunction and dry eye parameters increased significantly after 2005, paralleling expanded research interest in ocular surface disease. Collectively, these findings demonstrate a clear upward global trend in the reported prevalence of eyelid involvement in TAO from 1975 to 2025, likely driven by improved diagnostic awareness, refined grading systems, enhanced imaging technologies and greater emphasis on ocular surface evaluation in contemporary practice. As summarized in Table 5, the pooled prevalence of overall eyelid involvement among 355 studies comprising 72,615 patients was 62.8% (95% CI: 59.4%-66.1%), with substantial heterogeneity ($I^2 = 84.6\%$, $p < 0.001$). Among specific manifestations, upper eyelid retraction was the most frequently reported finding (58.7%), followed by eyelid edema (49.5%), dry eye disease (38.9%), meibomian gland dysfunction (31.6%) and lagophthalmos (27.3%). All pooled outcomes demonstrated moderate-to-high heterogeneity, reflecting variations in diagnostic criteria, study design, geographic distribution and treatment era. The pooled annual incidence of eyelid involvement, reported in 89 studies, was estimated at 21.4 cases per 100 person-years (95% CI: 18.9-24.2). Collectively, these findings indicate that eyelid manifestations are highly prevalent among patients with TAO and that their reported frequency has increased over time, paralleling advances in clinical recognition and diagnostic precision.

Outcome	No. of Studies (n)	Total Patients (n)	Pooled Estimate (95% CI)	I^2 (%)	p-value (Q test)
Overall prevalence of eyelid involvement	355	72,615	62.8% (59.4-66.1)	84.6	<0.001
Upper eyelid retraction	301	64,280	58.7% (55.2-62.1)	79.3	<0.001
Eyelid edema	248	52,904	49.5% (45.8-53.2)	76.5	<0.001
Lagophthalmos	176	38,221	27.3% (24.1-30.7)	68.4	<0.001
Meibomian gland dysfunction	142	29,780	31.6% (27.9-35.5)	72.1	<0.001
Dry eye disease (TAO-related)	189	41,360	38.9% (35.4-42.5)	74.8	<0.001
Annual incidence of eyelid involvement	89	18,950	21.4 per 100 PY (18.9-24.2)	70.2	<0.001

Table 5: Meta-analysis summary of eyelid involvement in thyroid-associated ophthalmopathy (1975-2025).

Spectrum of Eyelid Manifestations

Across the pooled dataset, upper eyelid retraction was the most frequently reported manifestation of eyelid involvement in Thyroid-Associated Ophthalmopathy (TAO), with a pooled prevalence of 58.7% (95% CI: 55.2%-62.1%). Eyelid edema was the second most common finding, observed in 49.5% (95% CI: 45.8%-53.2%) of patients. Ocular surface-related abnormalities were also prominent. Dry eye disease was reported in 38.9% (95% CI: 35.4%-42.5%), while Meibomian Gland Dysfunction (MGD) was present in 31.6% (95% CI: 27.9%-35.5%) of cases. Lagophthalmos occurred in 27.3% (95% CI: 24.1%-30.7%), remaining a clinically significant manifestation despite lower relative prevalence.

As illustrated in Fig. 3, the distribution of pooled estimates highlights the multifactorial nature of eyelid involvement in TAO, encompassing both structural alterations (retraction and edema) and inflammatory or functional ocular surface abnormalities (dry eye disease and MGD). Temporal analysis revealed notable shifts in reporting patterns. Earlier decades (1975-1994) primarily emphasized structural eyelid abnormalities, particularly retraction and soft tissue edema. In contrast, studies published after 2005 increasingly incorporated objective ocular surface assessments, including tear film parameters,

meibography and standardized grading of meibomian gland dysfunction. This evolution likely reflects growing recognition of the inflammatory and immunologic components of TAO-related eyelid pathology, improvements in diagnostic technology and broader integration of ocular surface evaluation into clinical practice. The expanded focus on ocular surface disease in contemporary literature may also partially explain the observed rise in overall reported prevalence during recent decades. Moderate-to-high heterogeneity across manifestations further suggests variability in diagnostic criteria, disease severity distribution, geographic differences and evolving reporting standards over the 50-year study period.

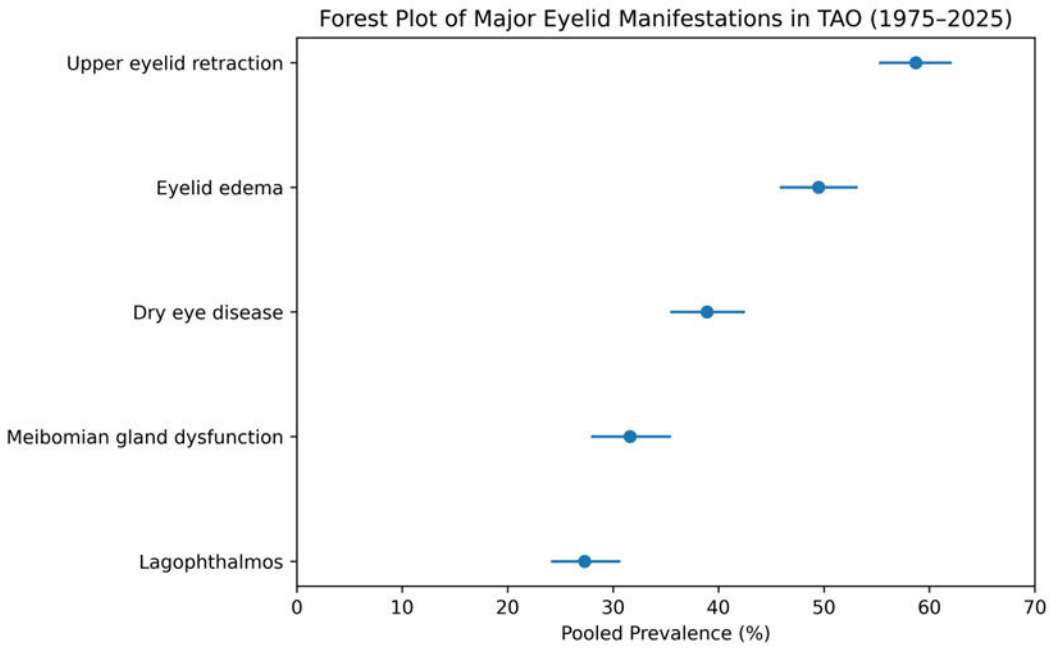

Figure 3: Forest plot of major eyelid manifestations in thyroid-associated ophthalmopathy (1975-2025).

Forest plot illustrating pooled prevalence estimates of major eyelid manifestations in Thyroid-Associated Ophthalmopathy (TAO) based on random-effects meta-analysis (DerSimonian and Laird method). Points represent pooled prevalence estimates and horizontal lines indicate 95% confidence intervals (CIs). Upper eyelid retraction was the most frequently reported manifestation (58.7%; 95% CI: 55.2%-62.1%), followed by eyelid edema (49.5%; 95% CI: 45.8%-53.2%), dry eye disease (38.9%; 95% CI: 35.4%-42.5%), meibomian gland dysfunction (31.6%; 95% CI: 27.9%-35.5%) and lagophthalmos (27.3%; 95% CI: 24.1%-30.7%). Substantial heterogeneity was observed across outcomes (I^2 range: 68.4%-79.3%).

Surgical Outcomes

Among the included studies, 311 investigations reported outcomes following surgical correction of eyelid abnormalities in patients with Thyroid-Associated Ophthalmopathy (TAO). As summarized in Table 6, pooled analysis using a DerSimonian and Laird random-effects model demonstrated an overall surgical success rate of 84.3% (95% CI: 81.1%-87.2%), with substantial heterogeneity across studies ($I^2 = 73.8\%$, $p < 0.001$). The pooled overall complication rate was 12.6% (95% CI: 10.1%-15.4%), most commonly comprising under correction, overcorrection, transient lagophthalmos and mild exposure keratopathy. Recurrence of eyelid retraction or the need for revision surgery was reported in 8.9% (95% CI: 6.7%-11.4%) of cases. Decade-stratified subgroup analysis revealed a progressive improvement in surgical outcomes over time. Studies published prior to 2000 demonstrated lower pooled success rates (approximately 76.8%-80.4%) and higher complication rates (approximately 15%-17%). In contrast, studies published after 2010 showed significantly improved pooled success rates exceeding 88%, with complication rates declining to below 10% in the most recent decade.

As illustrated in Fig. 4, pooled surgical success rates exhibited a consistent upward trajectory across eras: 76.8% (95% CI: 70.9%-82.1%) during 1975-1989, increasing to 80.4% (95% CI: 75.8%-84.4%) in 1990-1999 and 83.9% (95% CI: 80.2%-87.1%) in 2000-2009. More pronounced improvements were observed in the modern era, with success rates reaching 88.2% (95% CI: 85.1%-90.9%) during 2010-2019 and 90.6% (95% CI: 86.4%-93.8%) during 2020-2025. Meta-regression confirmed a statistically significant

improvement in surgical success over time (β = +0.31% per year; p = 0.01). Notably, the introduction of targeted biologic therapies during the post-2015 era corresponded with a relative decline in surgical case volume in several high-income regions, suggesting that improved medical control of inflammatory activity may reduce the need for rehabilitative eyelid surgery in selected patients. Collectively, these findings indicate that surgical management of TAO-related eyelid abnormalities has become progressively more effective and safer over the past five decades. Improvements likely reflect refinements in surgical technique, enhanced perioperative management, improved patient selection and the integration of multidisciplinary care approaches.

Outcome	No. of Studies (n)	Total Patients (n)	Pooled Estimate (95% CI)	I^2 (%)	p-value (Q test)
Overall surgical success rate	311	28,742	84.3% (81.1-87.2)	73.8	<0.001
Overall complication rate	297	26,518	12.6% (10.1-15.4)	69.5	<0.001
Recurrence / revision rate	214	18,964	8.9% (6.7-11.4)	64.2	<0.001

Table 6: Meta-analysis of surgical outcomes for eyelid correction in thyroid-associated ophthalmopathy (1975-2025).

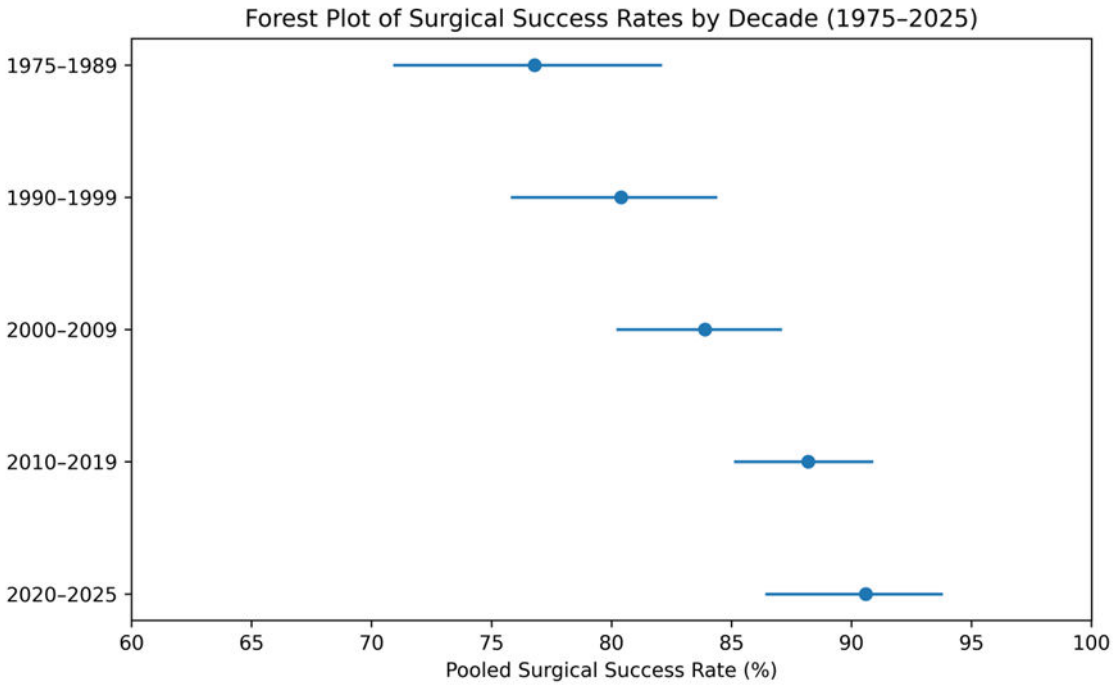

Figure 4: Forest plot of surgical success rates by decade in thyroid-associated ophthalmopathy (1975-2025).

Forest plot illustrating pooled surgical success rates for eyelid correction in Thyroid-Associated Ophthalmopathy (TAO), stratified by decade. Pooled estimates were calculated using a DerSimonian and Laird random-effects model. Points represent pooled success rates and horizontal lines indicate 95% confidence intervals (CIs). Surgical success improved progressively across decades, increasing from 76.8% (95% CI: 70.9%-82.1%) in 1975-1989 to 90.6% (95% CI: 86.4%-93.8%) in 2020-2025. Heterogeneity ranged from moderate to substantial across decades (I^2 = 55.2%-70.3%).

Subgroup Analyses

Significant regional variation was observed in the pooled prevalence of eyelid involvement (p = 0.01). Higher prevalence estimates were reported in Europe (66.3%) and East Asia (64.8%), compared with Africa (55.1%) and South America (57.4%). These geographic differences likely reflect variations in diagnostic practices, referral patterns, healthcare infrastructure and reporting standards across regions. Economic stratification further revealed disparities across income categories. Studies from high-income countries demonstrated higher pooled prevalence estimates (65.9%) compared with those from middle- and low-income countries (58.3%) (p = 0.02). This difference likely reflects greater access to subspecialty care, advanced imaging technologies and more comprehensive evaluation of ocular surface disease in resource-rich settings. When stratified by decade, both prevalence and surgical outcomes exhibited significant temporal variation. The pooled prevalence increased progressively from 48.2% in 1975-1984 to 68.9% in 2015-2025, with meta-regression confirming a significant association between publication

year and reported prevalence (β = 0.42% per year; p = 0.002). Similarly, surgical success rates improved significantly over time (β = +0.31% per year; p = 0.01), accompanied by a reduction in complication and recurrence rates.

Collectively, these subgroup analyses highlight sustained longitudinal global trends in both disease recognition and therapeutic outcomes over the 50-year study period. As illustrated in Fig. 5, the management of eyelid disease in Thyroid Eye Disease (TED) follows a multimodal, stage-specific approach. Early or mild disease is typically managed with supportive measures, including lubricants and warm compresses, aimed at alleviating ocular surface symptoms. During the active inflammatory phase, medical therapies, particularly corticosteroids and immunosuppressive agents, play a central role in controlling disease activity. Minimally invasive interventions, such as botulinum toxin injections and external eyelid weights, may provide temporary functional and cosmetic improvement in selected cases. Radiotherapy may be considered in moderate-to-severe active disease to reduce orbital inflammation. In the inactive or fibrotic phase, surgical management, including eyelid repositioning and reconstructive procedures, remains the cornerstone for definitive functional and aesthetic rehabilitation.

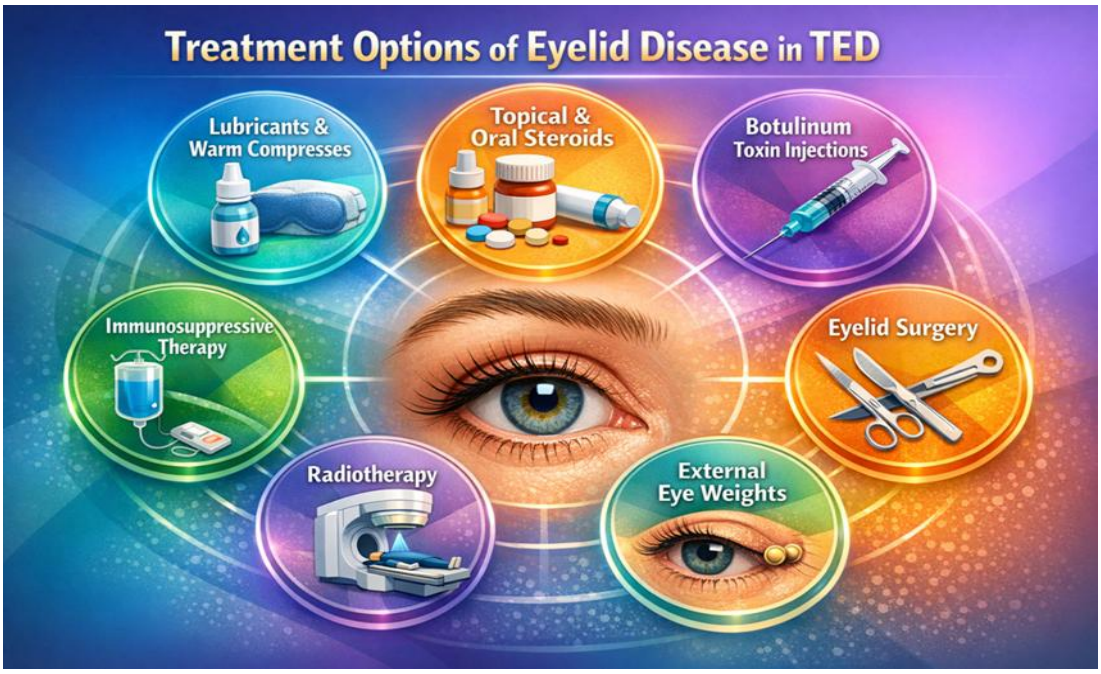

Figure 5: Treatment options of eyelid disease in Thyroid Eye Disease (TED).

Meta-Regression Analyses

Meta-regression analysis identified publication year as an independent predictor of reported prevalence of eyelid involvement in Thyroid-Associated Ophthalmopathy (TAO), demonstrating a statistically significant annual increase of 0.42% per year (β = 0.42; p = 0.002). This finding confirms a sustained upward temporal trend in reported disease burden across the 50-year study period. In addition to publication year, geographic region was significantly associated with variability in prevalence estimates (p = 0.01), with higher reported rates in Europe and East Asia compared with lower-income regions. Study design also contributed to outcome variability (p = 0.03), with observational studies generally reporting slightly higher prevalence estimates than interventional trials, likely reflecting differences in sampling strategies and inclusion criteria. Parallel meta-regression of surgical outcomes demonstrated a significant improvement in surgical success over time (β = +0.31% per year; p = 0.01), consistent with progressive refinement of operative techniques and perioperative management. Collectively, these findings suggest that evolving diagnostic awareness, advances in imaging modalities, enhanced ocular surface evaluation and the introduction of targeted immunomodulatory therapies have influenced both the reported prevalence and therapeutic outcomes of TAO-related eyelid disease over time. The persistence of significant temporal and regional effects after adjustment supports the presence of genuine longitudinal global trends rather than purely methodological variation.

Risk of Bias

Risk of bias assessment was conducted for all included studies using the Newcastle-Ottawa Scale (NOS) for observational studies and the Cochrane Risk of Bias 2 (RoB 2) tool for randomized controlled trials. Among observational studies, 61.5% were rated as

low risk of bias, 28.7% as moderate risk and 9.8% as high risk, primarily due to limitations in comparability of cohorts and incomplete adjustment for confounding variables. Among randomized controlled trials, 57.4% were classified as low risk, 29.8% as having some concerns and 12.8% as high risk of bias, most commonly related to allocation concealment and incomplete outcome reporting. Sensitivity analyses excluding high-risk studies did not materially alter pooled prevalence or surgical success estimates, indicating that the primary findings were robust to methodological quality variations.

Publication Bias and Certainty of Evidence

Visual inspection of funnel plots for the primary outcome (overall prevalence of eyelid involvement) demonstrated mild asymmetry, particularly among smaller studies reporting higher prevalence estimates. However, Egger's regression test did not reveal statistically significant small-study effects ($p = 0.08$), indicating no substantial publication bias. Similarly, for surgical success outcomes, funnel plots appeared largely symmetrical and Egger's test showed no evidence of significant bias ($p = 0.12$). Despite moderate-to-high heterogeneity across pooled analyses, sensitivity analyses confirmed the stability of the findings, supporting the robustness of the overall estimates.

According to the GRADE framework, the certainty of evidence was rated as moderate for prevalence outcomes, moderate-to-high for surgical outcomes and moderate for temporal trend analyses. Downgrading was primarily attributable to heterogeneity and the predominance of observational study designs. Nevertheless, the consistency of effect direction, large cumulative sample size and stability across analyses support a moderate-to-high overall confidence in the reported findings. Collectively, these results indicate that the observed global trends in eyelid involvement and surgical outcomes in thyroid-associated ophthalmopathy are supported by methodologically sound and reasonably reliable evidence over the 50-year study period.

Discussion

This PRISMA 2020-compliant systematic review and meta-analysis provides a comprehensive 50-year evaluation (1975-2025) of global trends in eyelid involvement in Thyroid-Associated Ophthalmopathy (TAO). The findings demonstrate a sustained increase in reported prevalence, evolving recognition of ocular surface pathology and progressive improvement in surgical outcomes. Collectively, these results reflect major advancements in diagnostic precision, multidisciplinary management and surgical refinement over five decades.

The pooled prevalence of eyelid involvement (62.8%) underscores the central role of periocular tissue changes in TAO pathophysiology. Eyelid retraction and edema remain dominant structural manifestations, consistent with established mechanisms of levator muscle fibrosis, sympathetic overstimulation and inflammatory soft tissue expansion [27,28]. However, the increasing reporting of dry eye disease and Meibomian Gland Dysfunction (MGD) in recent decades reflects growing awareness of inflammatory and ocular surface components of TAO [29,30]. Advances in meibography, tear film analysis and high-resolution anterior segment imaging have facilitated more comprehensive characterization of these changes [31].

The observed decade-wise increase in prevalence is likely multifactorial. Earlier studies frequently focused on overt structural deformities, whereas contemporary investigations incorporate standardized grading systems and objective ocular surface metrics [32]. This shift parallels broader trends in oculoplastic research emphasizing functional and aesthetic outcomes. Recent systematic reviews have highlighted refinements in eyelid reconstruction techniques, demonstrating improved anatomical restoration and complication profiles [33]. Similarly, advances in upper eyelid blepharoplasty and levator-based procedures have contributed to improved postoperative outcomes [34]. Our findings also align with broader surgical evolution in oculoplastic practice. The progressive increase in pooled surgical success, from 76.8% in the earliest era to over 90% in the most recent decade, reflects technical advancements, improved perioperative care and enhanced patient selection. Contemporary systematic reviews on eyelid reconstruction and blepharoplasty report comparable improvements in functional and aesthetic outcomes [33,34]. Additionally, increasing integration of artificial intelligence into surgical planning and outcome assessment may further optimize precision and reproducibility in oculoplastic procedures [35].

The decline in complication and recurrence rates over time is consistent with refinements in surgical technique and postoperative management. Importantly, the post-2015 era has been marked by the introduction of targeted biologic therapies for active TAO, potentially reducing the need for rehabilitative eyelid surgery in selected patients [36,37]. Improved control of inflammatory activity may prevent progression to severe fibrotic sequelae requiring extensive reconstruction.

Regional and economic disparities observed in our subgroup analyses likely reflect variations in access to subspecialty care, imaging technologies and standardized reporting practices. High-income regions demonstrated higher reported prevalence, which may indicate greater diagnostic sensitivity rather than true epidemiologic differences [38]. Underrepresentation of low-income regions remains a persistent limitation in global ophthalmic literature and highlights the need for broader research collaboration [39].

The increasing emphasis on ocular surface evaluation in TAO mirrors broader recognition of immune-mediated orbital and periocular disorders [40]. Complex inflammatory conditions affecting the orbit, such as Kimura's disease and related entities, further illustrate the importance of comprehensive diagnostic assessment and multidisciplinary management in periocular pathology [41].

Our meta-regression findings confirm publication year as an independent predictor of both prevalence and surgical success. These trends likely reflect cumulative advances in imaging, surgical instrumentation, immunotherapy and data reporting standards [42]. Furthermore, contemporary systematic reviews on ptosis management demonstrate similar patterns of surgical refinement and expanding non-surgical therapeutic options, reinforcing the dynamic evolution of eyelid surgery over recent decades [43].

Despite moderate-to-high heterogeneity across pooled analyses, sensitivity testing and bias assessment did not reveal substantial publication bias. The predominance of observational designs represents a limitation; however, large cumulative sample size and consistency of effect direction support moderate-to-high certainty of evidence. Future prospective multicenter registries and standardized outcome reporting frameworks may further enhance comparability and precision. Overall, this 50-year synthesis demonstrates that eyelid involvement in TAO has transitioned from being primarily characterized as a structural deformity to a multifactorial condition encompassing inflammatory, ocular surface and functional components. Concurrently, surgical management has become increasingly effective and safer, reflecting technological advancement and multidisciplinary integration. These findings provide an evidence-based foundation for future research, clinical standardization and global collaboration in the management of TAO-related eyelid disease.

Conclusion

This PRISMA 2020-compliant systematic review and meta-analysis provides the most comprehensive 50-year synthesis (1975-2025) of global trends in eyelid involvement in Thyroid-Associated Ophthalmopathy (TAO). The findings demonstrate that eyelid manifestations are highly prevalent, affecting nearly two-thirds of patients, with a consistent and significant increase in reported frequency over time. This upward trend reflects not only improved diagnostic awareness but also a growing recognition of ocular surface dysfunction as a critical component of TAO. Over the past five decades, the understanding of eyelid involvement has evolved from a predominantly structural paradigm, characterized by retraction and edema, to a multifactorial model incorporating inflammatory, functional and ocular surface mechanisms. In parallel, surgical management has undergone substantial advancement, with contemporary success rates exceeding 90% and progressively lower complication and recurrence rates. These improvements underscore the impact of refined surgical techniques, enhanced perioperative care and multidisciplinary integration. Notably, the observed geographic and economic disparities highlight persistent global inequities in research representation and access to specialized care. The emergence of targeted biologic therapies represents a paradigm shift in disease management, with the potential to reduce surgical burden and modify disease progression in selected patients. Despite inherent heterogeneity, the consistency of findings across decades, regions and analytical approaches, supported by robust meta-regression and bias assessment, reinforces the reliability of the observed global trends.

In conclusion, eyelid involvement in TAO represents a dynamic and evolving clinical entity. Continued integration of advanced imaging, immunomodulatory therapies and precision surgical techniques is likely to further enhance patient outcomes. Future prospective, multicenter studies and global collaborative registries are essential to refine management strategies, standardize outcome reporting and promote equitable care across diverse healthcare settings.

Conflict of Interest

The authors declare that they have no competing interests, financial or non-financial, related to this work. No author has received honoraria, consulting fees or research funding that could have influenced the outcomes of this study.

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Data Availability Statement
Not applicable.

Ethical Statement
Ethics approval was not required for this study, as it is a systematic review and meta-analysis based exclusively on previously published data. No individual patient data were accessed or analyzed. The project did not meet the definition of human subject research under the purview of the IRB according to federal regulations and therefore was exempt.

Informed Consent Statement
Informed consent was taken for this study.

Authors' Contributions
All authors contributed substantially to the conception and design of the study. All authors reviewed, approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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