

Evidence Gap Analysis of the Burden of Disease in Thyroid Eye Disease



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BACKGROUND

- Thyroid eye disease (TED) is a debilitating, sight-threatening autoimmune disorder associated with a variety of clinical manifestations, including eyelid retraction, ocular dryness/grittiness, redness, pain, pressure, and excessive tearing; patients may also develop proptosis, diplopia, and visual disturbances¹
- Significant impacts on mental health, work functioning, and overall quality of life have been reported in patients with TED, highlighting the considerable burden of disease¹

OBJECTIVES

- To review current evidence pertaining to TED burden of disease, including epidemiologic, clinical, humanistic, economic, and treatment-related aspects
- To identify knowledge gaps which could be used to guide future research and help address patient needs

METHODS

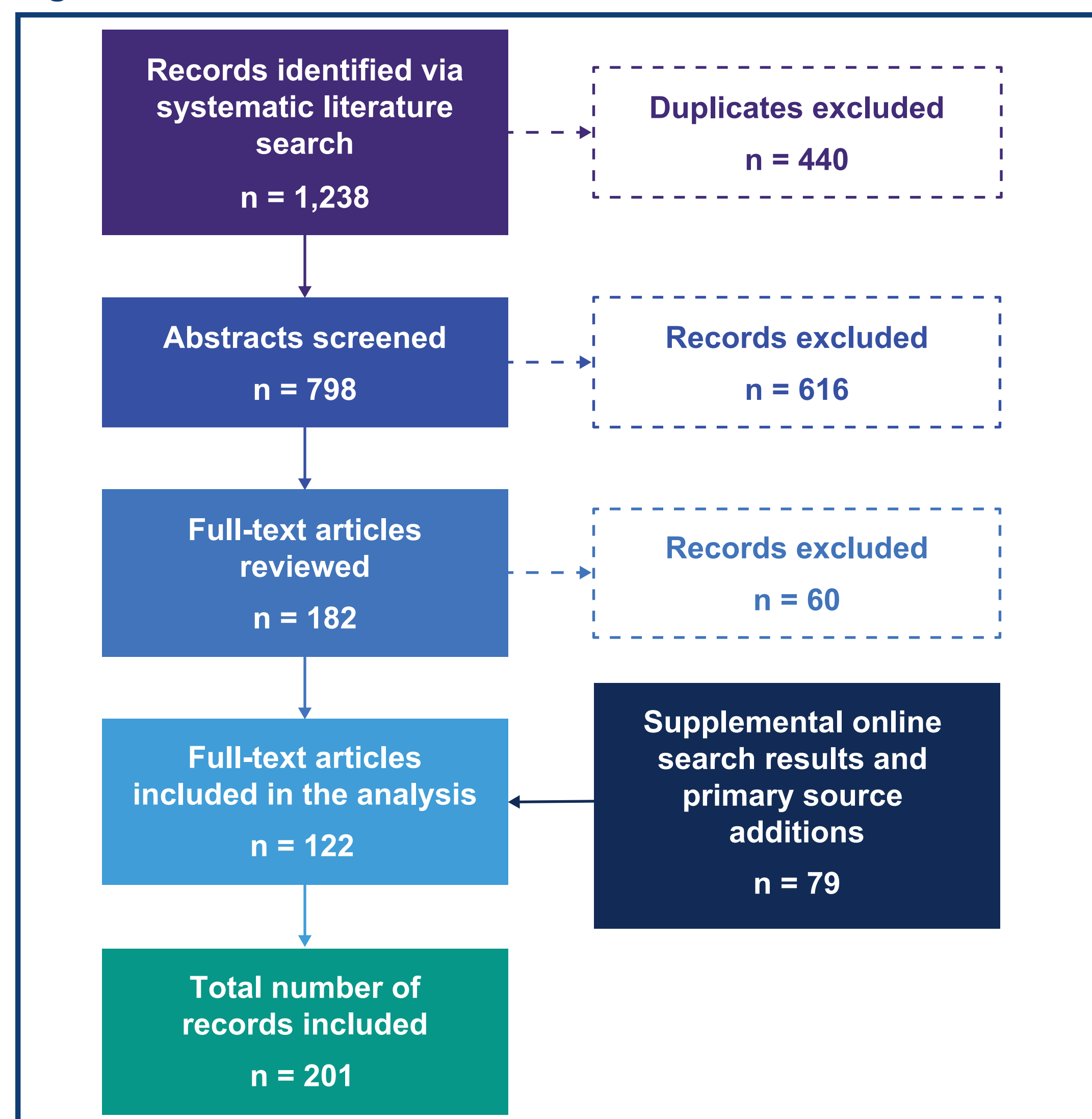
- This analysis included a structured review of scientific literature published from May 5, 2013 to May 5, 2023
 - Literature searches were carried out in PubMed, Embase, and the Cochrane library using predefined Boolean search strings to identify papers focused on the epidemiology, burden of disease (humanistic, clinical, and economic), treatments, practice patterns, and guidelines associated with TED
- Supplemental online searches were conducted to obtain information on health technology assessments, ongoing clinical trials, and primary sources for included review papers from the literature searches

RESULTS

Characterization of source material

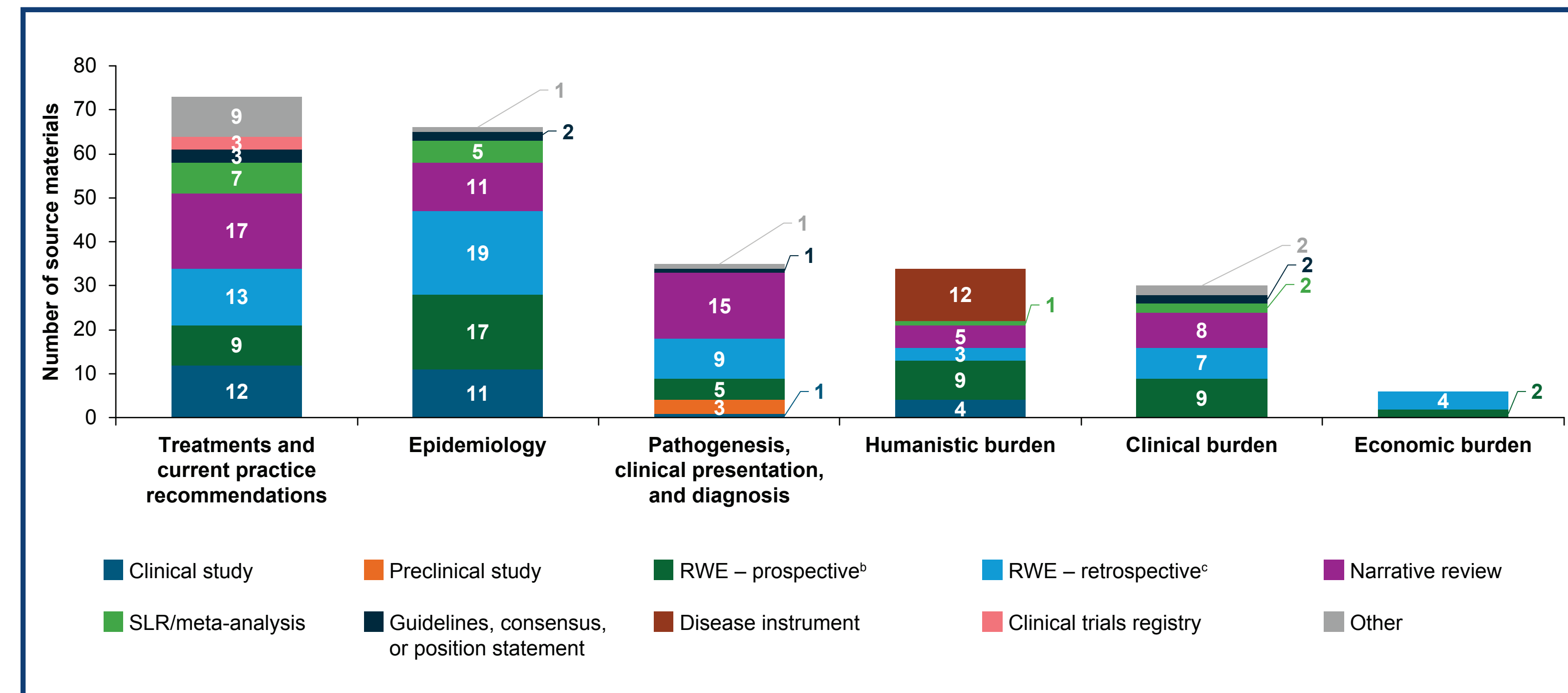
- A total of 201 unique records were included (Figure 1), which primarily included real-world evidence studies and narrative reviews (Figure 2)
- Few records described studies specifically focused on burden of disease (Figure 3)

Figure 1. Attrition of source materials



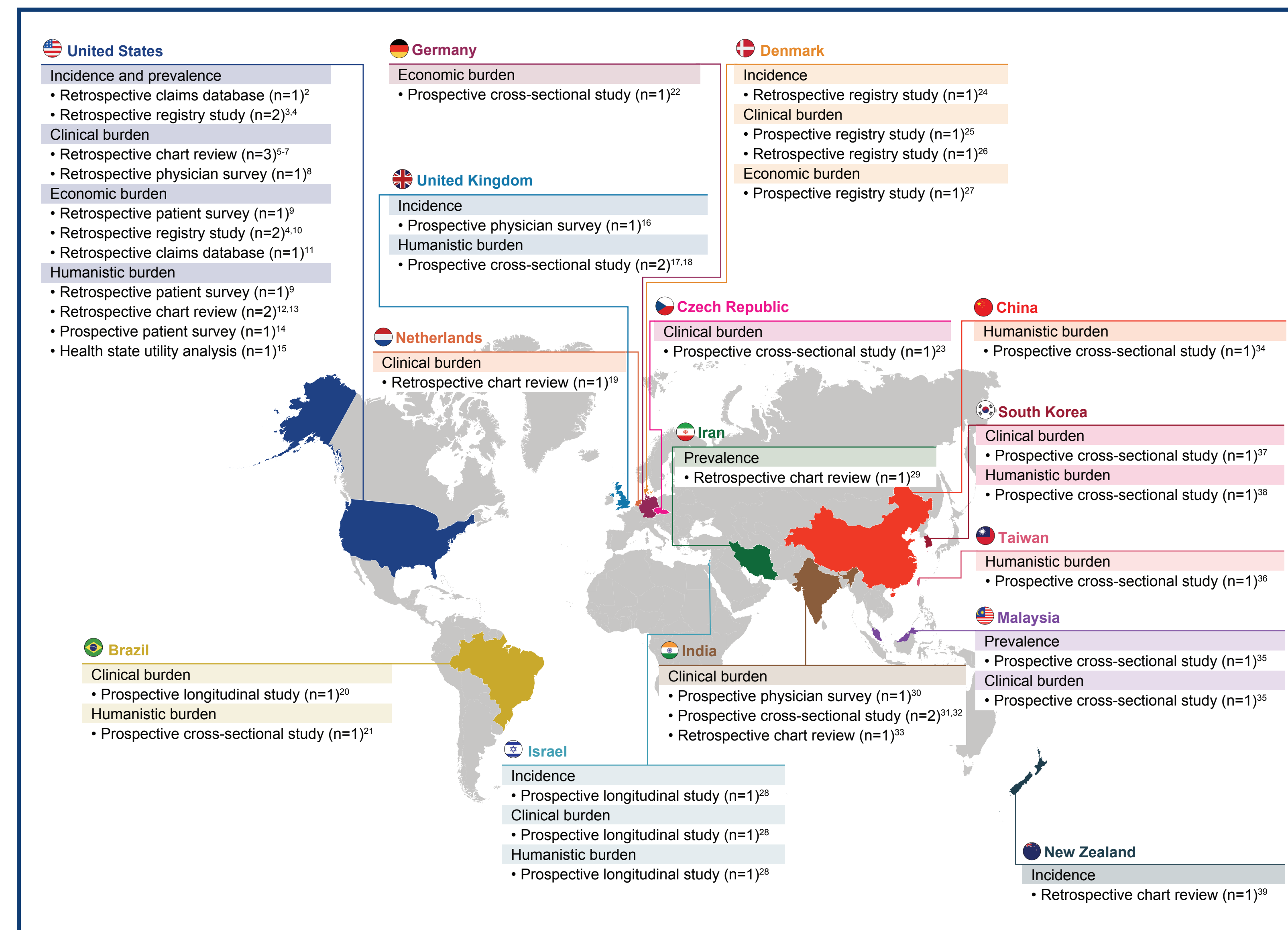
RESULTS

Figure 2. Characterization of sources included by topic^a and type



^aIndividual source materials may have covered >1 topic; ^bIncludes prospective cross-sectional, longitudinal, registry, survey, case report, health state utilities, and genetic studies; ^cIncludes retrospective chart reviews, registry, claims, and survey studies. RWE, real-world evidence; SLR, systematic literature review.

Figure 3. Availability of burden of disease data for TED^a



^aIncludes RWE studies. RWE, real-world evidence.

Summary of current evidence and key evidence gaps

Table 1. Epidemiologic burden

CURRENT EVIDENCE	EVIDENCE GAPS
<ul style="list-style-type: none">Estimates of incidence and prevalence are highly variable<ul style="list-style-type: none">Reported incidence rates ranged from 3.3 to 8.0 per 100,000 person-years in women, and 0.9 to 2.05 per 100,000 person-years in men^{22-24,40}Reported prevalence rates ranged from 19.2 to 155 per 100,000 persons²⁴Variability in epidemiologic rates is likely influenced by the numerous disease assessment tools (eg, CAS, EUGOGO, NOSPECS, VISA) and diagnostic indicators (eg, medical history, presenting symptoms, imaging, laboratory data) used for TED, and inconsistencies in how these are applied by clinicians^{42, 43}Moreover, a TED-specific ICD code is not available, therefore, in the US, TED is identified using various ICD codes for specific signs and symptoms, including proptosis (ICD-9-D-376.*), diplopia (ICD-9-D-368.2), lid retraction (ICD-9-D-374.41), strabismus (ICD-9-D-378.*), exposure keratopathy (corneal damage from a dry ocular surface; ICD-9-D-370.34), and optic neuropathy (ICD-9-D-377.49)⁴⁴Differences in epidemiologic rates are also observed across various ethnic populations, with one retrospective study in New Zealand reporting crude incidence rates of 9.5, 9.7, 12.5, 21.1, and 19.0 per 100,000 person-years among Pacific Peoples, European, Asian, Māori, and other populations, respectively²⁹Current incidence and prevalence data are largely based on studies from Europe,^{16,24} Asia,^{28,29,35,37} and the US,^{2,4} whereas information from other regions of the world (eg, Africa, Latin America) is limited or missing^{42,45}	<ul style="list-style-type: none">Standardized diagnostic protocol that minimizes subjectivity by treating cliniciansTED-specific ICD codeStudies characterizing epidemiology in Latin-American and African populations

CAS, Clinical Activity Score; EUGOGO, European Group on Graves' orbitopathy clinical practice guidelines; ICD, International Classification of Diseases; NOSPECS, N-No signs or symptoms; O-no signs, no symptoms; S-soft tissue involvement; P-proptosis; E-extraocular muscle involvement; C-corneal involvement; S-sight loss; TED, thyroid eye disease; US, United States; VISA, Vision, Inflammation, Strabismus, Appearance.

Table 2. Clinical burden

CURRENT EVIDENCE	EVIDENCE GAPS
<ul style="list-style-type: none">TED typically follows a biphasic progression pattern including an early inflammatory phase followed by a more stable, fibrotic, inactive disease state; however, irreversible damage may be caused during inflammation, preventing significant clinical improvements once the disease becomes inactive⁴³Identification of TED may be determined using any combination of medical history, presenting symptoms, radiographic findings, and laboratory data, and not all clinicians use the same tools, which presents diagnostic challenges⁴³Gender differences have been reported, with women having a shorter time from TED onset to CAS ≥3 than men (2.35 years vs 4.50 years)³⁹Differences in clinical presentation based on ethnicity or geographic location have been demonstrated in multiple studies; however, commonly used diagnostic tools were developed based on primarily Caucasian European and North American populations, which may impact clinicians' ability to diagnose TED and classify disease severity in other populations⁴²	<ul style="list-style-type: none">Standardized diagnostic protocol that minimizes subjectivity by treating cliniciansDiagnostic criteria and disease rubrics that account for population variations that can affect the measurement of clinical symptoms

CAS, Clinical Activity Score; TED, thyroid eye disease.

Table 3. Humanistic burden

CURRENT EVIDENCE	EVIDENCE GAPS
<ul style="list-style-type: none">Multiple instruments have been used to assess QOL in patients with TED, each with distinct advantages and drawbacks; however, a universal tool capable of sufficiently capturing the full patient experience has yet to be developed⁴⁶Additionally, the impact measured by various QOL scales appears to be out of proportion to measurable clinical manifestations, making the overall patient experience extremely difficult to quantify⁴⁶Studies characterizing the QOL of patients with TED tend to focus more on the acute, inflammatory phase of the disease, whereas information pertaining to long-term QOL is limited, and prospective longitudinal data are needed¹³	<ul style="list-style-type: none">Universal, TED-specific QOL assessments that (a) are routinely implemented in clinical practice and as outcomes in clinical trials, and (b) accurately capture physical disease domainsProspective, longitudinal studies tracking QOL over time in patients with TED

QOL, quality of life; TED, thyroid eye disease.

Table 4. Economic burden

CURRENT EVIDENCE	EVIDENCE GAPS
<ul style="list-style-type: none">Only 6 records reported on the economic burden of TED, including 4 studies from the US,^{4,9-11} one study from Germany,²² and one study from Denmark²⁷Notably, 3 of the 4 US studies were conducted prior to the commercial availability of teprotumumab^{4,9,10}Total annual direct costs ranged from \$135.5 million to \$200.1 million, and were primarily attributed to hospitalizations, emergency visits, and treatment-related costs^{10,22}The economic impact of indirect costs is even more consequential, with results from the German study estimating €1.4–2.8 billion (\$1.7–3.5 billion) in indirect costs among a population of 82 million people²²Factors contributing to indirect costs included sick leave, temporary or permanent disability, job loss, and early retirementSurgical interventions accounted for a significant proportion of direct costs, with one US study reporting >\$43.5 million in spending for TED-related surgery⁴Non-surgical treatments also contribute substantially to healthcare costs, with one US analysis reporting annual mean costs of \$386,424 for teprotumumab, followed by \$18,549 for rituximab, \$4,316 for orbital radiotherapy, and \$4,025 for IV methylprednisolone^{10,22}Sight-threatening disease can substantially increase costs, with one cross-sectional German study reporting average annual direct costs of €1,185 for patients with sight-threatening TED, compared with €332 for patients with mild disease and €373 for patients with moderate-to-severe disease²²	<ul style="list-style-type: none">Additional US and global studies that characterize the economic repercussions in different social systems, as well as the impact of new entrants to the therapeutic market (eg, teprotumumab in the US)Long-term data on healthcare costs, including the impact of clinical and QOL outcomes associated with teprotumumab treatmentGreater understanding of the natural history of TED to inform treatment pathways that can avert complications requiring surgery and the associated costsCost-effectiveness analyses of various treatment options for TED

IV, intravenous; TED, thyroid eye disease; US, United States.

Table 5. Treatment patterns

CURRENT EVIDENCE	EVIDENCE GAPS
<ul style="list-style-type: none">Duration of disease may influence treatment decisions^{8,47}Results from a physician survey conducted in the US found that while steroid use is similarly utilized in patients with short-term vs long-term disease, patients with long-term disease are more likely to receive topical treatments or undergo a surgical interventionIn addition, practice patterns are changing over time, with one cross-sectional study from 2012 showing an increase in the use of surgical treatments for mild inactive disease (27.3%) compared with findings from a 2000 cohort (17%)⁴⁸Practice patterns demonstrate a global trend of steroids, particularly IV glucocorticosteroids, as the preferred and most-used treatment for active TED^{30,49,50}Regional differences were observed⁵¹Selenium was more frequently used in Europe than the US for mild, active TEDIn patients with moderate-to-severe, active TED, there was a preference for teprotumumab in the US (the only country where it is approved), whereas IV steroids were more commonly used in Europe and other countries	<ul style="list-style-type: none">Studies exploring the importance of early TED treatment on disease progression and long-term outcomesTreatment pattern studies in Asian populations (eg, Japan and China)Further investigation of practice patterns in the UK where TED management varies (including the rates of orbital decompression surgeries) and does not reflect national or regional guidanceEfficacy data for commonly recommended over-the-counter medications to manage mild-to-moderate TEDHead-to-head data comparing novel therapies for TED with IV steroid therapy

IV, intravenous; TED, thyroid eye disease; US, United States.

CONCLUSIONS

- Diagnostic challenges represent a major limitation to understanding the complete epidemiologic landscape of TED
- Improved diagnostic and disease assessment tools capable of accurately and reliably measuring disease across diverse populations may help address clinical and humanistic aspects of patient burden
- Challenges with accurately assessing TED burden relate to lack of an established diagnostic code; an ICD-10 code for TED is imperative for population assessment and healthcare planning
- Evidence concerning the economic burden of TED is extremely limited; however, available data suggest direct costs of up to \$200.1 million annually, and indirect costs of up to \$3.5 billion, underscoring the need for further study in this area
- Given the evolving treatment landscape for TED, additional studies evaluating the efficacy and safety of emerging treatment options are needed

References, acknowledgments, and disclosures are accessible via QR code.

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DISCLOSURES

CM and VD are employees of RTI Health Solutions. LAMW, JS, and PMO are employees of Immunovant, Inc.