Review Article

Association of dry eye disease with smoking: A systematic review and meta-analysis

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There is conflicting evidence for the association between smoking and dry eye disease (DED). We conducted a meta-analysis to determine the true relationship between smoking and DED. A systematic literature search was performed using electronic databases, including PubMed, Embase and Cochrane Library, till August 2021 to identify observational studies with data on smoking as risk factor of DED. Quality assessment of the included studies was conducted using Joanna Briggs Institute (JBI) critical appraisal checklists. The random-effects model was used to calculate the pooled odds ratio (OR). Heterogeneity was evaluated by Cochrane Q and I^2 index; in addition, subgroup, sensitivity, and meta-regression analyses were performed. Publication bias was assessed using funnel plot and Egger's regression test. A total of 22 studies (4 cohort and 18 cross-sectional studies) with 160,217 subjects met the inclusion criteria and were included in this meta-analysis. There is no statistically significant relationship between current smokers ($OR_{adjusted}$ = 1.14; 95% CI: 0.95–1.36; P = 0.15; I^2 = 84%) and former smokers ($OR_{adjusted}$ = 1.06; 95% CI: 0.93–1.20; P = 0.38; I^2 = 26.7%) for the risk of DED. The results remained consistent across various subgroups. No risk of publication bias was detected by funnel plot and Eggers's test (P > 0.05). No source of heterogeneity was observed in the meta-regression analysis. Our meta-analysis suggest current or former smoking may not be involved in the risk of dry eye disease. Further studies to understand the mechanism of interaction between current smokers and formers smokers with DED are recommended.

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Dry eye disease (DED) is a highly prevalent ocular surface disease across the globe with an estimated prevalence ranging from 5% to 50%.[1] The International Dry Eye Workshop (DEWS) II has defined DED as a multifactorial disease affecting both the ocular surface and the tear film leading to tear film instability and damage to ocular surface, which results in symptoms of discomfort, irritation, visual disturbances, and photophobia.[2] These symptoms have significant societal impact owing to decreased productivity at work along with reduced quality of life for affected individuals.[3,4] Untreated severe cases can often lead to complications such as corneal scarring, infectious keratitis, and blindness.[5]

The pathogenesis for DED has been studied over the past few decades, and its understanding has evolved tremendously to now include concepts of tear hyperosmolarity, ocular surface inflammation, and neurosensory abnormalities.[6] Several risk factors have been identified in the occurrence of DED, namely aging, female sex, meibomian gland dysfunction, and certain comorbid autoimmune diseases such as Sjogren syndrome.[6] Cigarette smoking, a modifiable risk factor for a wide range of diseases, such as vascular disease, lung cancer, and chronic obstructive pulmonary disease, has been explored as a potential risk factor for DED in various population-based studies.[7-9] Various studies have reported the detrimental effects of smoking on the tear film and ocular surface, with a decrease in tear break-up time (TBUT) and Schirmer's scores, but some studies have no reported no significant difference in Schirmer's test, TBUT values, and fluorescein staining score between smokers and non-smokers.[10-14]

However, so far, the role of smoking in DED development remains unclear and evidence are contradictory. This observation has been attributed variously to small study sample size, imbalance of factors distributed in cases and controls, or unclear definition of smoking status.

A previously published meta-analysis on this topic concluded no association between smoking and risk of dry eye, but that study was limited by a relatively small number of studies and high heterogeneity within the included studies.[15] Therefore, we conducted this updated meta-analysis to quantitatively describe the relationship between smoking and DED using the currently available literature.

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Methods

Search strategy

This study was performed according to the Meta-analyses Of Observational Studies in Epidemiology (MOOSE) guidelines.[16] Three electronic databases including PubMed, Embase, and Cochrane Library were comprehensively searched out up to August 2021 for relevant papers reporting on the association between smoking and DED by using the following keywords in combination with MeSH terms and text words: dry eye, dry eye syndrome, dry eye disease, keratoconjunctivitis sicca, conjunctivitis sicca, keratitis sicca, combined with smoking, smoker, tobacco, tobacco use, cigarette, cigarette smoke, and nicotine. Additionally, references of all relevant articles were searched manually for further relevant articles. No restriction on language or publication year were applied during the literature search. Duplicated articles were removed, and a screening based on title and abstract was conducted by

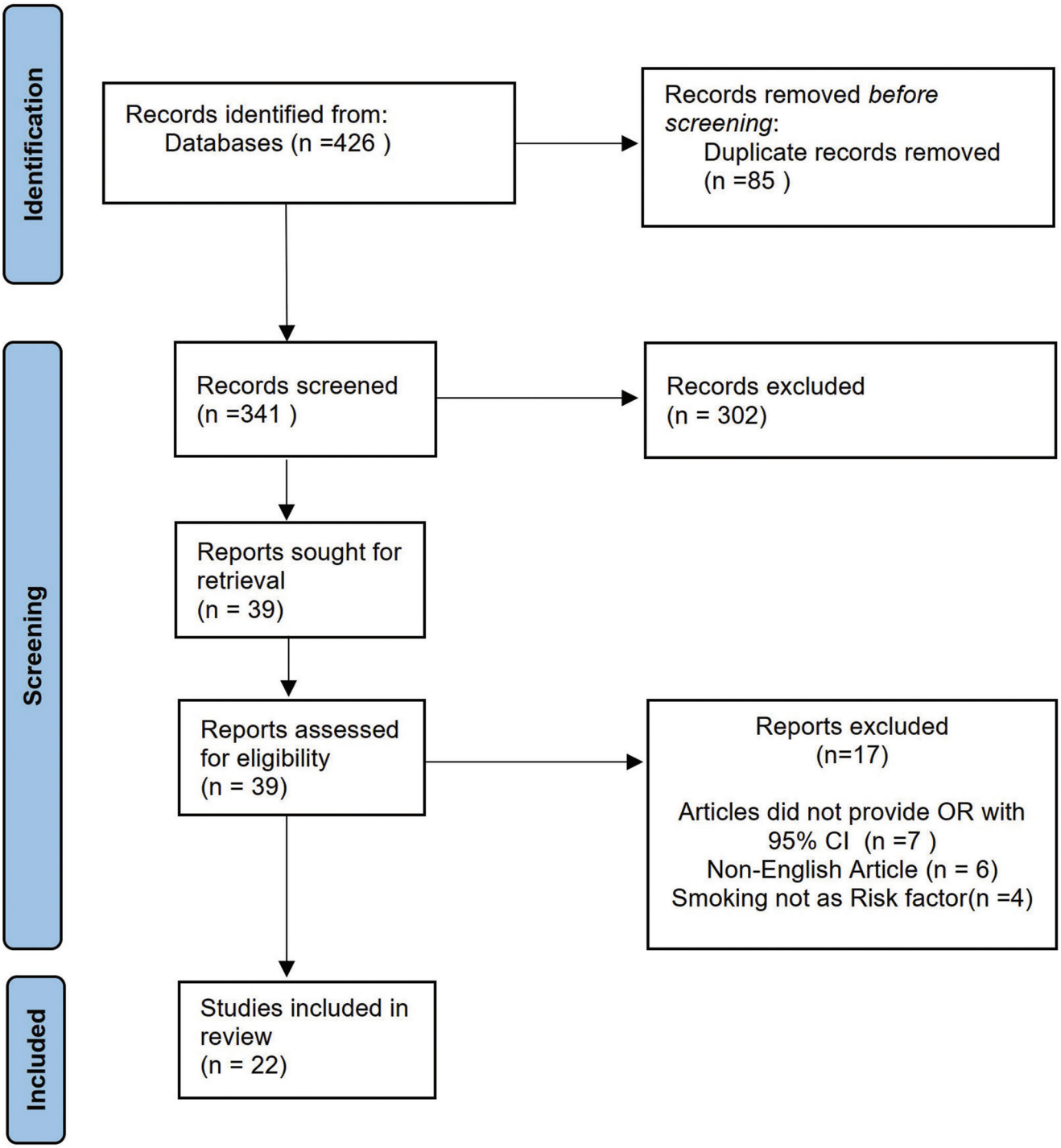

Figure 1: The flow diagram of study selection

Table 1: Characteristics of studies included in the meta-analysis

Author, Year (Study Name)	Country	Study Design	Study Size	Age (years)	Male/ Female Ratio	Number of Current smokers	Smoking Status	Population
Moss *et al*. 2000 (Beaver Dam Eye Study)	United States	Cohort Study	3722	65	1600/2122	548	Current smokers/Former Smokers/non-smokers	General Population
Lee *et al*. 2003	Indonesia	Cross Sectional	1058	37	505/553	147	Current smokers/Former Smokers/non-smokers	General Population
Chia *et al*. 2003 (Blue Mountains Eye Study)	Australia	Cohort Study	1174	60.8	519/655	184	Current Smoker/ non-smokers	General Population
Sahai *et al*. 2005	India	Cross Sectional	500	>20	276/224	163	Current Smoker/ non-smokers	Hospital Based Population
Moss *et al*. 2008	United States	Cohort Study	2414	63	1062/1352	325	Current smokers/Former Smokers/non-smokers	General Population
Uchino *et al*. 2008	Japan	Cross Sectional	4393	22-60	2640/909	1219	Current Smoker/ non-smokers	Office Workers using VDT
Guo *et al*. 2010 (Henan eye study)	China	Cross Sectional	2112	54.8	1125/987	NA	Current Smoker/ non-smokers	General Population
Uchino *et al*. 2011 (Koumi Study)	Japan	Cross Sectional	2644	>40	1221/1423	441	Current Smoker/ non-smokers	General Population
Uchino *et al*. 2013 (Osaka Study)	Japan	Cross Sectional	561	43.3	374/187	110	Current Smoker/ non-smokers	Office Workers using VDT
Ahn *et al*. 2014 (KNHANES)	Korea	Cross Sectional	11666	49.9	4993/6673	4480	Current Smoker/ non-smokers	General Population
Malet *et al*. 2014 (The Alienor Study)	France	Cross Sectional	963	80	354/561	45	Current smokers/Former Smokers/non-smokers	General Population
Man *et al*. 2017 (Singapore Malay Eye Study)	Singapore	Cohort Study	1682	57	750/932	297	Current Smoker/ non-smokers	General Population
Alhamyani *et al*. 2018	Saudi Arabia	Cross Sectional	482	50.2	173/309	61	Current Smoker/ non-smokers	Hospital-Based Population
Titiyal *et al*. 2018	India	Cross Sectional	15625	>10	11211/4414	350	Current Smoker/ non-smokers	Hospital Based Population
Alshamrani *et al*. 2017	Saudi	Cross Sectional	1858	39.3	892/966	284	Current Smoker/ non-smokers	General Population
Castro *et al*. 2018	Brazil	Cross Sectional	3107	40.5	2036/1071	193	Current Smoker/ non-smokers	General Population
Kim *et al*. 2019	Korea	Cross Sectional	4185	>65	1787/2398	490	Current smokers/Former Smokers/non-smokers	General Population
Arita *et al*. 2019 (The Hirado-Takushima)	Japan	Cross Sectional	384	55.5	141/243	NA	Current Smoker/ non-smokers	General Population
Inomata *et al*. 2020	Japan	Cross Sectional	4454	27.9	1482/2972	1058	Current Smoker/ non-smokers	General Population
Tandon *et al*. 2020 (SEED study)	India	Cross Sectional	9735	54.5	4429/5306	3584	Current Smoker/ non-smokers	General Population
Vehof *et al*. 2020 (Lifelines study)	Netherlands	Cross Sectional	79481	50.4	32187/47294	12540	Current smokers/Former Smokers/non-smokers	General Population
Chatterjee *et al*. 2021	India	Cross Sectional	2378	44.3	1397/981	205	Current Smoker/ non-smokers	General Population

two authors. Full text of relevant articles were obtained and screened against the eligibility criteria.

Eligibility criteria

To be included in the meta-analysis, studies have to fulfill all of the following inclusion criteria: (1) case–control or cohort or cross-sectional study published as an original article in the English language; 2) investigation of smoking as a potential risk factor for DED; 3) report the estimation of the relationship between smoking and the risk of DED expressed as odds ratio (OR) or relative risk (RR) with their corresponding 95% confidence intervals (CIs) or provided enough raw data for calculation. Animal studies, case reports, reviews, abstracts, conference proceedings, editorials, non-English articles, and

Table 2: Reported odds ratios and adjusted factors from individual studies

Author, Publication Year	Gender	Smoking Status	Reported OR (95% CI)	Adjusted Variables
Moss *et al*., 2000	Both	Current	1.82 (1.36-2.46)	Age, Gender, Gout History, Diabetes, Caffeine Use, Thyroid History, Cholesterol, Arthritis
		Past	1.22 (0.97-1.52)	
Lee *et al*., 2003	Both	Current	1.5 (1.0-2.2)	Age, Gender, Occupation, History of Pterygium
		Past	1.2 (0.6-2.4)	
Chia *et al*., 2003	Both	Current	0.7 (0.4-1.1)	Age, Gender
Sahai *et al*., 2005	Both	Current	1.42 (0.44-1.12)	None
Moss *et al*., 2008	Both	Current	0.88 (0.64-1.20)	None
Uchino *et al*., 2008	Both	Current	0.77 (0.53-1.12)	Age, Gender, VDT, Systemic Disease, Medication, Contact lens
Guo *et al*., 2010	Both	Current	1.06 (0.81-1.39]	Age, Gender, Pterygium, Cataract, Alcohol consumption, socioeconomic status
Uchino *et al*., 2011	Male	Current	0.78 (0.53-15)	None
	Female	Current	1.31 (0.75-2.28)	
Uchino *et al*., 2013	Both	Current	0.86 (0.54-1.35)	Age, Gender, VDT, Systemic Disease, Hypertension, Contact Lens
Ahn *et al*., 2014	Both	Current	0.7 (0.6-1.0)	Age, Gender, Occupation, Income, Education, Hypertension, Obesity, Alcohol, Sleep, Stress, Eye Surgery, Thyroid Disease, Rheumatoid Arthritis
Malet *et al*., 2014	Both	Current	0.80 (0.36-1.79)	Age, Gender
		Past	0.82 (0.54-1.24)	
Man *et al*., 2017	Male	Current	1.13 (0.56-2.27)	Age, Income, Contact Lens, Thyroid Disease, Pterygium, Cataract Surgery, Glaucoma
	Female	Current	1.11 (0.16-7.65)	
Alhamyani *et al*., 2017	Both	Current	1.23 (0.55-2.72)	None
Titiyal *et al*., 2018	Both	Current	2.14 (1.6-2.7)	Age, Gender, VDT, Alcohol, Ocular Allergy, Systemic Allergy, Contact Lens, Ocular Surgery
Alshamrani *et al*., 2017	Both	Current	1.40 (1.06-1.85)	Age, Gender, Residence (Urban vs Rural), Trachoma, Work Status, Contact Lens uses
Castro *et al*., 2018	Both	Current	1.44 (0.83-2.48)	None
Kim *et al*., 2019	Both	Current	0.82 (0.56-1.20)	Age, Gender
		Past	0.80 (0.57-1.14)	
Arita *et al*., 2019	Both	Current	0.25 (0.07-0.85)	None
Inomata *et al*., 2020	Both	Current	2.07 (1.49-2.88)	Age, Gender, Contact Len use, Hypertension, Diabetes, Systemic Disease, Eye Surgery
Tandon *et al*., 2020	Both	Current	1.2 (1.0-1.3)	Age, Hypertension, Gender, BMI, Location, Diabetes
Vehof *et al*., 2020	Both	Current	0.87 (0.80-0.94)	Age, Sex, BMI, Ophthalmic Surgery, Systemic Diseases, Diabetes etc.
		Past	1.09 (1.03-1.15)	
Chatterjee *et al*., 2021	Both	Current	1.09 (1.02-1.16)	Age, Gender, VDU, Education, Occupation, Use of Air-conditioning

Note: OR- Odds Ratio; CI- Confidence Interval, VDT-visual display terminal, BMI-Body mass Index

studies that did not analyze smoking as a risk factor were excluded.

Data extraction and quality assessment

Two investigators were independently involved in the extraction of the following information from each included study into Microsoft Excel spreadsheet: first author's name, year of publication, country of study, study design, sample size, mean age, smoking status, number of individuals who are current smokers, adjusted or unadjusted OR with corresponding 95% CI, and adjusted variables. Because only one model could be selected from studies reporting more than one adjustment mode, we selected the model in which the OR values were adjusted to the maximum extent for potentially confounding variables. Study authors were contacted for missing data. The smoking status was classified into three groups: never smoked, former smokers, and current smokers. Former smokers included those who had smoked in a predefined period of time in the past, and current smokers included those who had been smoking for a certain period of time and exceeded a predefined cumulative amount.

Two independent investigators were involved in the quality assessment of the eligible studies using the Joanna Briggs Institute (JBI) Critical Appraisal Checklists adapted for cohort and cross-sectional studies.[17] JBI critical appraisal checklist for cohort studies contains 11 questions, and the checklist for cross-sectional studies contains eight questions. Both checklists assess specific domains of the studies to determine the potential risk of bias that can be answered with yes, no, or unclear. If the answer was yes, the question was assigned a score of 1. If the answer was no, unclear, or not applicable, it was assigned a score of 0. Any disagreements were solved by discussion.

Table 3: JBI risk of bias quality assessment for cohort studies

Author-Year	Man-2017	Moss-2008	Chia - 2003	Moss - 2000
Were the two groups similar and recruited from the same population?	Y	Y	Y	Y
Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Y	Y	Y	Y
Was the exposure measured in a valid and reliable way?	N	N	N	N
Were confounding factors identified?	Y	U	Y	Y
Were strategies to deal with confounding factors stated?	Y	U	Y	Y
Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Y	Y	Y	Y
Were the outcomes measured in a valid and reliable way?	Y	Y	Y	Y
Was the follow-up time reported and sufficient to be long enough for outcomes to occur?	Y	Y	Y	Y
Was follow-up complete, and if not, were the reasons for loss to follow-up described and explored?	Y	Y	Y	Y
Were strategies to address incomplete follow-up utilized?	U	U	U	U
Was appropriate statistical analysis used?	Y	N	Y	Y
Risk of Bias	Low	Moderate	Low	Low

Statistical analysis

All statistical analyses were performed using Stata version 16.0 software (StataCorp, College Station, TX, USA). ORs and confidence intervals (CI) were pooled with DerSimonian and Laird random-effects model. The smoking status was classified into three groups: never smoked, former smokers, and current smokers. Heterogeneities among the included studies were evaluated using Cochran's Q statistic and an I2 index score; $P < 0.10$ and I2 >50% were considered statistically significant. Publication bias was assessed via visual inspection of the funnel plot and Eggers regression test for funnel plot asymmetry for outcomes with more than 10 studies. Subgroup analyses were conducted based on the design of observational studies (cohort study or cross-sectional study), smoking status (current smokers vs. former smokers), adjusted OR versus unadjusted OR, and study region. Forest plots for only adjusted OR are provided as they are more accurate estimates of the true associations. The sensitivity analyses were also performed to examine the influence of each study on the stability of the meta-analysis results. A meta-regression was conducted to analyze the source of heterogeneity. For all analyses, $P < 0.05$ was used as an indicator of statistical significance unless stated otherwise. DED was treated as the outcome measure, whereas cigarette smoking was analyzed as the independent variable.

Results

Study selection

The initial search of the databases yielded 426 articles. After removing duplicates, 341 papers were reviewed based on title and abstract by two independent reviewers. Thirty-nine papers were selected for full-text evaluation, and finally, 22 articles met the inclusion criteria and were eligible to be included in this systematic review and meta-analysis. The flow diagram summarizes the results of the study selection process for this systematic review and meta-analysis [Fig. 1].

Study characteristics

Twenty-two studies involving 160,217 participants were included in this systematic review and meta-analysis. The included observational studies were published between 2000 and 2021. Among the included studies, four were from India,[18-21] five from Japan,[22-26] two each from the US, Saudi Arabia, and Korea,[9,27-31] and one each from China, Brazil, Singapore, Indonesia, Australia, Netherlands, and France.[7,8,32-36] Among included studies, 18 were of cross-sectional and four were of cohort study design. The sample sizes ranged from 482 to 79,481 participants. Seventeen studies provided data only on smokers and non-smokers, while five studies provided data on smokers, non-smokers, and former smokers. Overall, 26,176 (16.9%) of participants were active smokers. Table 1 summarizes the study characteristics of the included studies. Five studies provided crude OR not adjusted for any confounding factors; most other studies were adjusted for age, sex, and other variables. Two articles that included two separate sets of data according to gender were also considered as two separate studies for purpose of this meta-analysis [Table 2]. The quality assessment of the included studies was low to moderate risk of bias [Tables 3 and 4].

Risk of dry eye in current smokers

All 22 studies (18 cross-sectional and four cohort studies) reported 24 separate sets of data on current smokers and the risk of dry eye, but five studies did not adjust the estimate for confounding factors. The confounder adjusted results from 17 studies (14 cross sectional and three cohort) revealed no significant association. [$OR_{adjusted} = 1.14$; 95% CI: 0.95–1.36; $P = 0.15$; $I^2 = 84.6\%$] [Fig. 2]. Sensitivity analysis revealed that none of the study have a significant effect on the overall effect size. Subgroup analysis by study region revealed no significant association of smoking with dry eye in the Asian population [$OR_{adjusted} = 1.16$; 95% CI: 0.94–1.37; $P = 0.16$; $I^2 = 81.2\%$] and non-Asian population [$OR_{adjusted} = 1.08$; 95% CI: 0.72–1.60; $P = 0.72$; $I^2 = 84.6\%$] [Fig. 3]. Additional details of subgroup analyses given in Tables 5 and 6.

Risk of dry eye in formers smokers

Six studies (four cross sectional and two cohort) reported on association between former smokers and dye eye, but one study did not adjust the estimates for confounding factors. The confounder adjusted results from five studies (four

Table 4: Risk of bias assessed by the JBI critical appraisal checklist for analytical cross-sectional studies

Study	Were the criteria for inclusion in the sample clearly defined?	Were the study subjects and the setting described in detail?	Was the exposure measured in a valid and reliable way?	Were objective, standard criteria used for measurement of the condition?	Were confounding factors identified?	Were strategies to deal with confounding factors stated?	Were the outcomes measured in a valid and reliable way?	Was appropriate statistical analysis used?	Risk of Bias
Lee 2003	Y	Y	N	Y	Y	Y	Y	Y	Low
Uchino 2008	Y	Y	Y	Y	Y	Y	Y	Y	Low
Guo 2010	Y	Y	N	Y	Y	Y	Y	Y	Low
Uchino 2011	Y	Y	N	Y	Y	Y	Y	N	Low
Malet 2013	Y	Y	N	Y	Y	Y	Y	Y	Low
Uchino 2013	Y	Y	N	Y	Y	Y	Y	Y	Low
Ahn 2014	Y	Y	U	Y	Y	Y	Y	Y	Low
Alhamyani 2017	Y	Y	N	Y	Y	N	Y	N	Moderate
Alshamrani 2017	Y	Y	N	Y	Y	Y	Y	Y	Low
Titiyal 2017	Y	Y	N	Y	Y	Y	Y	Y	Low
Castro 2018	Y	Y	N	Y	Y	N	Y	N	Low
Arita 2019	Y	Y	Y	Y	N	N	Y	Y	Low
Kim 2019	Y	Y	N	Y	Y	U	Y	Y	Low
Tandon 2020	Y	Y	N	Y	Y	Y	Y	Y	Low
Vehof 2021	Y	Y	N	Y	Y	Y	Y	Y	Low
Chatterjee 2021	Y	Y	N	Y	Y	Y	Y	Y	Low
Inomata 2021	Y	Y	N	U	Y	Y	U	N	Moderate

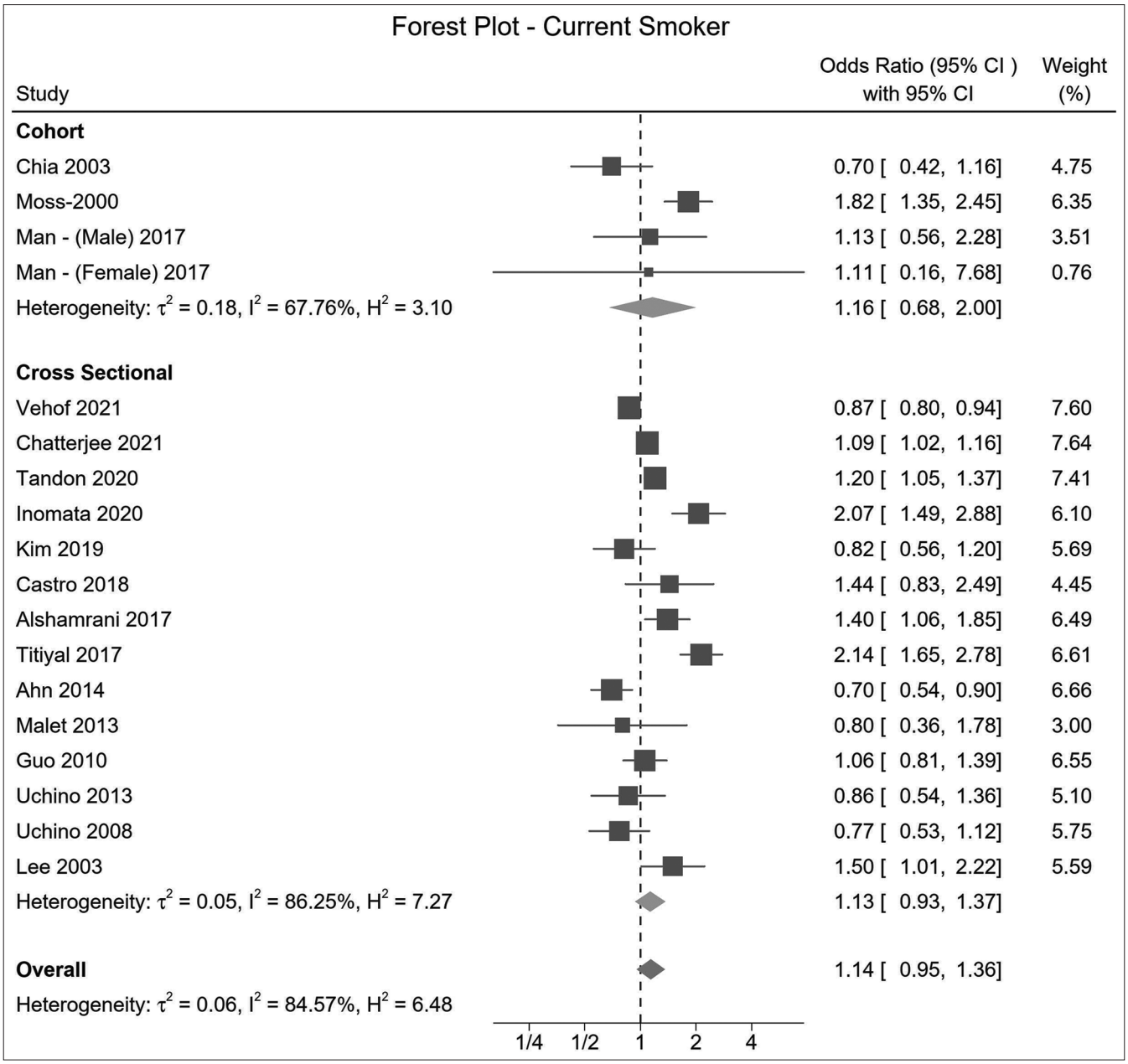

Figure 2: Forest plot of the association between the current smokers and dry eye disease with adjusted odds ratio and corresponding 95% CI

cross-sectional and one cohort) revealed no significant association [$OR_{adjusted}$ = 1.06; 95% CI: 0.93–1.20; *P* = 0.38; I2 = 30.1%] [Fig. 4]. Subgroup analysis by study region revealed no significant association of former smokers with dry eye in the Asian [$OR_{adjusted}$ = 0.87; 95% CI: 0.64–1.20; *P* = 0.41; I^2 = 2.0%] and non-Asian population [$OR_{adjusted}$ = 1.09; 95% CI: 0.97–1.23; *P* = 0.14; I^2 = 27.7] [Fig. 5]. Sensitivity analysis reported that the removal of study by Kim *et al*.[30] increased the overall OR to [1.11;95% CI: 1.05–1.17; *P* < 0.05]. Additional details of subgroup analyses given in Tables 5 and 6.

Risk of dry eye in the general population

Fourteen studies (11 cross-sectional and three cohort) reported on data on the general population. The confounder-adjusted results revealed no significant association. [$OR_{adjusted}$ = 1.13; 95% CI: 0.95–1.30; *P* = 0.17; I^2 = 82.2%] [Fig. 6]. Sensitivity analysis revealed that none of the studies have a significant effect on the overall effect size.

Publication bias and meta-regression

Publication bias was assessed by visual inspection of funnel plot asymmetry [Fig. 7].

Eggers regression for funnel plot asymmetry revealed no risk of publication bias (t = 0.57; *P* = 0.573). A meta-regression analysis was conducted to explore the influence of sample size, publication year, study region, percentage of females, mean age, and percentage of current smokers on the heterogeneity of the included studies, but none of the factors were proven to be the main source of heterogeneity (*P* > 0.05) [Table 7].

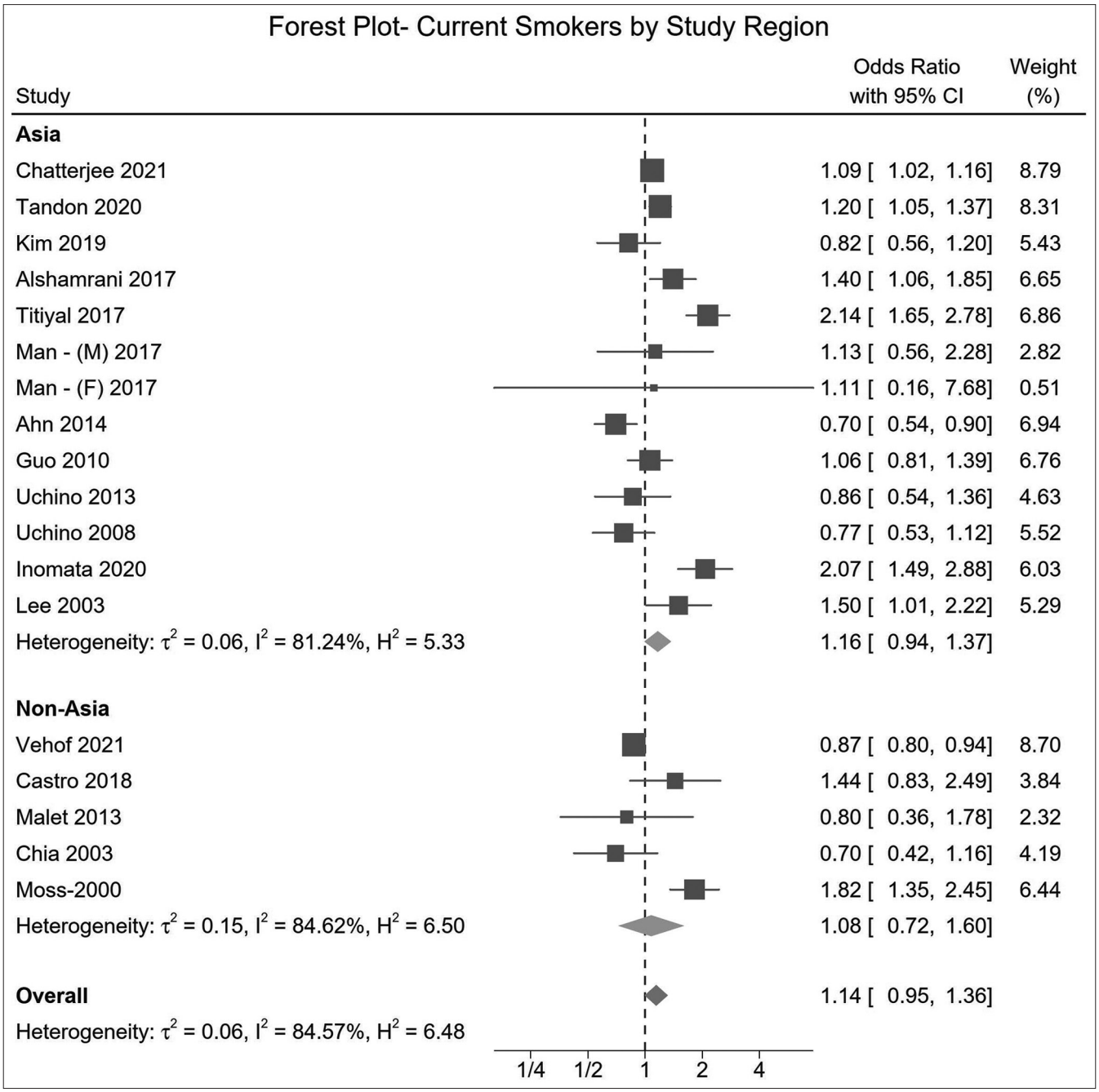

Figure 3: Forest plot of the association between the current smokers and dry eye disease by study region with adjusted odds ratio and corresponding 95% CI

Discussion

Our study aimed to examine the association between smoking and dry eye by conducting a meta-analysis of studies published till August 2021. Studies included in our analysis were very diverse in terms of study design, ethnicity of participants, and number of study participants. The results of this present meta-analysis indicate that current smokers and former smokers do not have an increased risk for DED. This association persisted across subgroups stratified by study design and study region. However, a careful interpretation is required due to the high heterogeneity observed in our result.

Cigarette smoking, an environmental and public health concern, is a complex mixture of hundreds of toxics distributed in the particulate and gaseous phases. The particulate phase is mainly composed of tar and nicotine, while the major components of the gaseous phase are carbon monoxide, carbon dioxide, and nitric oxide. In addition, cigarette smoke contains nitrosamines, polycyclic aromatic hydrocarbons, a wide range of pro-oxidant compounds, and heavy metals such as nickel, cadmium, aluminum, lead, and mercury.[37,38] The volatile fraction of cigarette smoke diffuses across the lung–blood barrier to enter the bloodstream from where it enters the cellular and biochemical transport system and induces

Table 5: Subgroup analysis for the association between smoking and dry eye disease

Subgroup	No. of studies	Overall effect		Heterogeneity		Comments
		OR (95% CI)	P	I^2 (%)	Cochran Q	
Current Smokers						
Cohort + Cross Sectional Studies	22	1.11 [0.98-1.26]	0.108	81.0	121.19	-
Cohort + Cross Sectional Studies	17	1.14 [0.95-1.36]	0.149	84.6	110.15	Adjusted Odds Ratios
Cross Sectional Studies	18	1.11 [0.97-1.27]	0.129	82.7	104.27	-
Cross Sectional Studies	14	1.13 (0.93-1.37)	0.103	86.3	94.57	Adjusted Odds Ratios
Cohort Studies	4	1.08 [0.69-1.69]	0.732	74.5	15.67	-
Cohort Studies	3	1.16 [0.68-2.00]	0.620	67.8	10.63	Adjusted Odds Ratios
Ever Smokers						
Cohort + Cross Sectional Studies	6	1.07 [0.98-1.16]	0.103	13.9	5.81	-
Cohort + Cross Sectional Studies	5	1.06 [0.93-1.20]	0.384	30.10	5.72	Adjusted Odds Ratio
Cross Sectional Studies	4	0.99 [0.83-1.19]	0.931	35.01	4.62	Adjusted Odds Ratio
Cohort Studies	2	1.13 [0.97-1.31]	0.129	0.0	0.92	-
Cohort Studies	1	1.22 [0.97-1.52]	-	-	-	Adjusted Odds Ratio

Table 6: Meta-analysis for association between smoking and dry eye disease by study region

Region	No. of studies	Overall effect		Heterogeneity		Comments
		OR (95% CI)	P	I^2 (%)	Cochran Q	
Current smoker						
Asia	12	1.16 [0.94-1.37]	0.159	81.2	63.97	Adjusted Odds Ratio
Non-Asia	5	1.08 [0.72-1.60]	0.721	84.6	26.01	Adjusted Odds Ratio
Ever Smoker						
Asia	2	0.87 [0.64-1.20]	0.407	2.40	1.02	Adjusted Odds Ratio
Non-Asia	3	1.09 [0.97-1.23]	0.136	27.7	2.76	Adjusted Odds Ratio

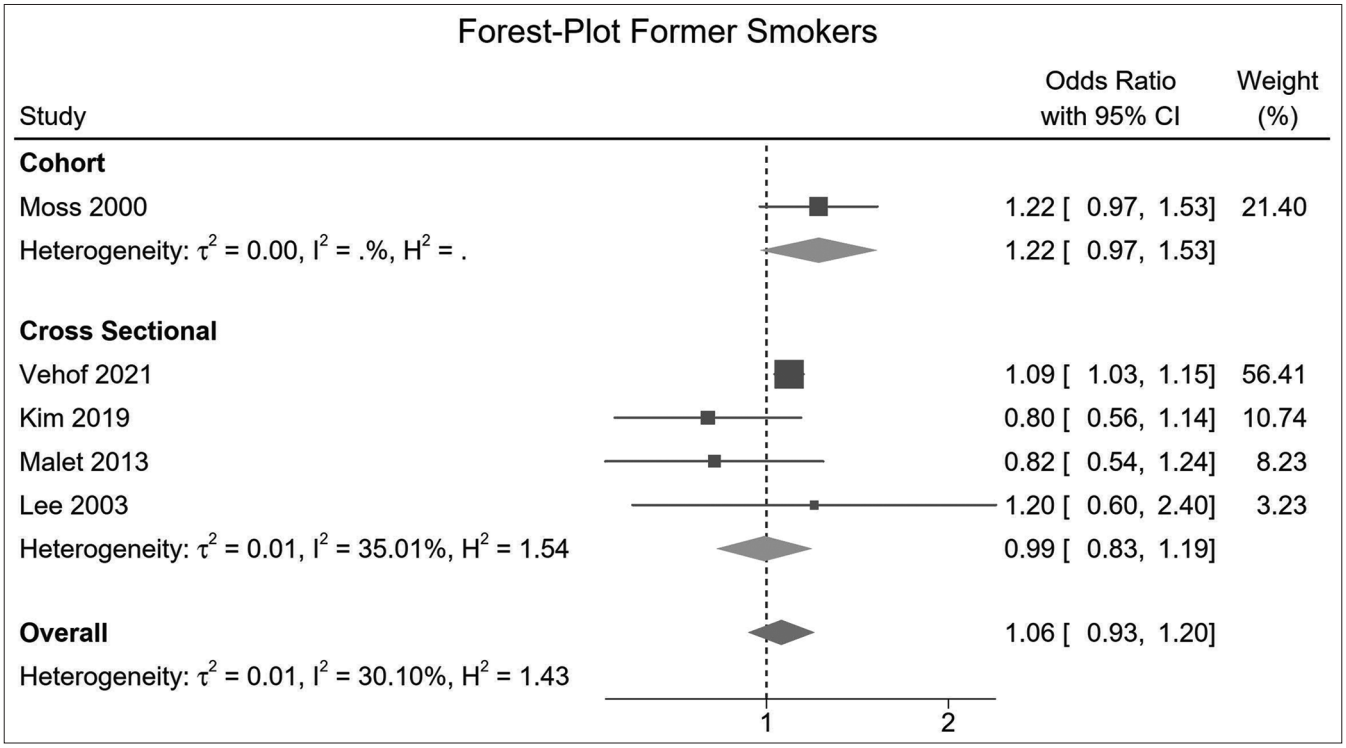

Figure 4: Forest plot of the association between the former smokers and dry eye disease with adjusted odds ratio and corresponding 95% CI

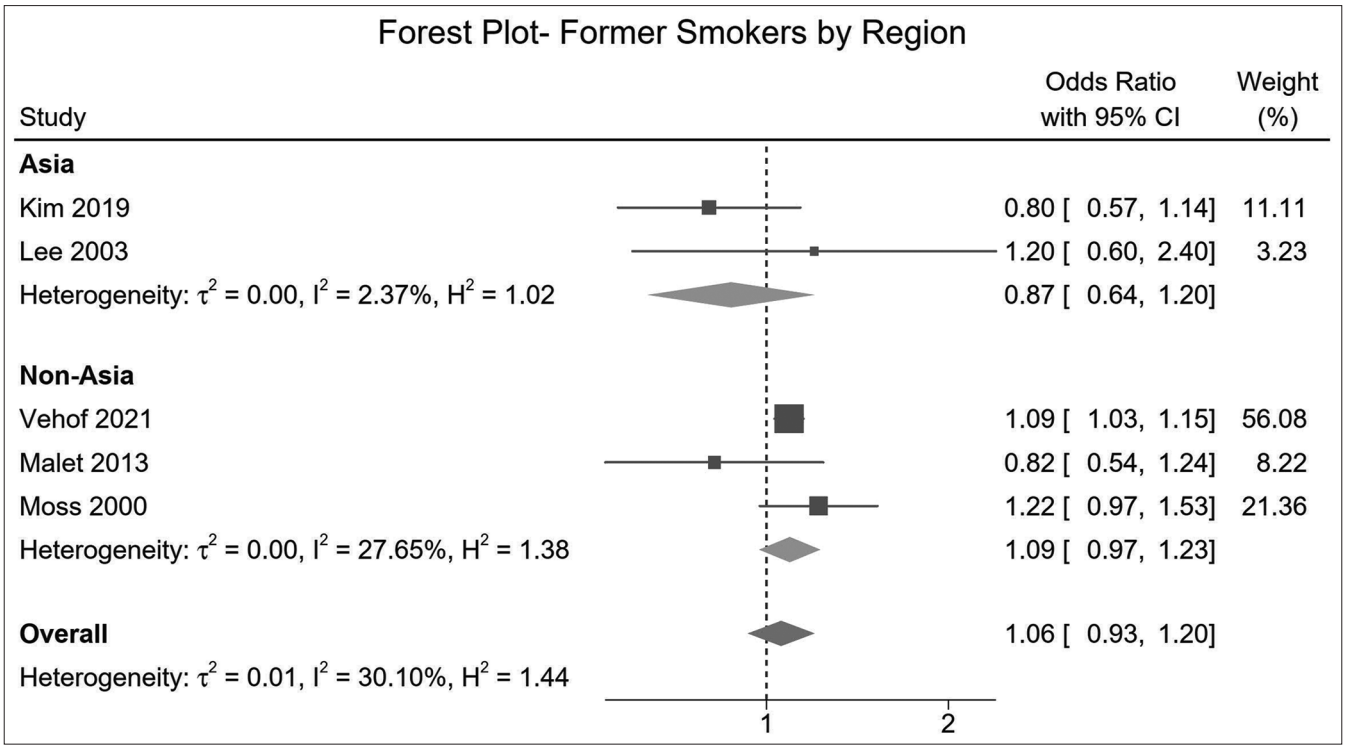

Figure 5: Forest plot of the association between the former smokers and dry eye disease with adjusted odds ratio and corresponding 95% CI

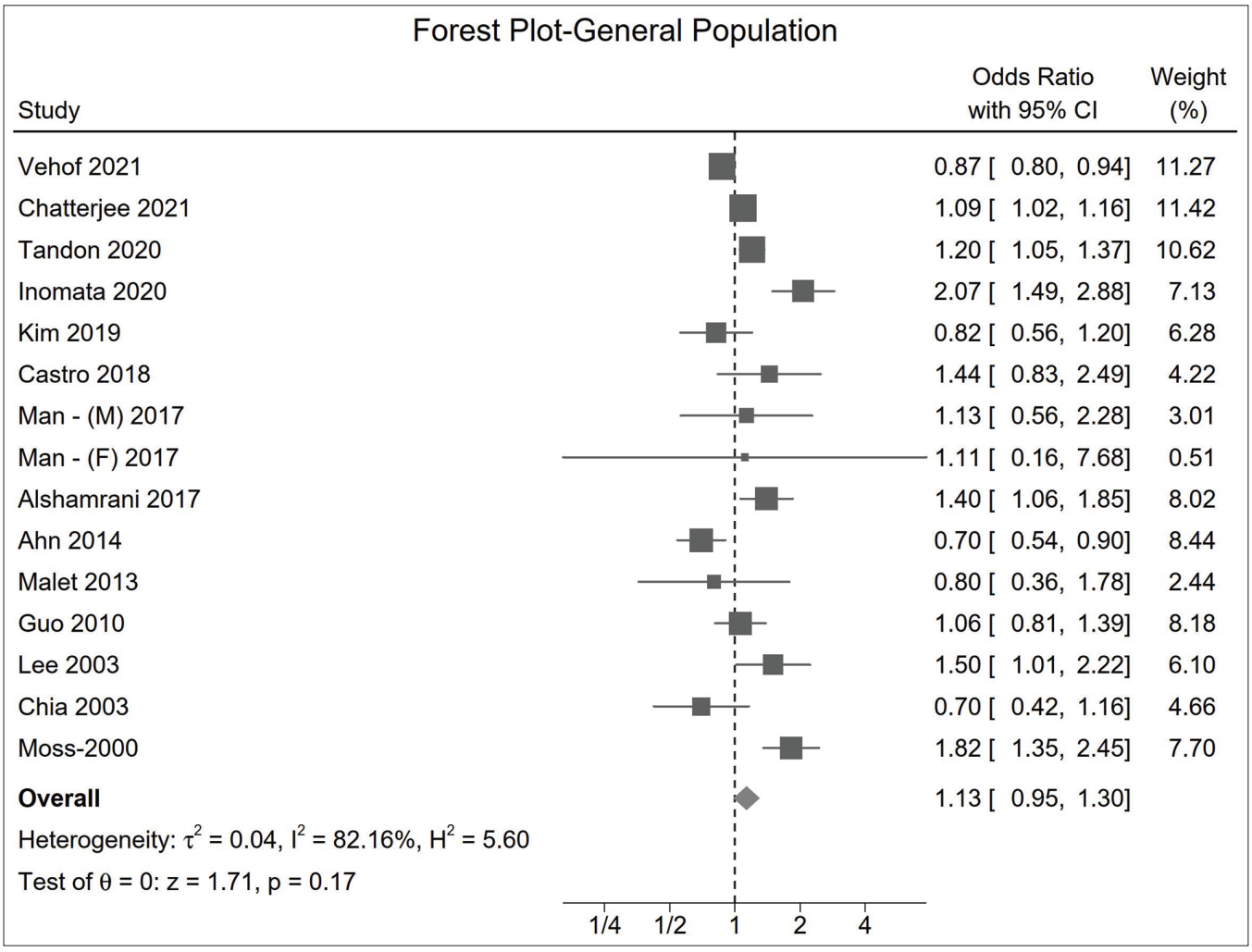

Figure 6: Forest plot of the association between smokers in the general population and dry eye disease with adjusted odds ratio and corresponding 95% CI

Table 7: Meta-regression analysis

Covariate	Coefficient	Standard Error	Z	P
Percentage of Female	0.006	0.073	0.91	0.375
Publication Year	0.001	0.0102	0.12	0.905
Percentage of current smokers	−0.011	0.007	−1.55	0.120
Mean Age	0.009	0.005	1.73	0.102
Study Region	−0.068	0.152	−0.45	0.654
Study Design	0.014	0.176	0.07	0.965

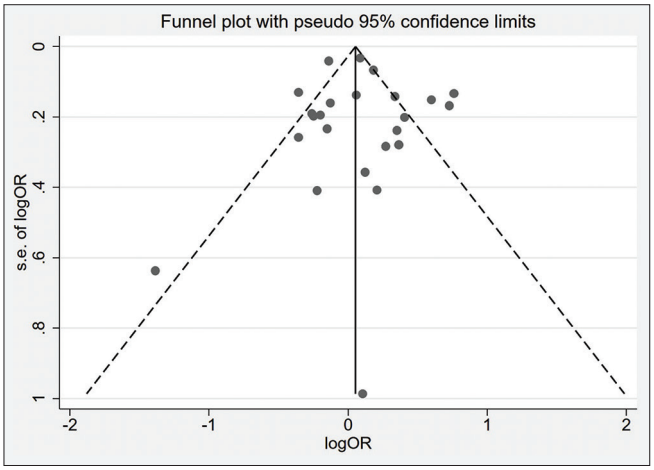

Figure 7: Funnel plot for publication bias analysis

detrimental effects on various organs of the body, including the eye. Multiple studies have confirmed the negative associations of smoking with many commonly encountered ocular diseases such as diabetic retinopathy, age-related macular degeneration, age-related cataract, and glaucoma.[39-42]

Several possible biologic mechanisms have been suggested for the association of smoking with DED. The free radicals and toxins produced by cigarette smoke are reported to affect the normal functionality of the ocular cells by promoting ischemia, hypoxia, and increasing the risk of microinfarction within ocular capillaries, thus preventing the flow of essential nutrients needed for normal eye physiology.[43,44] The lipids, aqueous, and mucin components of the tear film contributes toward the even distribution of tear film over the corneal surface, and help to maintain its homeostatic balance of the film leading to its integrity and stability, allowing the tear film to perform functions as lubrication, nutrition, and protection of the ocular surface.[45,46] The direct contact of fumes from burning cigarettes causes lipid peroxidation of the outer lipid layer of the precorneal tear film, resulting in tear film instability, decreasing lipid layer thickness, and breakdown of tear film leading to rapid tear film evaporation rate, thus contributing to symptoms of dry eye.[47]

Numerous studies have assessed tear-breakup time (TBUT), a measure of tear film stability, among smokers and non-smokers and have reported significantly lower TBUT values in smokers, signifying tear film instability among smokers.[10,11,48] Few studies have observed a remarkably higher rate of squamous metaplasia in conjunctival impression cytology among smokers.[49,50] In addition, it has been suggested that cigarette smoking leads to disturbances in the immune system, affecting the innate and adaptive immune response by altering the circulating levels of pro-inflammatory and anti-inflammatory cytokines and growth factors.[51,52] Studies have demonstrated smoking increases the production of proinflammatory cytokines such as tumor necrosis factor (TNF) alpha, interleukin (IL)-1, IL-6, IL-8, and granulocyte-macrophage colony-stimulating factor (GM-CSF), while decreasing the production of anti-inflammatory cytokines such as IL-6, IL-10, IL-1b, IL-2, and interferon-gamma (IFN-γ).[53] Such changes can trigger inflammatory reactions within the meibomian gland, leading to meibomian gland disorder, the leading cause of DED.

Two well-known population-based longitudinal studies in our meta-analysis presented conflicting reports regarding this association in current smokers. The Blue Mountains Eye Study studied the association of dry eye and smoking in 1174 adults, with a mean age of 60.8 years, reported a decreased prevalence of dry eye among smokers.[7] On the contrary, the Beaver Eye Dam Eye study with a participant size of 3722 with a 5-year follow-up examination reported a nearly 2 fold increase in the odds of dry eye in current smokers.[9] However, both studies used subjective self-reported questionnaires to determine the presence of dry eye and did not utilize objective tests such as Schimmer Test, fluorescein, or rose Bengal staining, and TBUT. A more recent Singapore Malay Eye cohort study in Asian Malays with a mean age of 57 years reported no significant association among the smokers for DED.[36] Similar conclusions have been reported in many cross-sectional studies conducted over the years. Interestingly, the results from Korea National Health and Nutrition Examination Survey (KNHANES) V and the Lifelines study from the Netherlands, with a combined sample size of 91,147 participants, which is larger than all other studies combined, suggest a protective role of smoking in DED which can be potentially mediated by a reduced sensitivity of ocular disease.[31,35] This highlights the need for more studies to examine this potential association. Among the included studies, five studies reported on the association of dry eye with individuals who used to smoke previously. Overall, no association was observed in our analysis; however, the Lifelines study with 79,866 participants reported a significant increase in dry eye among former smokers. This unexpected association demonstrates that the protective effect of smoking on dry eye disappears on cessation of smoking; a similar finding was observed in the Blue Mountains eye study indicating that the participants who quit smoking were more likely to suffer from a dry eye symptom by a odds of 1.22 compared to non-smokers. Further efforts should be made to study the biological

mechanism for this possible association. A previously published meta-analysis by Xu *et al*.[15] involving ten studies with 19,013 participants reported similar results as ours, but that study was limited by the number of studies included. In addition, it reported that smoking leads to a risk of DED in the general population. However, our analysis demonstrates no significant association of dry eye among smokers in the general population.

To interpret our study results properly, it is necessary to understand several limitations. First, only English-language articles that had been published were included. This may introduce language bias in our study as studies in other languages were excluded. Second, smoking status misclassification is another potential source of bias. The smoking data were self-reported in all included studies, inducing the potential for measurement bias. Patients may underestimate or under-report their smoking habits, resulting in misclassification of exposure status and inducing bias in estimates. Third, the association between the risk of DED and exposure level of cigarettes could not determine the dose-response relationship due to the lack of relevant data in the included studies. Fourth, the differences in study methodological and methods to adjust for confounders in original studies could lead to bias in our study. Finally, significant heterogeneity was detected by means of Cochran's Q statistic and I^2 index among the included studies in this meta-analysis but could not be explained by the means of a meta-regression analysis, thus highlighting the need for standardized methodologies in future studies. Some strengths of our study include the following: meta-analysis conducted in accordance to MOOSE guidelines, subgroup analysis by study design, and adjustment of confounders and study region were performed in addition to sensitivity analysis to increase the robustness and reliability of our findings. The sample sizes of most studies were large, and the cohort studies reported long follow-up periods of at least 5 years. Egger regression asymmetry test suggested no evidence of publication bias in our study. Our conclusions are based on estimates from studies that were all adjusted for age and gender, the most common risk factor for DED.

Conclusion

In conclusion, our results indicate that smoking may not be involved in the risk of DED. Due to conflicting evidence, a consensus has yet to be reached as to the effect of smoking on the risk of DED. Although some recent studies have reported a protective effect of smoking on DED, the overall damage to health from smoking outweighs the protective effect on DED by continued smoking. Ultimately, further investigations clarifying the causality between smoking and DED are warranted.

Author contributions

MAT and HA conceptualized the study and drafted the manuscript. BA and UA were involved in the acquisition of the data through literature search. MAT and AM performed data analysis. All of the authors approve the final manuscript.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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