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Dry eye disease in the young: A narrative review

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ABSTRACT

Dry eye disease (DED), a multifactorial ocular disease that significantly impacts quality of life, is most commonly reported in adults. This review describes the prevalence, risk factors, diagnosis and management of DED in children. A literature search, conducted from January 2000–December 2022, identified 54 relevant publications. Using similar diagnostic criteria to those reported in adults, namely standardized questionnaires and evaluation of tear film homeostatic signs, the prevalence of DED in children ranged from 5.5% to 23.1 %. There was limited evidence for the influence of ethnicity in children, however some studies reported an effect of sex in older children. Factors independently associated with DED included digital device use, duration of digital device use, outdoor time and urban living, Rates of DED were higher in children with ocular allergy and underlying systemic diseases. Compared with similar studies in adults, the prevalence of a prior DED diagnosis or a diagnosis based on signs and symptoms was lower in children, but symptoms were commonly reported. Treatment options were similar to those in adults, including lifestyle modifications, blinking, management of lid disease and unpreserved lubricants in mild disease with escalating treatment with severity. Management requires careful exploration of symptoms, medical history and the diagnosis and management of ocular comorbidities such as allergy and anterior blepharitis. Appropriately powered population-based studies are required to understand the prevalence of and risk factors for DED in children. Development of age-appropriate thresholds for signs and symptoms of DED would support better diagnosis of disease and understanding of natural history.

1. Introduction

Dry eye disease (DED) is one of the most common reasons for visits to an eye care practitioner [1]. The Tear Film & Ocular Surface Society (TFOS) Dry Eye Workshop (DEWS) II defines DED as "a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles" [2]. Patients with DED report redness, burning and stinging, ocular dryness, photophobia, foreign body sensation, grittiness, and visual disturbance, all of which significantly affect quality of life, such that up to 34 % of sufferers report impairment in daily activities [3,4]. The management and treatment of DED include patient education, environmental changes, dietary or lifestyle modifications, tear retention, replacement and stimulation approaches, ocular surface protection and topical and/or systemic anti-inflammatory medications, and in more severe cases, surgical intervention [5].

DED is a critical and significant public health issue affecting ~344 million people worldwide and over 20 million in the United States alone [6]. DED is considered a disease of adulthood, with an estimated prevalence ranging from 5% to 30 % in individuals aged ≥50 years and is higher in women [7,8]. Although the prevalence of DED increases with age in individuals older than 40 years, there are limited population-based studies in younger age groups [7,9]. Conceivably, the prevalence of DED in younger age groups may be under- or over-estimated due to challenges in diagnosis in this population, including the appropriateness or difficulty in use of the established questionnaires, difficulties in testing young populations [9], and the lack of agreed upon cut-off values for what are considered normal signs and symptoms in this population.

Young people with DED appear to experience a similar profile of symptoms to adults [9–11], and the impact of DED on quality of life is

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Abbreviations

CLDEQ	contact lens dry eye questionnaire
CsA	Cyclosporine A
CVSS17	Computer-Vision Symptom Scale
DED	dry eye disease
DEQS	Dry Eye–Related Quality-of-Life Score
DEWS	Dry Eye Workshop
FTBUT	fluorescein tear film breakup time
GVHD	Graft-versus-host-disease
HSCT	hematopoietic stem cell transplantation
OCI	ocular comfort index
IOSS	instant ocular symptoms survey
JRA	juvenile rheumatoid arthritis
MGD	meibomian gland dysfunction
OSDI	Ocular Surface Disease Index
SANDE	Symptoms Assessment in Dry Eye
SPEED	the Standardized Patient Evaluation of Eye Dryness
TBUT	tear film breakup time
T1DM	type 1 diabetes mellitus
TFOS	Tear Film & Ocular Surface Society
WHS	Women's Health Study

considerable, with effects on presenteeism, concentration, and performance at school and other activities, including reading and playing [9–11]. Risk factors for DED in young people may include changes in lifestyle associated with the increased use of electronic/digital media devices, allergies, inflammatory conditions, poor nutrition, and diabetes [9–11].

With lifestyle changes including those prompted by digital transformation and the pandemic, the risk of DED in young populations may be changing. The purpose of this review is to explore the epidemiology of DED in young people <18 years of age and describe current diagnostic and management approaches.

2. Methods

A literature search was performed on PubMed using the following search terms: *(dry eye disease OR DED) AND (pediatric OR paediatric OR adolescents OR child OR infants) AND (Diagnosis OR Treatment OR Risk Factors OR Management OR Prevalence)*. Studies in young individuals (mean age <18 years) and only English-language articles published between January 2000 and December 2022 for which full texts were available were included. Additional records identified through cross-referencing from the reference lists of publications identified were also included. The resulting citations were exported to Microsoft Excel® and were manually reviewed by the authors to identify relevant publications (Fig. 1).

The unadjusted prevalence of DED among young people aged <18 years retrieved from population-based studies was reported based on age, ethnicity, sex, and diagnostic classification. Ninety-five percent confidence intervals (CIs), if not reported in the paper, were calculated using the online software http://vassarstats.net with continuity correction [12].

Risk factors were reported from cohort, case control, and either population or hospital-based studies and independent risk factors were included where available. Systemic diseases including Vitamin A deficiency, Sjögren syndrome were described separately. Diagnostic and management approaches were summarized.

3. Results

The literature search yielded 2633 articles and 54 eligible studies were identified, after screening and removal of duplicates (Fig. 1).

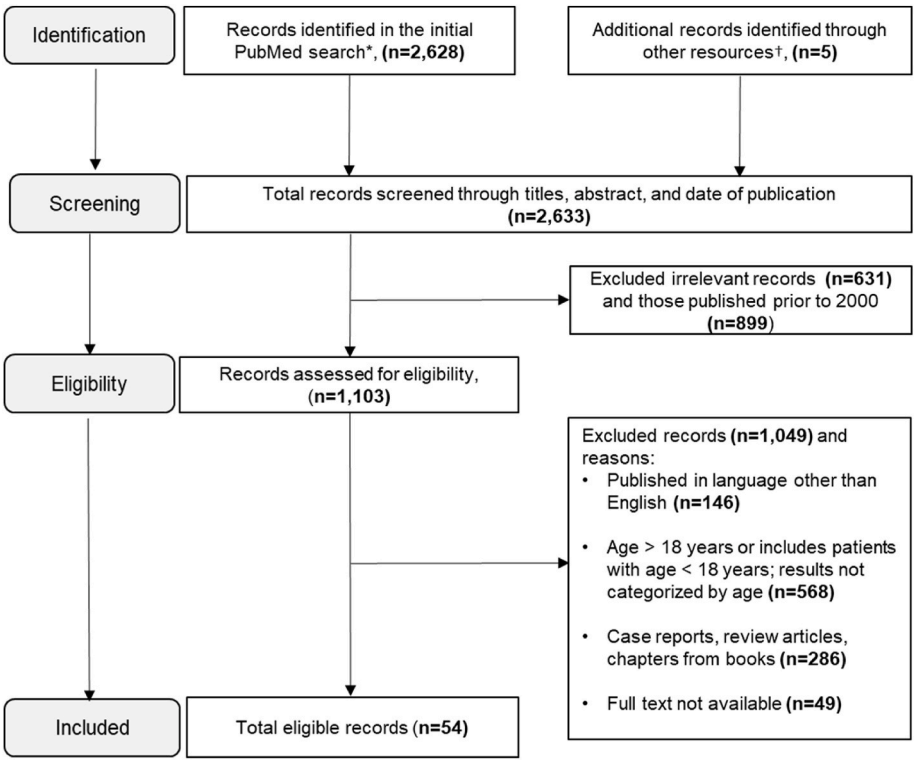

Fig. 1. Flow chart showing publication screening and inclusion
*Search string used: (dry eye disease OR DED) AND (pediatric OR paediatric OR adolescents OR child OR infants) AND (Diagnosis OR Treatment OR Risk Factors OR Management OR Prevalence); †Includes cross-references from the records identified from PubMed.

3.1. Prevalence of DED

The diagnostic criteria for DED used in studies identified in this review broadly included:

1. The Women's Health Study (WHS) criteria, which defined DED as a prior diagnosis of DED made by a clinician and/or severe symptoms (both dryness and irritation either constantly or often) [13].
2. The Tear Film and Ocular Surface Dry Eye Workshop II (TFOS DEWS II), Asia Dry Eye Society and Japanese Dry Eye Society criteria, which all required both symptoms and signs of disease to be present. Some studies did however vary the reference values for diagnosis.
   a. The TFOS DEWS II criteria included positive symptoms reported using DEQ-5 (score ≥6) or OSDI (score ≥13) questionnaires and at least one positive homeostasis marker, either tear breakup time (TBUT <10 s; recommended to be measured non-invasively), tear osmolarity above 308mOsm/L or a interocular difference of 7mOsm/L or ocular surface staining (greater than grade 1, Efron Scale) [2].
   b. The Asia Dry Eye Society criteria defined definite DED as positive symptoms (OSDI score ≥13) and TBUT ≤5 s [14].
   c. The Japanese Dry Eye Society criteria required the presence of any DED symptom using the Dry Eye–Related Quality-of-Life Score (DEQS) instrument, tear abnormalities (Schirmer 1 test ≤5 mm or TBUT ≤5s), and ocular surface staining greater than 3 points out of 9) [15].

Of the 54 publications identified, 16 reported some measure of disease frequency in the young population over the last 20 years and six of the 16 were population-based. The prevalence ranged from 5.5% to 65.4 % in population-based studies. Population-based studies reporting the frequency of ocular symptoms estimated symptoms to range from 8.7% to 65.4 %; those using the Women's Health Study (WHS) criteria ranged from 23.7 to 26.6 %, those reporting symptoms and at least one sign as recommended by the TFOS DEWS II, Asia Dry Eye Society or Japanese Dry Eye Society criteria ranged from 5.5% to 15.7 % (Table 1). Of the six population-based studies, five reported the prevalence of DED in East Asia including Korea, China, Japan, and Taiwan [11,14,16–18].

3.1.1. Population-based prevalence

3.1.1.1. Prevalence in studies using the WHS criteria. In a study of 3433 Japanese individuals aged 15–18 years [19], 4.3 % of males and 8.0 % of females had a prior diagnosis of DED and severe symptoms were observed in 21.0 % of males and 24.4 % of females [17]. A similar prevalence of severe symptoms (23.1 %) was reported in a recent Chinese study of 1885 senior high school students [18]. There was no effect of sex and low rate (1.3 %) had a prior diagnosis of DED.

3.1.1.2. Prevalence in studies using the TFOS DEWS II, Asia Dry Eye Society or Japanese Dry Eye Society criteria. Three population-based studies in East Asia have reported similar disease prevalence using a combination of signs and symptoms of DED. The prevalence of DED defined using a modified TFOS DEWS II criteria (OSDI score >20, ocular surface staining or TBUT <10 s), in 916 Korean children aged 7–12, was 6.6 %. There was a higher prevalence of DED in urban versus rural locations (8.3 % vs 2.8 %; p = 0.03) and in higher school grades (those aged 10–12 years; 9.1 %) compared to lower school grades (those aged 7–9 years; 4.0 %, p = 0.03) [11]. Similarly, 2694 Chinese primary school students between 7 and 8-years-old, the prevalence of DED using the Asia Dry Eye Society criteria was 5.5 % (95 % CI 4.7–6.4) with symptoms (OSDI ≥13) reported by 8.7 % (95 % CI 7.6–9.8) [14]. A slightly but not statistically higher rate was reported using the Japanese Dry Eye Society criteria in Japanese children aged 10, where prevalence was estimated at 16.8 % (95 % CI 4.1–24.4) [16].

3.1.1.3. Prevalence by symptoms. The prevalence of symptoms of ocular surface disease in a high-school students in Mexico (n = 759, mean age of 16 years) was 65.4 % based on an OSDI score of ≥13. Prevalence by severity was estimated at 18.6 % (mild; OSDI 13–22), 15.7 % (moderate; OSDI 23–32) and 31.1 % (severe; OSDI 33–100) [19]. Female students consistently had higher OSDI scores than males [19].

3.1.2. Non-population–based prevalence studies

Five hospital, medical records or clinic audits have been conducted using convenience samples over a wide geographical area, including USA, India, Japan, New Zealand and the Middle East. Rate of disease ranged from 0.4 % (hospital medical records audit in India [10])-76 % (pediatric ophthalmology clinic in Saudi Arabia) [23]. The inclusion criteria vary widely, and these data likely have limited generalizability to the population. The prevalence of dry eye symptoms in 225 American school students aged 8–17 years attending a university eye clinic was 17 % (both Standardized Patient Evaluation of Eye Dryness (SPEED) and OSDI scores of >6 and ≥ 13, respectively) [22].

In Japan, prevalence of DED was determined in 323 adolescents recruited from six eye clinic, based on the Japanese Dry Eye Society criteria. There was no difference in the rate of DED between early adolescent (10-15 years-old) boys (13.0 %, 95 % CI 5.1–20.9) and girls (12.8 %, 95 % CI 6.2–19.8). However, the rate in older girls (16–19 years) was 22.1 % (95 % CI 13.7–30.3) and boys 10.8 % (95 % CI 3.4–18.6) [15].

One small study directly examined the effect of ethnicity in DED in 70 children aged 5–18 years attending a research clinic in New Zealand. Based on the TFOS DEWS II diagnostic criteria, the prevalence of DED was 15.7 %. A higher proportion of the Asian population had incomplete blinking ($p < 0.001$) and meibomian gland shortening ($p < 0.05$) compared with Caucasians [24].

In a US insurance claims audit of 9,732,272 individuals aged above 2 years, the prevalence of severe DED in those aged 2–17 years old of 0.2 % compared with 11.7 % in those over 50 years. This was estimated using the diagnostic codes indicating DED care and the prescribing of topical cyclosporine, perhaps indicative of more severe disease. Within this age group, the prevalence was approximately double in young females compared to males (0.27 % vs 0.13 %) [20]. A similar approach to auditing insurance claims data in in 2917 children aged 0–17 in Taiwan, but only focussing on ICD-10 coding, medicine prescribing code and clinical features aligned with DED, established a disease prevalence of 18.1 % [21].

3.1.3. Xeropthalmia

Xerophthalmia refers to the pathological dryness of the conjunctival epithelium caused by dietary vitamin A deficiency [25]. The prevalence of xerophthalmia in young patients is reported in Table 2.

In a Cambodian population aged 18–60 months (n = 10,942), the adjusted prevalence for a history of night blindness was 0.7 % [26]. Two Indian studies, one in preschool children aged <5 years and the second, a house-to house survey involving children aged 0–15 years, estimated the prevalence of xerophthalmia, based on both signs and symptoms, to be 3.4%–5.4 % [25,27].

3.2. Risk factors for DED

Of the 54 eligible studies, 30 suggested potential risk factors for or associations with DED in a young population. Most studies were not hypothesis driven; some did not include an unaffected control group and may not have been adequately powered to identify independent risk factors.

3.2.1. Demographic characteristics

In adults, the most consistently reported demographic features of DED include age, female sex and Asian ethnic background [7]. Limited data exist on the impact of age on DED in those under 18 years (Table 1).

Table 1
The prevalence of DED in a young population.

Publication	Study design	Diagnostic criteria	Country	Sample size	Age	Prevalence (95 % CI)	Prevalence by sex (95 % CI)
Population-based studies							
Prior diagnosis or severe symptoms of DED (WHS)							
Uchino et al. (2008) [17]	Cross-sectional survey of high school students	WHS criteria based on prior diagnosis or severe symptoms	Japan	3433	15–18 years	All DED: 26.6 % Prior diagnosis: 4.9 % (4.2–5.7) Severe symptoms: 21.6 % (20.2–23.0)	Prior diagnosis: M: 4.3 % (3.9–4.6) F: 8.0 % (7.4–8.4) Severe symptoms: M: 21.0 % (20.1–21.8) F: 24.4 % (23.9–25.0)
Zhang et al. (2012) [18]	Cross-sectional survey of senior high school students	WHS criteria based on prior diagnosis or severe symptoms of DED	China	1889	Senior high school students*	All DED: 23.7 % Prior diagnosis: 1.3 % (0.9–2.0) Severe symptoms 23.1 % (21.3 %−25.1 %)	M: 24.9 % (22.2–27.8) F: 22.6 % (20.3–25.7)
Symptoms + at least one sign (similar to TFOS DEWS/Japanese Dry Eye Society/Asia Dry Eye Society)							
Moon et al. (2016) [11]	Cross-sectional study of primary school children	Ocular surface staining or TBUT <10 s plus OSDI score >20	Korea	916	7–12 years	All DED: 6.6 % (5.1–8.3) Urban vs rural areas: 8.3 % vs 2.8 % (p = 0.03)	Not reported
Arita et al. (2019) [16]	Population based cross-sectional study	Presence of any DED symptom (DEQS) and FTBUT of ≤5 s	Japan (Takushima Island)	356	6–19 years	10.9 % (95 % CI 4.1–24.4)	Adjusted odds ratio: Sex (M/F) 0.31x (0.2–0.6)
Ma J et al., 2022 [14]	Population-based cross-sectional study	Asia Dry Eye Society criteria: OSDI ≥13 points; and TBUT ≤5 s.	China	2694	7–8 years	Symptoms only 8.7 % (95 % CI 7.6–9.8) Symptoms and sign: 5.5 % (95 % CI 4.7–6.4)	Symptoms: @1.5x more common in F across all severities
Symptoms only							
Garza-León et al., 2021 [19]	A cross -sectional, high school–based survey	Ocular Surface Disease Index (OSDI) score, categorized as 13–22 (mild), 23–32 (moderate) and 33–100 (severe)	Mexico	759	15–20 years	All DED: 65.4 % (62.0–68.7) Mild: 18.6 % (16.0–21.5) Moderate: 15.7 % (13.3–18.4) Severe: 31.1 % (27.9–34.5)	M vs F Mild disease: 22 % (CI 17.6–26.4) vs 15.8 % (CI 12.5–19.5) Moderate disease: 15.5 % (CI 11.2–18.8) vs 15.8 % (CI 12.5–19.5) Severe disease: 22.9 % (CI 18.5–27.5) vs 37.6 % (TBC)
Health or insurance claim database estimates							
Dana et al. (2019) [20]	Retrospective analysis	US medical claims database, searched for diagnostic codes indicative of DED or related conditions, procedures, or treatments	US	9,732,272	2-≥80 years	DED: 5.3 % (5.3–5.3 %) Age 2–17 years: 0.20 % (0.2–0.2) 18–39 years: 2.0 % (2.0–2.0) 40–49 years:5.7 % (5.7–5.8) 50+ years – 11.7 % (11.6–11.7)	M vs F 0.13 % vs 0.27 %
Hung et al., 2021 [21]	Retrospective analysis	Taiwan National Health Insurance Research Database (1997–2013) searched for diagnostic code, drug codes, and clinical data (Schirmer I < 5 mm, corneal surface damage)	Taiwan	2917	0–17 years	18.1 % (16.7–19.5)	Not reported
Non-population-based hospital or eye clinic studies							
Ayaki et al. (2018) [15]	Cross-sectional study from 6 eye clinics	Japanese Dry Eye Society criteria based on signs and symptoms	Japan	323	10–19 years	15.2 % (95 % CI 11.6–19.5)	M vs F: 13.0 % (CI 5.1–20.9) vs 12.8 % (CI 6.2–19.8) (early adolescence); 10.8 % (CI 3.4–18.6) vs 22.1 %

(*continued on next page*)

Table 1 (*continued*)

Publication	Study design	Diagnostic criteria	Country	Sample size	Age	Prevalence (95 % CI)	Prevalence by sex (95 % CI)
							(CI 13.7–30.3) (late adolescence)
Tichenor et al. (2019) [22]	Cross-sectional study, University eye clinic-based population	Symptoms only based on SPEED >6 and OSDI≥13	US	225	8–17 years	17 % (95 % CI 12.6–22.3)	Not reported
Donthineni et al. (2020) [10]	Cross-sectional, hospital-based study	EyeSmart electronic medical record audited for both symptoms and signs of DED, including of meibomian gland dysfunction	India	259,969	Mean: 15.2 years	All DED: 0.4 % (0.37–0.41)	Not reported
Alnahdi et al., 2022 [23]	Cross-sectional study, outpatient pediatric ophthalmology clinic	Symptoms only based on OSDI ≥13, mild 13–22, moderate 23–32, severe >33	Saudi Arabia	329	1–18 years	76.1 % Severity: Mild 13.3 %; Moderate: 18.8 % Severe: 43.9 %	M vs F: 73 % vs 79 %
Kim et al., 2019 [24]	University research centre, observational study	Signs per TFOS DEWS II criteria (TBUT <10 s; or tear osmolarity above 308mOsm/L or interocular difference of 7mOsm/L or ocular surface staining >1) and OSDI score >13	New Zealand	70	5–18 years	15.7 % (9.0–26.0) ~2x higher in Asian compared with Caucasian ethnic background	Not reported

*Age range not reported.

CI, confidence intervals; DED, dry eye disease; DEWS II, Dry Eye Workshop II; KCS, keratoconjunctivitis sicca; OSDI, Ocular Surface Disease Index; SPEED, Standardized Patient Evaluation of Eye Dryness; TFOS, Tear Film & Ocular Surface Society; M, male; F, female; TBUT, tear breakup time; FTBUT, fluorescein breakup time; WHS, Women's Health Study.

Table 2
The prevalence of xeropthalmia.

Publication	Study design	Diagnostic criteria	Country	Sample size	Age	Prevalence (95 % CI)	Prevalence by sex (95 % CI)
History of night blindness							
Semba et al. (2004) [26]	Household survey using a case-control design	Parent/guardian reported history of night blindness	Cambodia	10,942	1.5–5 years	0.7 % (0.6–0.9)	–
Signs and symptoms							
Pal and Sagar (2008) [25]	Cross-sectional study amongst preschool children from 14 villages	Xerophthalmia based on the presence of Bitot's spots and symptoms of night blindness	India	4205	0.5–5.9 years	Xerophthalmia in children less than 5 years: 3.4 % (2.9–4.0)	–
Agrawal et al. (2013) [27]	Cross-sectional, house-to-house survey	Night blindness and ocular examination showing conjunctival xerosis and Bitot's Spots	India	802	0–15 years	Xerophthalmia: 5.4 % (4.0–7.1)	M vs F: 6.1 % vs 4.5 %

The association between female sex and DED is equivocal in children. Some population-based studies have reported a higher rate of DED in young Asian females compared with males, using the WHS criteria [17], Japanese [26] and Asia Dry Eye Society [14] criteria. Sex differences appear to be more marked in older children, but there are limited appropriately powered studies.

Similarly, the impact of ethnicity in a pediatric population is equivocal, with one small study reporting higher rates in Asian than Caucasian children in New Zealand [24]. Most studies have been conducted in Asian (Chinese, Japanese, or Korean) populations and there are limited comparable studies in Caucasian populations (Table 1).

3.2.2. Ocular or systemic associations

Risk factors for DED can include congenital, autoimmune, endocrine, and inflammatory disorders. The most common conditions reported are described below.

3.2.2.1. Meibomian gland dysfunction. While MGD is an established risk factor in adult DED [7] and is associated with the subsequent development of more severe disease [28], the association between DED in childhood and MGD is less clear.

A hospital-based cross-sectional study exploring DED among children and adolescents in India showed significant differences in the causes of dry eye by age group, with evaporative dry eye more common in adolescents than in the younger children and aqueous-deficient disease is more common in infancy and early childhood, due to Stevens–Johnson syndrome and vitamin A deficiency [10].

3.2.2.2. Ocular allergy. Ocular allergy affects 1 in 5 adolescents [29], however, its association with DED has not been fully explored in a young population. Allergic conjunctivitis was independently associated with DED (per the Asia Dry Eye Society definition) and with an OSDI score of $\geq$13 in a population-based study of 7–8 year-old children in China [14]. Three smaller studies from China (n = 163, 6–18 years old), South Korea (n = 100, 6–15 years old) and Turkey (n = 49, 6–18 years old) have reported a combination of increased DED symptoms and tear homeostasis signs (reduced Schirmer test, TBUT, tear meniscus height and lipid layer thickness) and reduced blink rate in children with allergic conjunctivitis compared to those without [30–32]. These findings suggest consideration of ocular allergy as a comorbidity in pediatric DED and the need for appropriately powered population-based studies with a larger age range in different population groups to further explore these associations.

3.2.2.3. Diabetes and insulin resistance. Diabetes is a consistent independent risk factor for DED in adults [7], however most studies in young people have compared ocular signs and symptoms in those with diabetes and those without rather than evidence being derived from appropriately powered population-based studies [33,34]. The associations between duration of diabetes [34], corneal sensation and glycosylated hemoglobin levels [33] and DED appear to be equivocal. Obese children, particularly those with insulin resistance, have reduced tear film production and stability compared with normal children [35].

3.2.2.4. Inflammatory and autoimmune diseases. Connective tissue disorders resulting in autoantibody production, including rheumatoid arthritis, Sjögren syndrome, systemic lupus erythematosus, systemic sclerosis, relapsing polychondritis and anklylosing spondylitis are independently associated with DED in adults [36]. Population-based studies to confirm associations in children have not been robustly conducted, although there is some lower-level evidence from observational studies, hospital audits and case reports.

Sjögren syndrome occurs in 10 % of adults with severe aqueous-deficient DED [37] and is overrepresented in DED compared with a rate of 0.5 % in the general population [38]. Case series have described Sjögren syndrome-related DED in those under 18 [39], and in a hospital-based cohort of pediatric DED, primary or secondary Sjögren syndrome was reported in 6.4 % of children and adolescents with DED [10].

Juvenile idiopathic arthritis describes a group of connective tissue diseases in children, in whom signs and symptoms of DED may be overrepresented. The evidence is low level and in two small clinic studies of children with juvenile rheumatoid arthritis, up to 75 % of those with symptoms of DED (n = 40) had ocular signs of DED [40] and 35 % (n = 120) had an anesthetized Schirmer result of $\leq$10 mm and at least one ocular symptom [41].

Graft-versus-host-disease (GVHD), is a serious complication of allogenic bone marrow transplantation or hematopoietic stem cell transplantation, used in the treatment of hematological malignancies, which is associated with DED in adults [7] Several small observational studies in GVHD reported that up 60 % of children and adolescents may experience DED when followed for up to 7 years post-hematopoietic stem cell transplantation [42–44].

Muco-cutaneous reactions to medications including Stevens-Johnson syndrome and toxic epidermal necrolysis can involve the ocular surface and be both vision and life-threatening. In 643 children and adolescents up to 18 years old seeking eyecare for DED across a hospital network in India [10], Stevens-Johnson syndrome was identified in 40.3 % of those diagnosed with DED.

3.2.2.5. Congenital and inherited diseases. Certain rare congenital diseases are associated with reduced tear production and DED in children. These include Riley–Day syndrome, ectodermal dysplasia syndromes, and epidermolysis bullosa [39]. Pseudophakic children may show transient reduction in tear film stability and meibomian gland function [45].

3.2.3. Lifestyle and environmental factors

Environmental and lifestyle factors in adult DED are well established and have been recently comprehensively reviewed [46], however associations in a younger population are less well established.

3.2.3.1. Living environment and outdoor activity. The prevalence of DED, based on both signs and symptoms, was significantly higher in Korean children (n = 916, aged 7–12 years) from urban compared with rural areas (8.3 % vs 2.8 %) [11]. In multivariable analysis, outdoor activity was protective for DED, (OR, 0.33; 95 % CI: 0.1–0.8; $p < 0.01$). A similar protective effect (based on similar diagnostic criteria) of more than 1 h a day of outdoor activity was reported in multivariable analysis in a large population-based study of children aged 7–8 years old in China [14].

3.2.3.2. Digital device use. The impact of the digital experience on DED may be influenced by confounders, where both device use and DED are related to another variable, such as time spent outdoors, obesity, a sedentary lifestyle, mental health disorders, impaired sleep, lockdown and other societal factors. Several studies of varying quality have explored the impact of digital experience including phone or screen use on signs and/or symptoms of DED in children mainly in Asia and India.

In multivariable analysis, daily use of a smartphone was an independent risk factor for DED (odds ratio [OR] 13.1; 95 % CI: 6.0–28.5; $p < 0.001$) in children aged 7–12 years in Korea [11]. When smartphone use was stopped for 4 weeks in the DED group (n = 60), the signs and symptoms of DED improved [11]. Similarly, the use of smartphones or tablets for more than 1 h per day over one year was independently associated with DED in children aged 7–8 years in China [14]. A similar finding was reported in a self-selected UK population aged 5–16 years, where each hour of screentime was associated with a 15 % increase in the OR for DED and increased sleep was protective [47]. In Japanese children aged 6–12 years, screen time before bed was independently associated with symptoms of DED (OR 1.31; 95 % CI: 1.15–1.50),

although there was no association with duration of screen use [48]. In two cross-sectional studies in Turkish and Indian children, there was a moderate univariate relationship between symptom score and screen time [49,50], but no association with DED signs [49].

3.2.3.3. Contact lenses. While contact lens wear is a consistent risk factor for DED in adults [7], the evidence in children is equivocal. Two population-based studies in high school students from Japan [17] and China [18] using the WHS criteria, have shown that contact lens wear is an independent risk factor for DED. One small study has suggested that children wearing contact lenses have fewer symptoms of DED than to adult contact lens wearers [51] The relationship between homeostatic signs related to DED and contact lens wear, however, has not been established.

3.2.3.4. Pandemic. Effects of the pandemic and public health measures such as mask use, online classes and digital device or screen use are associated with an increased risk of developing new or worsening existing ocular surface diseases in adults [52]. It is conceivable that young people might be more vulnerable due to pandemic-related e-schooling and increased use of mobile phones, tablets and computer screens in this cohort.

A study in Indian children (n = 654, aged 5–18 years) assessed digital eye strain during lockdown using the Computer-Vision Symptom Scale (CVSS17). At least one relevant ocular symptom was reported in 92.8 % of children and higher symptom report was associated with older age of the children and will duration of screen use [50].

As with digital device use, the relationship between the pandemic and DED is likely to be confounded by other variables. Most studies do not have a control group or evaluation pre- and post-pandemic.

3.3. Diagnosis of DED

Of the 50 eligible studies, 19 described the diagnosis of DED in children. The most widely used diagnostic approaches require the presence of symptoms plus one or more homeostatic markers, related to ocular surface staining, increased tear osmolarity or altered film stability.

Symptoms were evaluated using questionnaires previously validated in adults, including the OSDI [4,22,24,34,53–55], modified OSDI [11], visual analogue scales [56], Symptoms Assessment in Dry Eye (SANDE) instrument [55,56], DEQS [48], numerical rating scale [55], ocular comfort index (OCI) [55], dry eye questionnaire 5 (DEQ-5) [55], the instant ocular symptoms survey (IOSS) [55], and Standardized Patient Evaluation of Eye Dryness (SPEED) [22]. There were no questionnaires specifically designed for the young, and frequently the questionnaires were completed by parents or caregivers. One study evaluated the repeatability and reliability of adult questionnaires (SANDE, OSDI, numerical rating scale, OCI [n = 30], DEQ-5, and the IOSS) in a young population aged between 6 and 15 years (n = 62) and showed the shorter DEQ-5 and IOSS could be reliably used in children and their repeatability was comparable to adults [55]. Young children however take longer to complete the questionnaires and may require assistance from their parents or caregivers in interpreting the meaning of certain questions [55]. There is some evidence in the literature that ocular symptoms may not be volunteered by children [9], suggesting the importance of questionnaires suitable for this population and/or more explicit exploration of ocular symptoms and their impact during clinical examinations.

Most studies evaluated standard clinical signs (tear film stability, corneal or conjunctival staining, tear meniscus height, tear production), using thresholds based on adult values [15,28,39,42–44,53,57–62]. Some studies also included eyelid signs in the diagnosis of evaporative DED [10,16,53].

3.4. Management

Very few publications have described management strategies for DED in the young population, beyond the use of unpreserved lubricants or artificial tears and environmental modifications in line with adult therapy [5,63]. Safety and efficacy have not been established for most pharmacological or natural agents in children, although there is some safety evidence based on use of steroids, for example, in allergic eye disease in children [64]. One small randomised controlled study has shown a beneficial effect in signs of DED (TBUT and conjunctival redness) in children aged 9–14 with the use of topical 0.2 % hyaluronic acid with 0.1 % arnica extract compared with topical hyaluronic acid alone over a 4-week period [65]. Both preparations significantly improved symptoms measured with OSDI [65]. There is no robust evidence for the use of tear replacement, tear stimulation or tear conservation approaches in children.

In more severe disease, such as that associated with autoimmune diseases, oral cyclosporine A or methotrexate have been used to treat immune suppression in conjunction with unpreserved lubricants, topical autologous serum and/or topical cyclosporine A [9,57,63,66,67]. Topical steroids may be used to treat inflammation, although care must be taken to limit the side effects of raised intraocular pressure and posterior subcapsular cataracts [63]. Systemic antibiotic treatment for MGD has not been deemed safe for children. Systemic tetracyclines are not recommended for young children (under 8 years) due to the impact on calcifying tissues such as teeth, cartilage and bone [68]. A meta-analysis of studies including patients over 12 years of age concluded that the adverse event profile was significantly better with the oral macrolide, azithromycin, compared with doxycycline, although this was not explicitly compared for the younger age group [69].

One study explored the treatment of DED in those under 18 with GVHD over a 6-month period [70], using non-preserved artificial tears, cyclosporine A 0.05 % (65 %), autologous/allogeneic serum eye drops (80 %) and punctal plugs (28 %), with beneficial effects on the ocular surface and in best-corrected visual acuity. The safety and efficacy of lymphocyte function-associated antigen 1 antagonists in those below the age of 17 years is not established, and off-label use in the young population has not been reported.

Vitamin A deficiency, as a cause of xerophthalmia and childhood DED in developing nations, can be modulated through support for changing the dietary habits of the population. Periodic supplementation with vitamin A–rich food sources along with raising awareness and educating parents regarding appropriate nutrition should be prioritized to limit vitamin A deficiency [25,71–74].

Environmental modifications have been infrequently studied in children. Lifestyle interventions through reducing the continuous screen time or smartphone usage may offer a partial solution in children with DED [11,48,54,75]. While the rate of DED-related signs and symptoms decreased with smartphone cessation for a 4-week period ($p < 0.001$), it is not clear whether other environmental factors such as outdoor activities increased during this time [11]. While screen time before bedtime as well as the duration of screen time is thought to contribute to DED [48], there have been no randomized controlled trials to explore this hypothesis.

4. Summary and Implications

This review has explored prevalence, risk factors, underlying comorbidities, and the diagnosis and management of DED in a young population.

In the pediatric population, the prevalence of DED ranged between 5.5 % and 26.6 %, although one study from Mexico reported very high rates of ocular symptom reporting in high school students (65.4 %). Study methodology, definitions of DED, ethnicity, climate and geographical and socio-economic variations likely underpin these differences. The report of ocular symptoms may be confounded by the

Table 3
Prevalence studies in children and adults using similar diagnostic criteria and in the same region.

Diagnostic criteria	Population	Study location	Prevalence in Adults (95 % CI)	Prevalence in Children (95 % CI)
WHS	High school students (Uchino et al., 2008) (n = 3433) [17]	Japan	All DED 23.4 % 16.4 % (16.1–16.8) men	All DED: 26.6 % 25.4 % (23.8–27.0) boys
	Population based adults (Yamanishi, 2021) (n = 85,264) [76]		29.2 % (28.8–29.6) women	32.5 % (28.8–36.4) girls Prior diagnosis: 4.9 % (4.2–5.7) Severe symptoms: 21.6 % (20.2–23.0)
Symptoms and Signs (TFOS DEWS II, Japanese Dry Eye Society Classification, other)	Children and adolescent population based (Arita, 2019) (n = 356) [16]; Adults – office workers using computers (Uchino, 2018) (n = 516) [77]	Japan	8.0 % (5.5–11.3) men 18.7 % (13.4–25.1) women	Age: 6–19 years 10.9 % (4.1–24.4) 8.3 % (0.2–25.8) boys 13.6 % (4.7–33.3) girls
	Primary school population (n = 916) (Moon 2016) [11]; Adults: subset of KNHANES population-based study (Lee, 2015) (n = 15,878) [78]	South Korea	16.0 % (10.7 % men; 21.6 % women)	All DED: 6.6 % (5.1–8.3)
Symptoms only	Clinic-based pediatric population (Tichenor 2019) (n = 225) [24]; Population based study in adults over 18 (Farrand, 2017) (n = 75,000) [79]	USA	6.8 % (4.5 % men; 8.8 % women)	17 % (12.6–22.3)
Insurance claim database	Retrospective analysis of claims data (Dana, 2019) (n = 9,732,272) [21]	USA	50+ years – 11.7 % (11.6–11.7)	2–17 years 0.20 % (0.20–0.20) 0.13 % (0.12–0.14) boys 0.27 % (0.26–0.28) girls

presence of other ocular or systemic comorbidities or the use of contact lens wear, and it is important to be aware of and appropriately manage potential confounders.

Perhaps surprisingly, differences in disease prevalence between adults and children were equivocal. There are a limited number of population studies in both groups conducted at the same location, with similar methodology (Table 3). Symptom reporting rates in adults and children are similar and some studies show a sex difference, with higher rates in female children and adults. The lower frequency of a prior diagnosis or medical claims for DED in children is not unexpected.

Several studies reported a higher prevalence of DED in young females [10,11,16,24,21], and this was statistically significant for symptomatic disease, with one study showing greater sex differences with more severe DED symptoms. A better appreciation of ocular symptom reporting in children is important as mild to moderate symptoms of chronic DED in young patients may be underreported and consequently overlooked during the examination [9].

As expected, a higher prevalence of DED was reported in young populations with underlying comorbid conditions compared to otherwise healthy subjects [9,36]. This does suggest the importance of managing comorbidities which may include ocular or systemic allergy, autoimmune, endocrine, congenital or nutritional conditions in conjunction with the ocular surface effects of DED.

There are a limited number of appropriately powered studies to determine independent risk factors associated with DED in a young population. Potential lifestyle risk factors include daily smartphone use [11] and possible associations with smartphone use before bedtime [48], screen use [54] and contact lens wear [11,18,19,79]. Contact lens wear is a probable risk factor for dry eye symptoms in adults [7] and given the wide uptake of contact lenses in children for the slowing of myopia, a better understanding of this relationship in children and with different modalities of lens wear is important.

Smartphone use was an independent risk factor for DED when controlling for urban and rural living conditions, in a young population. While a period without phone use is associated with a reduction in symptoms, this is not a practical solution but potentially regular breaks, limiting continuous duration of use and reducing screen time before bedtime may be useful for limiting DED in young people [11,48]. A protective effect of outdoor time should also be explored. The increased use of digital devices and online learning during the COVID-19 pandemic, led to an increased reporting of ocular symptoms and it is not unreasonable to assume that these pandemic-mitigating measures might persist post-pandemic [52].

In adults, DED generally involves a component of evaporative disease, most commonly associated with MGD [80]. The pattern seems similar in children, where MGD associated with evaporative DED was the leading single cause of DED in early adolescence (51 %) and late adolescence (66 %) [10]. In addition, evidence of early changes in the structure and function of meibomian glands can be seen in young children [24,81,82], although not necessarily associated with symptoms. As would be expected in multifunctional disease, a single diagnostic test result may not necessarily be indicative of disease. Studies evaluating the natural history of structural and functional gland changes and ocular symptoms are required to understand their relationship to pediatric DED.

While the diagnostic approaches align with those developed for use in DED in adults, normative data and cut off thresholds for signs or symptoms have not been established in a pediatric population, nor has the testing been particularly designed for children. Thresholds in adults have been described reflecting normal aging [56] and these may not be appropriate during childhood and adolescence. As an example, healthy children may have a thin lipid layer (<75 nm) which is not associated with symptoms nor overt meibomian gland changes [81]. Similarly, alterations in the appearance and function of meibomian glands may be found in children as young as 6 years old [24,81,82]. Schirmer testing is believed to have less utility in children due to the invasive nature of the

test, and tests which involve administration of drops (such as FBUT and ocular surface staining) may be less well accepted in children [9]. Taken together, these findings suggest a rethink for what should be considered normal ocular surface signs in children, 'abnormal' values in adult population may be normal and not indicative of dysfunction in children. As with adults, it is also important in children to disaggregate symptoms which may be associated with common comorbidities such as allergic eye disease.

The treatment options for young patients with DED are largely aligned with those for adults [63], with lubricants and environmental modifications common for mild disease, with anti-inflammatory approaches in more severe forms of the disease. However, none of these suggested active treatment options have been evaluated for their efficacy and safety in the young population [63] and the use of systemic tetracyclines would generally be contraindicated in young children. While no there was no evidence in the literature, potentially the poor acceptance of 'invasive' testing in children might suggest that frequent topical treatment is also not ideal, there may be benefit in longer release or longer acting agents which can be formulated using alternate administration approaches, such as sprays. Beyond the limited safety and efficacy data of pharmacological treatments, there is also a lack of data on compliance in children.

For clinicians, evidence-based approaches to the diagnosis and management of DED in children include the use of validated adult questionnaires (DEQ5 and OSDI) to measure and monitor symptoms of DED, to expect and manage evaporative disease especially in older children, to manage symptomatic disease and to carefully screen for and manage co-morbid diseases, including allergy, anterior blepharitis, demodex and ocular surface changes due to cataract or refractive surgery. This may be particularly important for those families considering contact lens wear for refractive or myopia control applications, including orthokeratology. Topical unpreserved lubricants, blinking, warm compresses, lid hygiene and environmental modifications can be considered in mild disease with escalated treatment in more severe DED. Preventative strategies may also include reduction of screen time, particularly before bedtime, regular screen breaks and increased outdoor activity.

In summary, the prevalence of DED in the young population based on a prior diagnosis of dry eye or signs of dry eye is slightly lower than that in adults; however, symptomatic disease is common. Development of age-appropriate thresholds for signs and symptoms of DED may support better diagnosis of disease and understanding of the natural history in a young population. It is conceivable that DED may be underdiagnosed owing to underreporting in children with chronic DED symptoms and the lack of tools designed specifically for the young population. There is limited evidence on treatment protocols and both short- and long-term safety and efficacy of most DED treatments in children. Appropriately powered population-based studies are required to understand risk and mitigating factors in children. Treatment trials with robust and appropriately powered endpoints (patient-reported outcome measures and biomarkers) will further improve understanding of DED and limit its impact in young people.

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