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 I² 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\textsubscript{adjusted} = 1.14; 95% CI: 0.95–1.36; \textit{P} = 0.15; I² = 84%) and former smokers (OR\textsubscript{adjusted} = 1.06; 95% CI: 0.93–1.20; \textit{P} = 0.38; I² = 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 (\textit{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 former smokers with DED are recommended.

Key words: Cigarette smoking, dry eye disease, meta-analysis, smoking

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.\[^{[3]}\]

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.\[^{[5]}\] 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. 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          | 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          | 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           | China            | Cross Sectional | 2112   | 54.8        | 1125/987           | NA                        | Current Smoker/Non-smokers                | General Population |
| Uchino et al. 2011        | Japan            | Cross Sectional | 2644   | >40         | 1221/1423          | 441                       | Current Smoker/Non-smokers                | General Population |
| Uchino et al. 2013        | Japan            | Cross Sectional | 561    | 43.3        | 374/187            | 110                       | Current Smoker/Non-smokers                | Office Workers using VDT |
| Ahn et al. 2014           | Korea            | Cross Sectional | 11666  | 49.9        | 4993/6673          | 4480                      | Current Smoker/Non-smokers                | General Population |
| Malet et al. 2014         | France           | Cross Sectional | 963    | 80          | 354/561            | 45                        | Current Smokers/Former Smokers/Non-smokers | General Population |
| Man et al. 2017           | 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 |
| Alishamrani et al. 2017   | Saudi Arabia     | 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         | 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        | India            | Cross Sectional | 9735   | 54.5        | 4429/5306          | 3584                      | Current Smoker/Non-smokers                | General Population |
| Vehof et al. 2020         | 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 (0.53-1.5)      | 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 |
| Titiyai 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, 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. 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 former 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       |
| Al shamrani 2017    | Y                                                             | Y                                                           | N                                                      | Y                                                                      | Y                                   | Y                                                       | Y                                                      | Y                                                    | Low            |
| Tityal 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                                                      | N                                                                      | 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       |
cross-sectional and one cohort) revealed no significant association \([\text{OR}_{\text{adjusted}} = 1.06; 95\% \text{ CI}: 0.93-1.20; P = 0.38; I^2=30.1\%]\) [Fig. 4]. Subgroup analysis by study region revealed no significant association of former smokers with dry eye in the Asian \([\text{OR}_{\text{adjusted}} = 0.87; 95\% \text{ CI}: 0.64-1.20; P = 0.41; I^2=2.0\%]\) and non-Asian population \([\text{OR}_{\text{adjusted}} = 1.09; 95\% \text{ CI}: 0.97-1.23; P = 0.14; I^2=27.7\%]\) [Fig. 5]. Sensitivity analysis reported that the removal of study by Kim et al.\(^{29}\) increased the overall \(\text{OR} = [1.11, 95\% \text{ CI}: 1.05-1.17; P < 0.05]\). 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 data on the general population. The confounder-adjusted results revealed no significant association. \(\text{OR}_{\text{adjusted}} = 1.13; 95\% \text{ CI}: 0.95-1.30; P = 0.17; I^2=82.2\%\) [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].
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. 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             | I2 (%) | 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    |
| 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     |
| 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     |

| 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      |
| Cross Sectional Studies                       | 4              | 0.99 [0.83-1.19] | 0.931         | 35.01  | 4.62      |
| Cohort Studies                                | 2              | 1.13 [0.97-1.31] | 0.129         | 0.0    | 0.92      |
| Cohort Studies                                | 1              | 1.22 [0.97-1.52] | -             | -      | -         |

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             | I2 (%) | Cochran Q |
| Current smoker   |                |               |               |          |           |
| Asia             | 12             | 1.16 [0.94-1.37] | 0.159         | 81.2   | 63.97     |
| Non-Asia         | 5              | 1.07 [0.72-1.60] | 0.721         | 84.6   | 26.01     |
| Ever Smoker      |                |               |               |          |           |
| Asia             | 2              | 0.87 [0.64-1.20] | 0.407         | 2.40   | 1.02      |
| Non-Asia         | 3              | 1.09 [0.97-1.23] | 0.136         | 27.7   | 2.76      |

Forest-Plot Former Smokers

| Study               | Odds Ratio with 95% CI | Weight (%) |
|---------------------|------------------------|------------|
| Cohort              |                        |            |
| Moss 2000           | 1.22 [ 0.97, 1.53]     | 21.40      |
| Heterogeneity: $\tau^2 = 0.00$, $I^2 = .\%$, $H^2 = .\%$ | 1.22 [ 0.97, 1.53] |            |
| Cross Sectional     |                        |            |
| Vehof 2021          | 1.09 [ 1.03, 1.15]     | 56.41      |
| Kim 2019            | 0.80 [ 0.56, 1.14]     | 10.74      |
| Malet 2013          | 0.82 [ 0.54, 1.24]     | 8.23       |
| Lee 2003            | 1.20 [ 0.60, 2.40]     | 3.23       |
| Heterogeneity: $\tau^2 = 0.01$, $I^2 = 35.01\%$, $H^2 = 1.54$ | 0.99 [ 0.83, 1.19] |            |
| Overall             |                        |            |
| Heterogeneity: $\tau^2 = 0.01$, $I^2 = 30.10\%$, $H^2 = 1.43$ | 1.06 [ 0.93, 1.20] |            |

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

| Study       | Odds Ratio with 95% CI | Weight (%) |
|-------------|------------------------|------------|
| Vehof 2021  | 0.87 [0.73, 1.04]      | 59.66      |
| Malet 2013  | 0.82 [0.64, 1.04]      | 8.22       |
| Moss 2000   | 1.22 [0.97, 1.53]      | 21.36      |

Heterogeneity: $\tau^2 = 0.00, I^2 = 27.65\%, H^2 = 1.38$

Overall
Heterogeneity: $\tau^2 = 0.01, I^2 = 30.10\%, H^2 = 1.44$

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

| Study       | Odds Ratio with 95% CI | Weight (%) |
|-------------|------------------------|------------|
| Vehof 2021  | 0.87 [0.80, 0.94]      | 11.27      |
| Chatterjee 2021 | 1.09 [1.02, 1.16] | 11.42      |
| Tandon 2020 | 1.20 [1.05, 1.37]      | 10.62      |
| Inomata 2020 | 2.07 [1.64, 2.88]  | 7.13       |
| Kim 2019    | 0.82 [0.56, 1.20]      | 6.28       |
| Castro 2018 | 1.44 [1.03, 2.00]      | 4.22       |
| Man - (M) 2017 | 1.13 [0.83, 1.56] | 3.01       |
| Man - (F) 2017 | 1.11 [0.81, 1.60] | 0.51       |
| Alshamrani 2017 | 1.40 [0.96, 1.84] | 8.02       |
| Ahn 2014    | 0.70 [0.54, 0.90]      | 8.44       |
| Malet 2013  | 0.80 [0.56, 1.26]      | 2.44       |
| Guo 2010    | 1.06 [0.81, 1.39]      | 8.18       |
| Lee 2003    | 1.50 [1.01, 2.22]      | 6.10       |
| Chia 2003   | 0.70 [0.42, 1.16]      | 4.66       |
| Moss-2000   | 1.82 [1.35, 2.45]      | 7.70       |

Overall
Heterogeneity: $\tau^2 = 0.04, I^2 = 82.16\%, H^2 = 5.60$

Test of $\theta = 0$: z = 1.71, p = 0.17
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. 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. The lipids, aqueous, and mucin components of the tear film contribute 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. The direct contact of fumes from burning cigarettes causes lipoxidation 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.

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 |

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. On the contrary, the Beaver 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. 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. 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. 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. 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 methodologies 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 P 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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Conflicts of interest
There are no conflicts of interest.

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