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Identified risk factors for dry eye syndrome: A systematic review and meta-analysis

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Abstract

A meta-analytic approach was used to identify potential risk factors for dry eye syndrome. PubMed, Embase, and the Cochrane library were systematically searched for studies investigated the risk factors for dry eye syndrome from their inception until September 2021. The odds ratio (OR) with 95% confidence interval (CI) was calculated using the random-effects model. Forty-eight studies comprising 493,630 individuals were included. Older age (OR: 1.82; $P<0.001$), female sex (OR: 1.56; $P<0.001$), other race (OR: 1.27; $P<0.001$), visual display terminal use (OR: 1.32; $P<0.001$), cataract surgery (OR: 1.80; $P<0.001$), contact lens wear (OR: 1.74; $P<0.001$), pterygium (OR: 1.85; $P = 0.014$), glaucoma (OR: 1.77; $P = 0.007$), eye surgery (OR: 1.65; $P<0.001$), depression (OR: 1.83; $P<0.001$), post-traumatic stress disorder (OR: 1.65; $P<0.001$), sleep apnea (OR: 1.57; $P = 0.003$), asthma (OR: 1.43; $P<0.001$), allergy (OR: 1.38; $P<0.001$), hypertension (OR: 1.12; $P = 0.004$), diabetes mellitus (OR: 1.15; $P = 0.019$), cardiovascular disease (OR: 1.20; $P<0.001$), stroke (OR: 1.32; $P<0.001$), rosacea (OR: 1.99; $P = 0.001$), thyroid disease (OR: 1.60; $P<0.001$), gout (OR: 1.40; $P<0.001$), migraines (OR: 1.53; $P<0.001$), arthritis (OR: 1.76; $P<0.001$), osteoporosis (OR: 1.36; $P = 0.030$), tumor (OR: 1.46; $P<0.001$), eczema (OR: 1.30; $P<0.001$), and systemic disease (OR: 1.45; $P = 0.007$) were associated with an increased risk of dry eye syndrome. This study reported risk factors for dry eye syndrome, and identified patients at high risk for dry eye syndrome.

Introduction

Dry eye syndrome (DES) is defined as a multifactorial disease of the tears and ocular surface that could cause discomfort and visual disturbance, with potential damage to the ocular surface. These symptoms could affect quality of life and activities of daily living [1, 2]. The prevalence of DES is increasing and is seen in nearly one in five adults. Thus, this needs more attention from ophthalmologists [3, 4]. The role of the tear film has already been demonstrated. It has been shown to provide lubrication to the eyes, as well as nutrition and oxygen, and eliminate debris from the ocular surface [5]. Moreover, individuals with dry eyes also suffer from systemic diseases [4]. However, the prevalence of dry eyes is often underestimated

Competing interests: The authors have declared that no competing interests exist.

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DES, dry eye syndrome; DM, diabetes mellitus; HR, hazard ratio; MGD, meibomian gland dysfunction; NOS, Newcastle-Ottawa Scale; OR, odds ratio; PTSD, post-traumatic stress disorder; RR, relative risk; VDT, visual display terminal.

because of varying presentation and symptoms [6]. Studies have demonstrated that age and sex are significantly associated with increased risk of DES; however, the pathogenesis of DES is not fully understood [7, 8].

Several studies have already identified risk factors for DES. Major risk factors include older age, female sex, having undergone postmenopausal estrogen therapy or ocular surface surgery, and using antihistamine medications [9]. Moreover, the occupational risk factor of visual display terminal (VDT) use was related to the progression of DES, which could be explained by a decreased blink rate and increased proportion of incomplete blinks that could be caused by the increased exposure of the ocular surface to the environment. Outdoor environments, sunlight, and air pollution in tropical countries are also associated with an elevated risk of DES [10, 11]. Furthermore, other risk factors for DES include vitamin D deficiency and diabetes mellitus (DM) [12, 13]. However, whether the comorbidities of individuals could affect the risk of DES remained controversial. We, therefore, performed a systematic review and meta-analysis to independently identify risk factors for DES.

Methods

Data sources, search strategy, and selection criteria

The current study was performed and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement [14]. Studies reporting the risk factors of DES were eligible in our study, and publication language was restricted to English. PubMed, Embase, and the Cochrane library were systematically searched for eligible studies from their inception until September 2021, and using the following text word or Medical Subject Heading terms: "dry eye syndrome", "dry eye disease", "Keratoconjunctivitis Sicca", "Xerophthalmia", and "Risk Factors". The details of search strategy in PubMed are listed in S1 File. The reference lists of relevant original and review articles were manually screened to identify further eligible studies.

Two reviewers (QL and WW) independently performed study assessment following a standardized approach. Any disagreement between reviewers was settled by discussion until a consensus was reached. A study was included if the following criteria were met: (1) it was a cross-sectional, retrospective, or prospective observational study; (2) risk factors were reported for $\geq$ 3 studies [15] and included such factors as age, sex, race, residence, education level, obesity, dyslipidemia, alcohol, smoking, VDT use, cataract surgery, contact lens wear, pterygium, glaucoma, age-related maculopathy, eye surgery, depression, post-traumatic stress disorder (PTSD), sleep apnea, asthma, allergy, hypertension, DM, cardiovascular disease (CVD), stroke, rosacea, thyroid disease, chronic obstructive pulmonary disease (COPD), gout, migraines, arthritis, osteoporosis, tumor, meibomian gland dysfunction (MGD), eczema, and systemic disease; and (3) it reported effect estimates (relative risk [RR], hazard ratio [HR], or odds ratio [OR]) and 95% confidence interval (CI) for risk factors of DES. Interventional study, animal study, review, and letter to editor was excluded.

Data collection and quality assessment

Two reviewers (QL and WW) independently abstracted the following items, including study group or first author's name, publication year, country, study design, sample size, age, % of males, population status, % of DES cases, definition of DES, risk factors, adjusted factors, and reported effect estimates. The effect estimate with maximal adjustment for potential confounders was selected if a study reported several multivariable-adjusted effect estimates. Study quality was assessed using the Newcastle-Ottawa Scale (NOS), which has already been validated for assessing the quality of observational studies in meta-analysis [16]. A total of 8 items in 3

subscales were included in NOS. The star system in each study ranged from 0–9. Inconsistent results for the data abstracted and quality assessment between the two reviewers were settled following mutually discussion referred to the original article.

Statistical analysis

Identified risk factors for DES were analyzed based on the OR, RR, or HR, with its 95% CI, in individual studies. Then the pooled ORs with 95%CI were calculated using the random-effects model [17, 18]. I^2 and Q statistic were applied to assess heterogeneity across included studies. Significant heterogeneity was defined as $I^2 > 50.0\%$ or $P < 0.10$ [19, 20]. Sensitivity analysis was performed for factors reported in ≥ 4 studies to assess the robustness of pooled conclusion through sequentially removing individual studies [21]. Subgroup analyses were performed for factors reported in ≥ 4 studies on the basis of the country. The difference between subgroups was assessed using the interaction *P* test [22]. Visual inspections of funnel plots for factors reported in ≥ 4 studies were performed to qualitatively assess publication bias. The Egger or Begg tests were used to quantitatively assess publication bias [23, 24]. The *P*-value for all pooled results was 2-sided, and the inspection level was 0.05. All of the statistical analysis in our study was performed using software STATA (version 12.0; Stata Corporation, College Station, TX, USA).

Results

Literature search

A total of 1,672 studies were identified from initial electronic searches. Details of the study selection process are presented in Fig 1. Of these, 912 articles were removed because they were duplicates. A further 671 articles were excluded owing to irrelevant titles or abstracts. The remaining 89 studies were retrieved for full-text evaluations, with 41 studies removed because

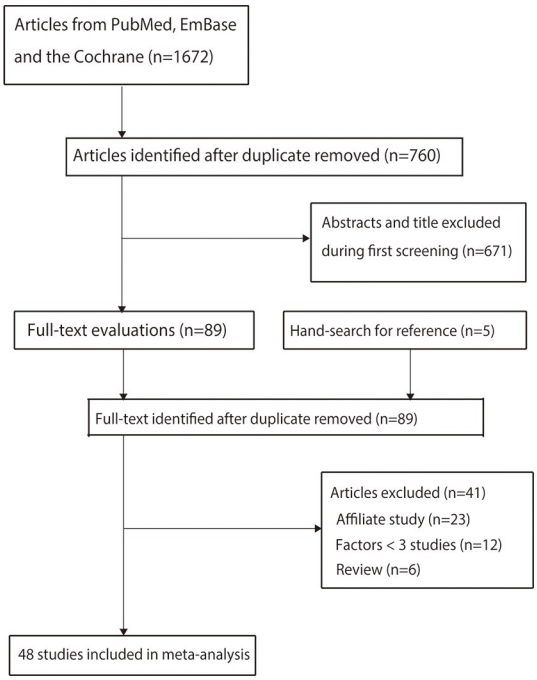

Fig 1. Details of the literature search and study selection processes.

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of: affiliate study (n = 23), evaluated factors < 3 studies (n = 12), and review-type articles (n = 6). A manual search of the reference lists of relevant articles did not yield any additional studies. Finally, 48 studies were selected for the final meta-analysis [25–71]. Characteristics of the included studies and involved individuals are summarized in Table 1.

Study characteristics

Of 48 included studies, 39 studies were designed as cross-sectional, 7 studies were designed as retrospective, and 2 studies designed as prospective. A total of 493,630 individuals were included, and the sample size ranged from 86 to 102,582. The mean age of included individuals ranged from 10.9 to 82.2. Twenty-nine studies were performed in Eastern countries, with the remaining 19 studies conducted in Western countries. Thirty-nine studies were population based. The remaining 9 studies were hospital based. The DES definition based on questionnaire were reported in 33 studies, 10 studies used TBUT, ST, or FSS defined DES, 3 studies applied ICD9 code and the remaining 2 studies used clinician-diagnosed defined DES. Study quality was assessed using the NOS; 11 studies had 8 stars, 18 had 7 stars, and the remaining 19 had 6 stars (S1 Table). The quality of included studies mainly affect by the representativeness of the exposed cohort, and comparability on the basis of the design or analysis.

Meta-analysis

Demographic factors. The number of studies that reported on the association of age, sex, and race as risk factors for DES was 15, 29, and 5, respectively (Fig 2 and S2 File). We noted that older adults (OR: 1.82; 95%CI: 1.47–2.26; $P<0.001$), females (OR: 1.56; 95%CI: 1.36–1.78; $P<0.001$), and those of other race (OR: 1.27; 95%CI: 1.11–1.44; $P<0.001$) had an increased risk of DES. There was significant heterogeneity for age ($I^2 = 96.0\%$; $P<0.001$), sex ($I^2 = 95.0\%$; $P<0.001$), and race ($I^2 = 52.1\%$; $P = 0.080$). Sensitivity analysis indicated these pooled conclusions were robust and not altered by sequentially excluding individual studies (S3 File). The results of subgroup analyses were consistent with overall analysis when stratified according to the region (Table 2). There were no significant publication biases for age (*P*-value for Egger: 0.175; *P*-value for Begg: 1.000), sex (*P*-value for Egger: 0.417; *P*-value for Begg: 0.253), and race (*P*-value for Egger: 0.174; *P*-value for Begg: 0.806) regarding risk for DES (S4 File).

The number of studies reporting an association of residence, education level, obesity, and dyslipidemia regarding the risk of DES were 4, 8, 4, and 7, respectively (Fig 2 and S2 File). We noted that residence (urban versus rural) (OR: 1.41; 95%CI: 0.96–2.08; $P = 0.078$), education level (high versus low) (OR: 1.09; 95%CI: 0.88–1.34; $P = 0.443$), obesity (OR: 1.04; 95%CI: 0.87–1.24; $P = 0.671$), and dyslipidemia (OR: 1.18; 95%CI: 0.97–1.45; $P = 0.104$) were not associated with increased risk for DES. There was significant heterogeneity for residence ($I^2 = 87.8\%$; $P<0.001$), education level ($I^2 = 76.9\%$; $P<0.001$), and dyslipidemia ($I^2 = 92.9\%$; $P<0.001$), while there was no evidence of heterogeneity for obesity ($I^2 = 0.0\%$; $P = 0.530$). Sensitivity analyses indicated that residence, education level, and dyslipidemia might be associated with an elevated risk of DES, while the association between obesity and DES persisted (S3 File). Subgroup analyses demonstrated that education level and dyslipidemia were associated with an increased risk of DES when pooling studies conducted in Eastern countries (Table 2). No significant publication bias for residence (*P*-value for Egger: 0.875; *P*-value for Begg: 0.734), education level (*P*-value for Egger: 0.985; *P*-value for Begg: 0.902), and obesity (*P*-value for Egger: 0.638; *P*-value for Begg: 0.308) with the risk of DES was noted, whereas potential significant publication bias for dyslipidemia (*P*-value for Egger: 0.037; *P*-value for Begg: 1.000) with the risk of DES was seen (S4 File).

Table 1. The baseline characteristics of included studies.

Study	Country	Study design	Sample size	Age (years)	Male (%)	Population	DES (%)	Definition of DES	Reported factors	Adjusted factors
BDES 2000 [25]	USA	C	3,722	65.0	43.0	PB	14.4	Questionnaire	DM, arthritis, TD, osteoporosis, gout, ES, CLW, alcohol, smoking	Age and sex
Lee 2002 [26]	Indonesia	C	1,058	37.0	47.7	PB	27.5	Questionnaire	Sex, smoking, pterygium	Sex, age, occupation, smoking, and pterygium
BMES 2003 [27]	Australia	C	1,174	60.8	44.2	PB	57.5	Questionnaire	Arthritis, asthma, DM, gout, smoking, alcohol	Age and sex
Sahai 2005 [28]	India	C	500	> 20.0	55.2	HB	18.4	Questionnaire	Smoking	Age and sex
Nichols 2006 [29]	USA	C	360	31.1	32.0	HB	55.3	Questionnaire	Sex	Nominal water content, PLTF
Uchino 2008 [30]	Japan	C	3,549	22.0–60.0	74.4	PB	10.1	Questionnaire	Age, sex, VDT, systemic disease, smoking, contact lens	Age, gender, VDT use, systemic disease systemic medication, smoking, contact lens use
Lu 2008 [31]	China	C	1,840	56.3	56.0	PB	52.4	TFBT, ST, FSS	Age, education level, smoking alcohol	Crude
PHS 2009 [32]	USA	C	25,444	64.4	100.0	PB	23.0	Questionnaire	Age, race, hypertension, tumor, DM	Crude
TSES 2009 [33]	Spain	C	654	63.6	37.2	PB	11.0	Questionnaire	Sex, VDT use, CLW, rosacea, allergy, DM, hypertension, COPD, education level, alcohol, smoking	Age and sex
BES 2009 [34]	China	C	1,957	56.5	43.1	PB	21.0	Questionnaire	Sex, residence, glaucoma, MD, DM, hypertension, smoking, alcohol	Age, sex, region, undercorrection of refractive error, and nuclear cataract
THES 2010 [35]	China	C	1,816	54.9	53.9	PB	50.1	TBUT, ST, FSS	Pterygium, age, sex, education level, smoking, alcohol	Crude
Kim 2011 [36]	Korea	C	650	71.9	48.3	PB	30.5	Questionnaire	Sex, residence, depression, MGD	Crude
Koumi Study 2011 [37]	Japan	C	2,791	> 40.0	43.7	PB	16.5	Questionnaire	Age, smoking, alcohol, BMI, education level, VDT use, CLW, stroke, CVD, hypertension, DM	Age, smoking, alcohol, BMI, education level, VDT use, CLW, stroke, CVD, hypertension, DM
USVAP 2011 [38]	USA	R	16,862	NA	NA	PB	12.2	ICD9 code	Sex, race, DM, hypertension, dyslipidemia, CVD, stroke, PTSD, depression, alcohol, arthritis, gout, TD, tumor, sleep apnea, rosacea, glaucoma	Age and sex
Zhang 2012 [39]	China	C	1,885	< 18.0	50.8	PB	23.7	Questionnaire	CLW, sleep apnea	CLW, sleep apnea, myopia, inadequate refractive correction, topical ophthalmic medication
TNHRI 2012 [40]	China	R	48,028	52.4	26.6	PB	25.0	ICD9 code	Hypertension,CVD, dyslipidemia, stroke, migraines, arthritis, COPD, asthma, DM, TD, depression, and tumor	Age, sex, region, and incomes
TOS 2013 [41]	Japan	C	561	43.3	66.7	PB	11.6	Questionnaire	Sex, age, smoking, VDT use, CLW, systemic disease, hypertension	Sex, age, smoking, VDT use, CLW, systemic disease, hypertension

(*Continued*)

Table 1. (Continued)

Study	Country	Study design	Sample size	Age (years)	Male (%)	Population	DES (%)	Definition of DES	Reported factors	Adjusted factors
TwinUK 2014 [42]	UK	C	3,824	57.1	0.0	PB	9.6	Questionnaire	CLW, CS, glaucoma, MD, osteoporosis, asthma, allergy, TD, arthritis, dyslipidemia, hypertension, DM, cancer, stroke, migraine, depression	Age
KNHNES 2014 [43]	Korea	C	11,666	49.9	42.8	PB	8.0	Questionnaire	Age, sex, education level, residence, hypertension, obesity, dyslipidemia, arthritis, TD, smoking, alcohol, sleep apnea, ES	Age, sex, education level, residence, hypertension, obesity, dyslipidemia, arthritis, TD, smoking, alcohol, sleep apnea, ES
Moon 2014 [44]	Korea	C	288	10.9	49.3	PB	9.7	Questionnaire	VDT use	Age, and sex
BDOS 2014 [45]	USA	C	3,275	49.0	45.4	PB	14.5	Questionnaire	Age, sex, CLW, arthritis, allergies, TD, migraine	Age, and sex
TNHI 2015 [46]	China	R	10,325	61.9	36.7	PB	20.0	ICD9 code	DM, hypertension, dyslipidemia, CVD	DM, hypertension, dyslipidemia, CVD
Yang 2015 [47]	China	R	1,908	56.2	41.4	HB	41.4	TFBT, ST, and FSS	DM, arthritis, tumor, acne rosacea, PTSD, VDT use	DM, arthritis, tumor, acne rosacea, PTSD, VDT use
Tan 2015 [48]	Singapore	C	1,004	38.2	44.1	PB	12.3	Questionnaire	Sex, age, CLW, alcohol	Crude
Shah 2015 [49]	India	C	400	58.6	48.0	HB	54.3	TBUT	DM, ES, MGD	Occupation, indoor table work, DM previous ocular surgery, MGD
Olaniyan 2016 [50]	Nigeria	C	363	59.1	48.2	PB	32.5	Questionnaire	Age, ES	Age, work place, medication use, ocular surgery, postmenopausal state
Alshamrani 2017 [51]	Saudi Arabia	C	1,858	39.3	48.0	PB	32.1	Questionnaire	Sex, age, residence, smoking, CLW, DM, hypertension, asthma, CVD, TD, arthritis, gout, osteoporosis	Sex, age, residence, work status, smoking, currently wearing, and history of trachoma
NHWS 2017 [52]	USA	C	73,211	> 18.0	48.4	PB	6.9	Questionnaire	Age, sex, race, education level	Age and sex
SMES 2017 [53]	Singapore	P	1,682	56.9	44.6	PB	5.1	Questionnaire	DM, hypertension, smoking, CLW, stroke, CVD, TD, glaucoma, MGD, pterygium	Sex, age, income, smoking, CLW, cataract surgery, thyroid disease
Gong 2017 [54]	China	C	1,015	54.6	29.7	PB	27.8	Questionnaire	VDT use, DM, hypertension, arthritis, smoking, alcohol	Sex, age, VDT use, DM, hypertension, arthritis, dry mouth, smoking, alcohol, and spicy diets
Asiedu 2017 [54]	Ghana	C	650	22.0	66.6	PB	44.3	Questionnaire	Age, sex, allergies, alcohol, VDT use	Age, sex, allergies, alcohol, VDT use
Graue-Hernandez 2018 [55]	Mexico	C	1,508	64.7	40.3	PB	41.1	Questionnaire	Sex, smoking, DM, alcohol, hypertension	Sex, smoking, DM, alcohol, hypertension
SES 2018 [56]	Spain	C	264	56.8	32.7	PB	25.4	TBUT, ST, FSS	Sex, education level, VDT use, alcohol, smoking, hypertension, DM, COPD, CVD, TD, rosacea	Age
Iglesias 2018 [57]	USA	R	86	71.0	95.0	HB	32.1	Questionnaire	Race, DM, depression, PTSD, sleep apnea, glaucoma	Crude

(*Continued*)

Table 1. (Continued)

Study	Country	Study design	Sample size	Age (years)	Male (%)	Population	DES (%)	Definition of DES	Reported factors	Adjusted factors
TMS 2018 [58]	France	C	1,045	82.2	71.8	PB	34.4	Questionnaire	Obesity, smoking, alcohol, education level, hypertension, DM, depression, CS, MD, glaucoma	Age, and sex
Shehadeh-Mashor 2019 [59]	Israel	R	25,317	27.0	55.0	PB	6.0	TBUT, and ST	Sex, CLW	Age and sex
Zhang 2019 [60]	China	C	31,124	NA	49.1	HB	57.6	ST, and FSS	Sex, age, DM, arthritis, TD, ES	Sex, age, refractive surgery
Yasir 2019 [61]	Saudi Arabia	C	890	> 40.0	55.5	PB	35.9	Questionnaire	Glaucoma, DM, and hypertension	Crude
HTS 2019 [62]	Japan	C	356	55.5	37.4	PB	33.4	Questionnaire	Sex, smoking, CLW, hypertension	Sex, eye makeup use, smoking CLW, hypertension, sleeping pills
Hyon 2019 [63]	Korea	C	232	> 20.0	15.1	PB	42.7	Questionnaire	Sex, VDT use	Sex, and VDT use
Ben-Eli 2019 [64]	Israel	R	331	53.6	24.8	HB	36.3	Clinician-diagnosed	Smoking, alcohol	Ethnicity, smoking, alcohol, hospitalization for infection
Yu 2019 [65]	China	C	23,922	NA	48.8	HB	61.6	TBUT, and FSS	Sex, age, ES, arthritis, TD	Humidity, air pressure, and air temperature
Rossi 2019 [66]	Italy	C	194	41.8	34.5	HB	16.5	TBUT, and FSS	Sex, VDT use	Age, sex, VDT use, visual acuity, and presbyopia
Wang 2020 [67]	New Zealand	C	372	39.0	40.3	PB	29.0	Clinician-diagnosed	Sex, CLW, anxiety, asthma, DM, depression, dyslipidemia, hypertension, cancer, migraine, TD, CS, ES	Age, CLW, ethnicity, migraine, menopause, systemic disease, thyroid disease, antidepressant medication, and oral contraceptive therapy
Shanti 2020 [68]	Palestine	C	769	43.6	47.3	PB	64.0	TBUT, ST, FSS	Sex, VDT use, smoking, DM, hypertension	Age, sex, VDT use, smoking, systemic disease
JPHC 2020 [69]	Japan	P	102,582	58.3	46.2	PB	24.6	Questionnaire	VDT use	Age, smoking, education status, income, and public health area
Alkabbani 2021 [70]	United Arab Emirates	C	452	> 17.0	36.3	PB	62.6	Questionnaire	Age, sex, CLW, ES, VDT use, smoking	Age, sex, CLW, ES, VDT use, smoking
LCS 2021 [71]	Netherlands	C	79,866	50.4	40.8	PB	9.1	Questionnaire	Sex, CLW, MD, glaucoma, ES, CS, arthritis, gout, CVD, stroke, migraine, depression, PTSD, COPD, asthma, sleep apnea, rosacea, allergy, DM, osteoporosis, TD, anemia	Age, and sex

*BMI: body mass index; C: cross-sectional; CLW: contact lens wear; COPD: chronic obstructive pulmonary disease; CS: cataract surgery; CVD: cardiovascular disease; DM: diabetes mellitus; ES: eye surgery; FSS: fluorescein staining score; HB: hospital-based; MD: macular degeneration; MDG: meibomian gland dysfunction; MI: myocardial infarction; NA: not available; P: prospective; PB: population-based; PLTF: prelens tear film; PTSD: post-traumatic stress disorder; R: retrospective; ST: Schirmer test; TBUT: tear film break-up time; TD: thyroid disease; TFBT: tear film breakup time; VDT: visual display terminal

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The number of studies reporting an association of alcohol, smoking, and VDT use with the risk of DES was 15, 22, and 14, respectively (Fig 2 and S2 File). We noted that alcohol intake (OR: 0.98; 95%CI: 0.81–1.18; $P = 0.808$) and current smoking (OR: 1.00; 95%CI: 0.86–1.16; $P = 0.986$) were not associated with risk for DES, while VDT use was associated with an increased risk of DES (OR: 1.32; 95%CI: 1.17–1.49; $P<0.001$). There was significant

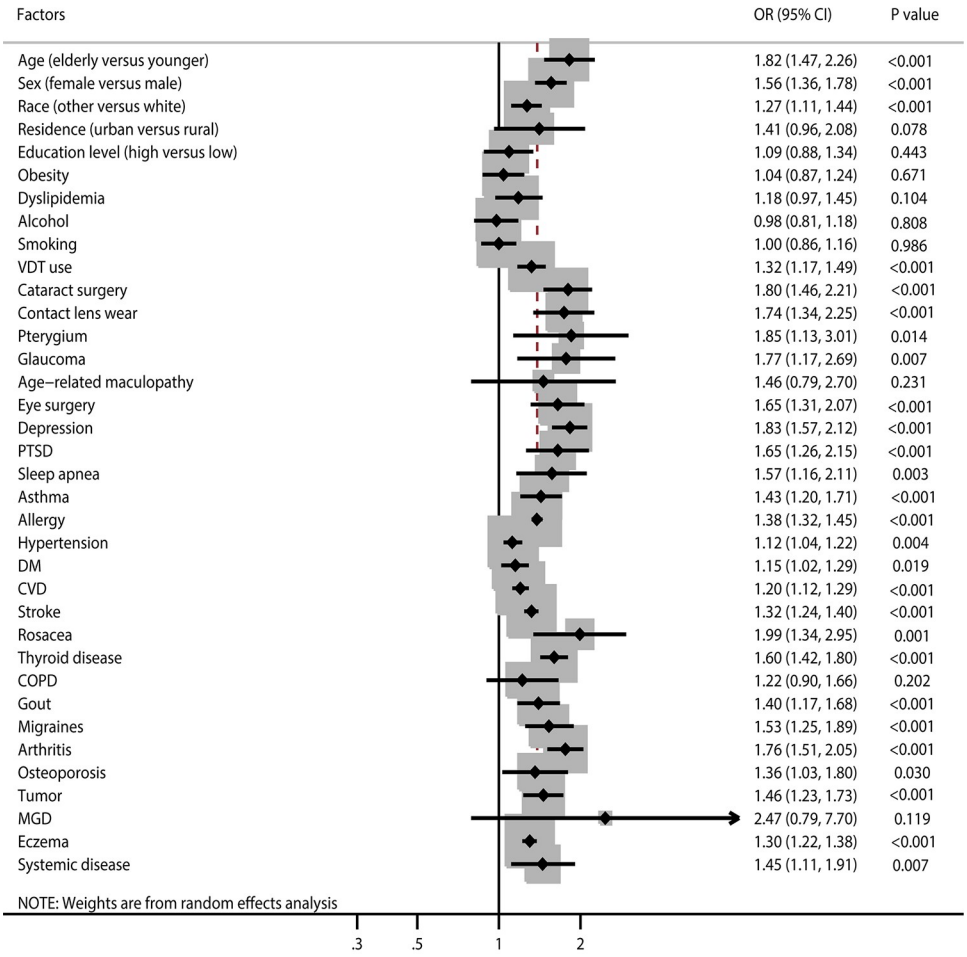

Fig 2. Summary results of risk factors for dry eye syndrome.

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heterogeneity for alcohol (I^2 = 62.2%; P = 0.001), smoking (I^2 = 64.6%; P<0.001), and VDT use (I^2 = 80.1%; P<0.001). Sensitivity analysis indicated that alcohol intake might play an important role in the risk of DES, while the pooled results for the associations of smoking and VDT use with the risk of DES were robust (S3 File). The results of subgroup analyses were consistent with the overall analysis (Table 2). No significant publication bias for smoking (P-value for Egger: 0.569; P-value for Begg: 0.822) and VDT use (P-value for Egger: 0.370; P value for Begg: 0.827) with the risk of DES was found, whereas potential significant publication bias for alcohol (P-value for Egger: 0.032; P-value for Begg: 0.921) with the risk of DES was noted (S4 File).

Clinical characteristics. The number of studies that reported on the association of cataract surgery, contact lens wear, pterygium, glaucoma, age-related maculopathy, and eye surgery with the risk of DES were 7, 17, 4, 9, 3, and 8, respectively (Fig 2 and S2 File). We noted that cataract surgery (OR: 1.80; 95%CI: 1.46–2.21; P<0.001), contact lens wear (OR: 1.74; 95% CI: 1.34–2.25; P<0.001), pterygium (OR: 1.85; 95%CI: 1.13–3.01; P = 0.014), glaucoma (OR: 1.77; 95%CI: 1.17–2.69; P = 0.007), and eye surgery (OR: 1.65; 95%CI: 1.31–2.07; P<0.001) were associated with an increased risk of DES, while age-related maculopathy was not associated with risk of DES (OR: 1.46; 95%CI: 0.79–2.70; P = 0.231). Significant heterogeneity was noted for cataract surgery (I^2 = 64.8%; P<0.001), contact lens wear (I^2 = 93.5%; P<0.001),

Table 2. Subgroup analyses according to region.

Factors	Subgroup	OR and 95%CI	*P* value	I^2 (%)	$P_{heterogeneity}$	*P* value between subgroups
Age (elderly versus younger)	Eastern countries	1.78 (1.46–2.19)	< 0.001	89.4	< 0.001	< 0.001
	Western countries	2.04 (1.05–3.97)	0.036	98.7	< 0.001	
Sex (female versus male)	Eastern countries	1.53 (1.36–1.72)	< 0.001	84.0	< 0.001	< 0.001
	Western countries	1.52 (1.20–1.92)	< 0.001	95.8	< 0.001	
Race (other versus white)	Eastern countries	-	-	-	-	-
	Western countries	1.27 (1.11–1.44)	< 0.001	52.1	0.080	
Residence (urban versus rural)	Eastern countries	1.41 (0.96–2.08)	0.078	87.8	< 0.001	-
	Western countries	-	-	-	-	
Education level (high versus low)	Eastern countries	1.28 (1.01–1.63)	0.041	60.2	0.057	0.007
	Western countries	0.86 (0.56–1.33)	0.505	80.7	0.001	
Obesity	Eastern countries	1.02 (0.83–1.25)	0.866	2.1	0.360	0.685
	Western countries	1.11 (0.77–1.60)	0.576	-	-	
Dyslipidemia	Eastern countries	1.35 (1.01–1.80)	0.046	94.7	< 0.001	< 0.001
	Western countries	1.05 (0.82–1.35)	0.676	77.2	0.004	
Alcohol	Eastern countries	1.04 (0.90–1.20)	0.589	0.0	0.429	0.177
	Western countries	0.92 (0.64–1.32)	0.641	76.1	<0.001	
Smoking	Eastern countries	0.96 (0.81–1.15)	0.668	65.2	< 0.001	0.046
	Western countries	1.09 (0.82–1.45)	0.554	60.0	0.020	
VDT use	Eastern countries	1.33 (1.17–1.53)	< 0.001	85.5	< 0.001	0.436
	Western countries	1.33 (1.06–1.68)	0.015	0.0	0.457	
Cataract surgery	Eastern countries	2.16 (1.62–2.89)	< 0.001	0.0	0.792	0.561
	Western countries	1.69 (1.28–2.21)	< 0.001	76.0	0.002	
Contact lens wear	Eastern countries	2.01 (1.48–2.71)	<0.001	72.8	<0.001	0.003
	Western countries	1.41 (0.93–2.14)	0.105	97.1	<0.001	
Pterygium	Eastern countries	1.85 (1.13–3.01)	0.014	89.0	< 0.001	-
	Western countries	-	-	-	-	
Glaucoma	Eastern countries	2.15 (1.29–3.58)	0.003	26.1	0.255	0.516
	Western countries	1.57 (0.92–2.68)	0.098	96.5	< 0.001	
Age-related maculopathy	Eastern countries	0.31 (0.07–1.35)	0.118	-	-	0.007
	Western countries	1.91 (1.21–3.01)	0.005	62.9	0.067	
Eye surgery	Eastern countries	1.62 (1.23–2.14)	0.001	93.6	<0.001	<0.001
	Western countries	1.82 (1.39–2.37)	< 0.001	32.1	0.229	
Depression	Eastern countries	2.12 (1.95–2.32)	< 0.001	0.0	0.876	< 0.001
	Western countries	1.66 (1.43–1.93)	< 0.001	67.0	0.010	
PTSD	Eastern countries	1.45 (1.04–2.01)	0.027	-	-	0.121
	Western countries	1.71 (1.19–2.46)	0.004	53.0	0.119	
Sleep apnea	Eastern countries	1.22 (1.11–1.35)	< 0.001	4.5	0.370	< 0.001
	Western countries	2.17 (1.95–2.41)	< 0.001	0.0	0.749	
Asthma	Eastern countries	1.19 (0.98–1.45)	0.076	29.0	0.235	< 0.001
	Western countries	1.62 (1.49–1.77)	< 0.001	0.0	0.869	
Allergy	Eastern countries	-	-	-	-	-
	Western countries	1.38 (1.32–1.45)	< 0.001	0.0	0.418	
Hypertension	Eastern countries	1.06 (0.95–1.17)	0.306	63.7	0.001	0.005
	Western countries	1.27 (1.14–1.41)	< 0.001	24.8	0.231	
DM	Eastern countries	1.20 (1.06–1.37)	0.005	79.0	< 0.001	< 0.001
	Western countries	1.08 (0.87–1.34)	0.460	88.5	< 0.001	

(*Continued*)

Table 2. (Continued)

Factors	Subgroup	OR and 95%CI	*P* value	I^2 (%)	$P_{heterogeneity}$	*P* value between subgroups
CVD	Eastern countries	1.26 (1.15–1.39)	< 0.001	0.0	0.753	0.084
	Western countries	1.15 (1.00–1.32)	0.049	18.5	0.293	
Stroke	Eastern countries	1.31 (1.22–1.41)	< 0.001	0.0	0.978	0.667
	Western countries	1.35 (1.20–1.51)	< 0.001	0.0	0.589	
Rosacea	Eastern countries	3.75 (1.97–7.12)	< 0.001	-	-	0.032
	Western countries	1.74 (1.20–2.52)	0.004	53.1	0.094	
Thyroid disease	Eastern countries	1.57 (1.29–1.91)	< 0.001	86.0	<0.001	0.752
	Western countries	1.64 (1.45–1.84)	< 0.001	26.9	0.223	
COPD	Eastern countries	1.06 (0.84–1.34)	0.625	-	-	0.006
	Western countries	1.37 (1.00–1.89)	0.051	23.2	0.272	
Gout	Eastern countries	1.56 (0.70–3.49)	0.275	83.3	0.014	0.175
	Western countries	1.34 (1.17–1.53)	< 0.001	0.0	0.860	
Migraines	Eastern countries	1.76 (1.57–1.98)	< 0.001	-	-	< 0.001
	Western countries	1.41 (1.19–1.68)	< 0.001	54.2	0.088	
Arthritis	Eastern countries	1.74 (1.31–2.29)	< 0.001	95.6	< 0.001	0.776
	Western countries	1.80 (1.57–2.07)	< 0.001	74.7	0.001	
Osteoporosis	Eastern countries	0.81 (0.51–1.29)	0.377	-	-	0.004
	Western countries	1.53 (1.21–1.93)	< 0.001	75.8	0.016	
Tumor	Eastern countries	2.27 (0.83–6.22)	0.111	94.7	< 0.001	0.339
	Western countries	1.33 (1.17–1.50)	<0.001	39.5	0.175	

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pterygium (I^2 = 89.0%; *P*<0.001), glaucoma (I^2 = 93.4%; *P*<0.001), age-related maculopathy (I^2 = 76.5%; *P* = 0.005), and eye surgery (I^2 = 94.0%; *P*<0.001) with the risk of DES. Sensitivity analyses indicated that the pooled results for the association of cataract surgery, contact lens wear, pterygium, glaucoma, and eye surgery with the risk of DES persisted, whereas age-related maculopathy might be associated with the risk of DES (S3 File). Although most results in the subgroup analyses were consistent with the overall analysis, we noted that contact lens wear and glaucoma were not associated with the risk of DES when pooling studies performed in Western countries. Moreover, age-related maculopathy was associated with an increased risk of DES when pooling studies conducted in Western countries (Table 2). There was no significant publication bias for the association of cataract surgery (*P*-value for Egger: 0.194; *P*-value for Begg: 0.548), contact lens wear (*P*-value for Egger: 0.791; *P*-value for Begg: 0.387), pterygium (*P*-value for Egger: 0.681; *P*-value for Begg: 0.734), glaucoma (*P*-value for Egger: 0.950; *P*-value for Begg: 0.917), and eye surgery (*P*-value for Egger: 0.760; *P*-value for Begg: 0.266) with the risk of DES, while potential significant publication bias was noted for age-related maculopathy (*P*-value for Egger: 0.017; *P*-value for Begg: 0.308) with the risk of DES (S4 File).

Comorbidities. The number of studies that reported on the association of depression, PTSD, sleep apnea, asthma, and allergy with the risk of DES were 9, 4, 7, 6, and 6, respectively (Fig 2 and S2 File). We noted that depression (OR: 1.83; 95%CI: 1.57–2.12; *P*<0.001), PTSD (OR: 1.65; 95%CI: 1.26–2.15; *P*<0.001), sleep apnea (OR: 1.57; 95%CI: 1.16–2.11; *P* = 0.003), asthma (OR: 1.43; 95%CI: 1.20–1.71; *P*<0.001), and allergy (OR: 1.38; 95%CI: 1.32–1.45; *P*<0.001) were associated with an increased risk of DES. There was significant heterogeneity for depression (I^2 = 80.7%; *P*<0.001), PTSD (I^2 = 55.0%; *P* = 0.083), sleep apnea (I^2 = 91.5%; *P*<0.001), and asthma (I^2 = 76.5%; *P* = 0.001), while no evidence of heterogeneity for allergy was observed (I^2 = 0.0%; *P* = 0.418). Sensitivity analyses indicated that pooled conclusions for

the association of depression, PTSD, sleep apnea, asthma, and allergy with the risk of DES were stable after sequentially removing individual studies (S3 File). The results of subgroup analyses were consistent with overall analysis, except that asthma was not associated with the risk of DES if pooled studies were performed in Eastern countries (Table 2). No significant publication bias for the role of depression (*P*-value for Egger: 0.679; *P*-value for Begg: 0.348), PTSD (*P*-value for Egger: 0.415; *P*-value for Begg: 0.734), sleep apnea (*P*-value for Egger: 0.959; *P*-value for Begg: 0.764), asthma (*P*-value for Egger: 0.949; *P*-value for Begg: 1.000), and allergy (*P*-value for Egger: 0.189; *P*-value for Begg: 0.707) with DES were observed (S4 File).

The number of studies reporting on the association of hypertension, DM, CVD, stroke, rosacea, thyroid disease, and COPD with the risk of DES were 21, 24, 8, 7, 5, 14, and 4, respectively (Fig 2 and S2 File). We noted that hypertension (OR: 1.12; 95%CI: 1.04–1.22; $P = 0.004$), DM (OR: 1.15; 95%CI: 1.02–1.29; $P = 0.019$), CVD (OR: 1.20; 95%CI: 1.12–1.29; $P<0.001$), stroke (OR: 1.32; 95%CI: 1.24–1.40; $P<0.001$), rosacea (OR: 1.99; 95%CI: 1.34–2.95; $P = 0.001$), and thyroid disease (OR: 1.60; 95%CI: 1.42–1.80; $P<0.001$) were associated with an increased risk of DES, while COPD was not associated with risk of DES (OR: 1.22; 95%CI: 10.90–1.66; $P = 0.202$). There was significant heterogeneity for hypertension ($I^2 = 60.2\%$; $P<0.001$), DM ($I^2 = 86.7\%$; $P<0.001$), rosacea ($I^2 = 63.6\%$; $P = 0.027$), thyroid disease ($I^2 = 74.6\%$; $P<0.001$), and COPD ($I^2 = 70.6\%$; $P = 0.017$), while no significant heterogeneity was observed for CVD ($I^2 = 4.8\%$; $P = 0.393$) and stroke ($I^2 = 0.0\%$; $P = 0.964$). The pooled conclusions for the association of hypertension, CVD, stroke, rosacea, and thyroid disease with the risk of DES were stable, while the conclusions for DM and COPD with DES were variable (S3 File). Although the results of subgroup analyses were consistent with the overall analysis in most subsets, we noted that hypertension was not related to DES if pooling in Eastern country studies, while DM was not associated with the risk of DES if pooled studies were performed in Western countries (Table 2). There was no significant publication bias for hypertension (*P*-value for Egger: 0.331; *P*-value for Begg: 0.928), DM (*P*-value for Egger: 0.765; *P*-value for Begg: 0.862), CVD (*P*-value for Egger: 0.357; *P*-value for Begg: 0.711), stroke (*P*-value for Egger: 0.485; *P*-value for Begg: 0.368), rosacea (*P*-value for Egger: 0.759; *P*-value for Begg: 0.806), thyroid disease (*P*-value for Egger: 0.996; *P*-value for Begg: 0.228), and COPD (*P*-value for Egger: 0.267; *P*-value for Begg: 1.000) (S4 File).

The number of studies reporting on the association of gout, migraines, arthritis, osteoporosis, tumor, MGD, eczema, and systemic disease with the risk of DES was 6, 5, 13, 4, 6, 3, 3, and 3, respectively (Fig 2 and S2 File). We noted that gout (OR: 1.40; 95%CI: 1.17–1.68; $P<0.001$), migraines (OR: 1.53; 95%CI: 1.25–1.89; $P<0.001$), arthritis (OR: 1.76; 95%CI: 1.51–2.05; $P<0.001$), osteoporosis (OR: 1.36; 95%CI: 1.03–1.80; $P = 0.030$), tumor (OR: 1.46; 95%CI: 1.23–1.76; $P<0.001$), eczema (OR: 1.30; 95%CI: 1.22–1.38; $P<0.001$), and systemic disease (OR: 1.45; 95%CI: 1.11–1.91; $P = 0.007$) were associated with an increased risk of DES, while MGD was not associated with risk of DES (OR: 2.47; 95%CI: 0.79–7.70; $P = 0.119$). There was significant heterogeneity for migraines ($I^2 = 86.4\%$; $P<0.001$), arthritis ($I^2 = 92.4\%$; $P<0.001$), osteoporosis ($I^2 = 82.1\%$; $P = 0.001$), tumor ($I^2 = 79.9\%$; $P<0.001$), and MGD ($I^2 = 85.2\%$; $P = 0.001$), while no significant heterogeneity for gout ($I^2 = 41.8\%$; $P = 0.126$), eczema ($I^2 = 0.0\%$; $P = 0.609$), and systemic disease ($I^2 = 0.0\%$; $P = 0.007$) was observed. The pooled conclusions for the association of gout, migraines, arthritis, osteoporosis, and tumor with the risk of DES were robust after sequentially removing individual studies (S3 File). Although the results of subgroup analyses were consistent with the overall analysis in most subsets, gout, osteoporosis, and tumor were not associated with risk of DES if pooled studies were performed in Eastern countries. There was no significant publication bias for gout (*P*-value for Egger: 0.902; *P*-value for Begg: 0.707), migraines (*P*-value for Egger: 0.249; *P*-value for Begg: 0.806), arthritis

(*P*-value for Egger: 0.169; *P*-value for Begg: 0.360), osteoporosis (*P*-value for Egger: 0.137; *P*-value for Begg: 0.308), and tumor (*P*-value for Egger: 0.721; *P*-value for Begg: 1.000) (S4 File).

Discussion

This systematic review and meta-analysis was based on published observational studies explored potential risk factors for DES and included 493,630 individuals from 48 studies. We found that risk factors for DES included older age, female sex, other race, VDT use, cataract surgery, contact lens wear, pterygium, glaucoma, eye surgery, depression, PTSD, sleep apnea, asthma, allergy, hypertension, DM, CVD, stroke, rosacea, thyroid disease, gout, migraines, arthritis, osteoporosis, tumor, eczema, and systemic disease. Moreover, country of origin could affect association for age, sex, education level, dyslipidemia, smoking, contact lens wear, age-related maculopathy, eye surgery, depression, sleep apnea, asthma, hypertension, DM, rosacea, COPD, migraines, and osteoporosis regarding the risk of DES.

This current study primarily identified potential risk factors for DES, although several factors have already been demonstrated in individual studies. Prior studies have demonstrated that a 5-year incidence of dry eye rises from 10.7% to 17.9% alongside increasing age [72]. A potential reason could be the reduction of tear secretion with biological aging [2, 73]. Moreover, the sex difference in DES could be explained by various hormonal effects on the ocular surface and lacrimal gland [8]. The potential impact for VDT use could be due to increasing rates of incomplete blinks and accelerated evaporation of the tear film [74]. The increased risk of DES after cataract surgery could be explained by cataract surgery inducing tear film dysfunction [75]. The role of contact lens wear on DES could be explained in that placing a lens on the eye could cause disturbance of the tear film [76]. DES could be considered as a precipitating factor of primary pterygium [77]. The treatment of glaucoma could alter the surface of the eye through disturbing tear secretion, which could affect the progression of DES [78]. Studies have already found that open eye surgery could affect altered tear secretion in nearly 91% of patients, thus playing an important role in the risk of DES [79]. The potential role of depression and PTSD could be explained by the dysregulation of neuropeptides coupled with serotonin in human tears and serotonin receptors in human conjunctivae [80]. Sleep apnea is significantly associated with neuropathic pain, which could induce the progression of dry eye syndrome [81]. The role of asthma and allergy on the risk of DES could be explained by antihistaminic and anti-inflammatory agents used for asthma and allergy treatment, which could potentially cause an elevated risk of DES [82].

This study found that hypertension and DM were associated with an increased risk of DES, which was consistent with the results of a prior meta-analysis [83]. A potential reason for this could be hypertension was not direct affect the risk of DES, while the use of anti-hypertensive medication could increase the risk of DES [33]. In addition, the risk of DES were not increased in hypertensive patients treated with anti-hypertensive medications, such as Angiotension Converting Enzyme inhibitors might play a protective role on the risk of DES [34]. Moreover, DM could induce a decrease in corneal sensation and tear production, impaired metabolic activity, and loss of cytoskeletal structure, all of which could affect the progression of DES [84]. The underlying therapies for CVD, stroke, and tumor could be regarded as disposing of factors for DES [25]. Rosacea is a well known risk factor for DES due to is pro-inflammatory effects that induce meibomian gland dysfunction and evaporative DES [85]. Studies have already found that thyroid disease is significantly related to ocular surface damage, eyelid retraction/impaired Bell's phenomenon, and reduced tear production [86]. Gout was associated with the tophaceous deposits in different locations of the eye, including eyelids, conjunctiva, cornea, iris, sclera, and orbit, a similar reason could explain the role of arthritis on DES [87]. The role

of migraines on DES could be explained by an inflammatory status in migraine patients potentially activating inflammation in the eyes [88]. The inflammation and hormone imbalance caused by osteoporosis could explain an elevated risk of DES [89]. The treatment for eczema and systemic disease could cause an elevated risk of DES [90].

Our study found that potential associations for age, sex, education level, dyslipidemia, smoking, contact lens wear, age-related maculopathy, eye surgery, depression, sleep apnea, asthma, hypertension, DM, rosacea, COPD, migraines, and osteoporosis with the risk of DES could be affected by country of origin. The disease distribution for DES is different in Eastern and Western countries, and the health policy in various countries could further affect the progression of DES. Moreover, environmental, dietary, and lifestyle factors among various countries differ, which could affect the progression of DES [91, 92].

Several shortcomings of this study should be acknowledged. First, this study contained cross-sectional, retrospective, and prospective observational studies, and the causality relationships between risk factors and DES could not available. Second, the heterogeneity for most risk factors was substantial, which was not fully explained by sensitivity and subgroup analyses. Third, the comorbidity and underlying therapies for individuals were not fully adjusted, which could affect the progression of DES. Fourth, the cutoff value for age, and definition for systemic disease, eye surgery, and DES are different across included studies, which could induce potential uncontrolled biases. Fifth, the climate type could affect the progression of DES, and nearly all of included studies did not address the climate type. Sixth, the analysis based on published articles, the gray literature and unpublished data were not available, and the publication bias was inevitable. Seventh, the analysis using the pooled data, and the detailed analyses were restricted. Finally, this study was not registered in PROSPERO, and the transparency was restricted.

Conclusions

This study identified comprehensive risk factors for DES, including older age, female sex, other race, VDT use, cataract surgery, contact lens wear, pterygium, glaucoma, eye surgery, depression, PTSD, sleep apnea, asthma, allergy, hypertension, DM, CVD, stroke, rosacea, thyroid disease, gout, migraines, arthritis, osteoporosis, tumor, eczema, and systemic disease. Further large-scale prospective cohort studies should be performed to verify the results of this study.

Supporting information

S1 Checklist. PRISMA 2020 checklist.
(PDF)

S1 Table. Quality scores of prospective cohort studies using Newcastle-Ottawa Scale.
(DOCX)

S1 File. Search strategy in PubMed.
(DOCX)

S2 File. Forest plots for the risk factors of dry eye syndrome.
(DOCX)

S3 File. Sensitivity analyses for the risk factors of dry eye syndrome.
(DOCX)

S4 File. Funnel plots for the risk factors of dry eye syndrome.
(DOCX)

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