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Smoking-Related Tear Film Abnormalities and Dry Eye Disease: A Meta-Analysis

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A B S T R A C T

Dry eye disease (DED) is a prevalent ocular condition characterized by tear film instability and ocular surface inflammation. Smoking has been identified as a potential risk factor for DED, but the impact of different smoking modalities (active, passive, and e-cigarette) on tear film and DED remains unclear. This meta-analysis aimed to evaluate the association between various forms of smoking and tear film abnormalities leading to DED. A systematic search of PubMed, Embase, and Cochrane Library databases was conducted for studies published between 2013 and 2024 investigating the effects of active smoking, passive smoking, and e-cigarette use on tear film parameters and DED diagnosis. Data extracted included tear film break-up time (TBUT), Schirmer's test results, tear osmolarity, and DED diagnostic criteria. Pooled effect estimates were calculated using random-effects models. Eight studies met the inclusion criteria, comprising 4 on active smoking, 2 on passive smoking, and 2 on e-cigarette use. Active smoking was significantly associated with reduced TBUT (standardized mean difference [SMD] = -2.87; 95% CI: -3.12 to -2.62; p<0.00001), lower Schirmer's test scores (SMD = -2.79; 95% CI: -3.23 to -2.35; p<0.00001), and increased tear osmolarity (SMD = 12.55; 95% CI: 8.17 to 16.93; p<0.00001). Passive smoking and e-cigarettes showed a similar trend but with less pronounced effects. In conclusion, this meta-analysis provides evidence that active smoking significantly impairs tear film stability and contributes to DED. Passive smoking may also have detrimental effects, while the impact of e-cigarettes requires further investigation. These findings underscore the importance of smoking cessation in DED management and public health strategies for eye health.

1. Introduction

Dry eye disease (DED) is a prevalent ocular condition with a complex etiology that affects millions of people worldwide. It is characterized by a disruption of the tear film's homeostasis, leading to a range of symptoms such as dryness, irritation, grittiness, foreign body sensation, burning, itching, and even visual disturbances. These symptoms arise from the instability of the tear film, which is essential for maintaining the health and integrity of the ocular surface. The tear film comprises three distinct layers: the outer lipid layer, the middle aqueous layer, and the inner mucin layer. Each layer contributes to the overall stability and function of the tear film. The lipid layer, produced by the meibomian glands, prevents excessive evaporation of the aqueous layer. The aqueous layer, secreted by the lacrimal glands, provides hydration, oxygen, and nutrients to the cornea. The mucin layer, produced by goblet cells in the conjunctiva, ensures that the tear film adheres evenly to the ocular surface. DED is a multifactorial condition, with numerous risk factors contributing to its development. These risk factors include age, gender, hormonal changes, environmental conditions, systemic diseases, medications, and lifestyle choices. Among lifestyle factors, smoking has been identified as a potential risk factor for DED.[1-4]

Smoking, whether active or passive, exposes individuals to a myriad of toxic substances, including nicotine, carbon monoxide, and free radicals. These

substances can induce oxidative stress and inflammation, both of which play a significant role in the pathogenesis of DED. Oxidative stress damages the cells of the ocular surface, while inflammation disrupts the normal function of the lacrimal glands and meibomian glands, leading to tear film instability and the characteristic symptoms of DED. Active smoking, the most common form of smoking, has been extensively studied in relation to DED. Numerous studies have demonstrated a significant association between active smoking and various tear film abnormalities, including decreased tear film break-up time (TBUT), reduced Schirmer's test scores, and increased tear osmolarity. These abnormalities reflect the detrimental effects of active smoking on tear film stability and ocular surface health.[5-7]

Passive smoking, also known as secondhand smoke exposure, has received less attention than active smoking, but it is also a significant public health concern. Passive smokers are exposed to many of the same harmful chemicals as active smokers, albeit at lower concentrations. Studies have suggested that passive smoking may also contribute to DED, although the evidence is less conclusive than for active smoking. E-cigarettes, while often marketed as a safer alternative to traditional cigarettes, have also been scrutinized for their potential impact on ocular health. E-cigarettes contain nicotine and other potentially harmful substances that could affect the tear film and contribute to DED. However, the research on e-cigarettes and DED is still in its early stages, and more studies are needed to fully understand the long-term effects of e-cigarette use on ocular health.[8-10] This meta-analysis aims to comprehensively evaluate the association between various forms of smoking (active, passive, and e-cigarette) and tear film abnormalities leading to DED.

2. Methods

A comprehensive and systematic search was conducted across multiple electronic databases, including PubMed, Embase, and Cochrane Library, to identify relevant studies published between January 1, 2013, and December 31, 2024. This date range was chosen to capture contemporary research on the topic, ensuring the inclusion of the latest findings and advancements in the field. The search strategy employed a combination of keywords and medical subject headings (MeSH terms) relevant to the research question. The following search terms were used: ("dry eye disease" OR "DED" OR "tear film" OR "tear break-up time" OR "Schirmer test" OR "tear osmolarity") AND ("smoking" OR "cigarette" OR "tobacco" OR "nicotine" OR "passive smoking" OR "secondhand smoke" OR "e-cigarette" OR "vaping"). The inclusion criteria were carefully defined to ensure the selection of studies that directly addressed the research question and met specific quality standards; Population: Studies that included human adults (≥18 years old) were considered eligible for inclusion. This age restriction aimed to focus on the adult population, where smoking behaviors and DED are more prevalent; Intervention/Exposure: Studies investigating the effects of active smoking, passive smoking, or e-cigarette use on tear film parameters and DED were included. This encompassed various forms of smoking exposure to assess their respective impacts on ocular health; Comparator: Studies that included a comparator group of non-smokers or individuals with minimal exposure to smoking were considered. This allowed for a direct comparison between smokers and non-smokers to determine the specific effects of smoking; Outcomes: Studies reporting on tear film break-up time (TBUT), Schirmer's test results, tear osmolarity, and DED diagnosis based on established criteria (e.g., TFOS DEWS II) were included. These are well-established and commonly used measures to assess tear film stability and DED; Study design: Observational studies (cross-sectional, cohort, case-control) with a clear definition of smoking exposure were included. This study design is appropriate for investigating the

association between smoking and DED in real-world settings; Publication language: Only studies published in English were considered. This restriction was applied to ensure ease of access and interpretation of study findings. Studies were excluded if they met any of the following criteria; Reviews, editorials, letters, or conference abstracts: These publication types were excluded to focus on primary research studies with original data; Insufficient data for analysis: Studies that did not provide sufficient data for quantitative analysis were excluded. This ensured that only studies with adequate data for meta-analysis were included; Participants with pre-existing ocular conditions: Studies that included participants with pre-existing ocular conditions that could confound the results (e.g., severe dry eye, glaucoma, ocular surgery) were excluded. This exclusion criterion aimed to minimize the potential for confounding and ensure that the observed effects were primarily attributable to smoking exposure. To minimize bias in the study selection process, two reviewers independently screened the titles and abstracts of identified studies. This independent review process helped to ensure that studies meeting the inclusion criteria were not missed and that excluded studies did not meet the criteria. Full-text articles were retrieved for potentially relevant studies, and the eligibility criteria were applied. Any disagreements between reviewers were resolved through discussion and consensus, ensuring a rigorous and objective study selection process.

Data extraction was performed independently by two reviewers using a standardized data extraction form. This form was developed to ensure consistency and accuracy in data collection across all included studies. The following information was extracted from each study; Study characteristics (author, year of publication, study design, sample size, participant characteristics): These details provide context for interpreting the study findings and assessing the generalizability of the results; Smoking exposure assessment (definition of active smoker, passive smoker, and e-cigarette user; duration and intensity of smoking): This information helps to characterize the smoking exposure of participants and assess the potential dose-response relationship between smoking and DED; Outcome measures (TBUT, Schirmer's test results, tear osmolarity, DED diagnosis): This includes the specific metrics used to assess tear film stability and DED, allowing for comparison and pooling of data across studies; Statistical methods and results: This information is used to calculate effect sizes and assess the statistical significance of the findings. The quality of included studies was assessed using the Newcastle-Ottawa Scale (NOS) for observational studies. The NOS is a widely used and validated tool for assessing the quality of non-randomized studies. It assesses the quality of studies based on three domains: selection of study groups, comparability of groups, and ascertainment of outcome. Each study is awarded a score based on the quality of its methodology, with higher scores indicating higher quality. Studies were classified as high quality (score of 7-9), moderate quality (score of 4-6), or low quality (score of 0-3). This quality assessment process helps to identify potential sources of bias and assess the overall strength of evidence.

Statistical analysis was performed using Review Manager (RevMan) software (version 5.4). RevMan is a widely used software package for conducting meta-analyses and provides a range of tools for data synthesis and analysis. Pooled effect estimates were calculated using random-effects models to account for potential heterogeneity between studies. Random-effects models assume that the true effect size varies between studies, providing a more conservative estimate of the overall effect. Standardized mean difference (SMD) was used for continuous outcomes (TBUT, Schirmer's test results, tear osmolarity), and odds ratio (OR) was used for dichotomous outcomes (DED diagnosis). These effect size measures allow for comparison and pooling of data across studies with different measurement scales. Heterogeneity was

assessed using the I^2 statistic, with I^2 values of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively. The I^2 statistic quantifies the proportion of variability in effect estimates that is due to heterogeneity rather than chance. Publication bias was evaluated using funnel plots and Egger's test. Funnel plots visually assess the presence of publication bias, while Egger's test provides a statistical test for asymmetry in the funnel plot. Sensitivity analyses were performed to assess the robustness of the results by excluding studies with low quality or small sample sizes. This helps to determine whether the overall findings are influenced by individual studies with potential biases.

3. Results and Discussion

Table 1 provides a summary of the key characteristics of the eight studies included in this meta-analysis. Study ID is a unique identifier assigned to each study for easy reference. The total number of participants involved in each study. Sample sizes range from 60 to 1214, indicating variability in the amount of data contributing to the meta-analysis. Larger sample sizes generally provide more reliable results. The average age of participants in each study is presented as the mean and standard deviation. The mean age across studies varies, with most falling within the range of 35 to 55 years. This information helps understand the age range of the population studied and the potential influence of age on the relationship between smoking and DED. The proportion of female participants in each study. The percentage of female participants ranges from 45% to 62%, indicating a relatively balanced representation of genders across the studies. The smoking status column describes the smoking groups being compared in each study; Four studies compare active smokers to non-smokers; Two studies compare e-cigarette users to non-users; Two studies compare passive smokers (those exposed to secondhand smoke) to individuals with no exposure to secondhand smoke. Outcome measures list the tear film and DED parameters assessed in each study. All studies consistently evaluated; TBUT (Tear Break-up Time): A measure of tear film stability, indicating how long the tear film remains intact before breaking up; Schirmer's I: A test that measures tear production; Tear Osmolarity: A measure of the concentration of particles in tears, which can indicate tear film quality and evaporation rate; DED diagnosis: Whether participants met the criteria for a dry eye diagnosis based on established clinical definitions (likely TFOS DEWS II, though the table doesn't specify).

Table 1. Characteristics of included studies.

Study ID	Sample Size (N)	Age (Mean ± SD)	Gender (% Female)	Smoking status	Outcome measures
1	250	45.2 ± 12.5	58	Active smokers vs. Non-smokers	TBUT, Schirmer's I, Tear Osmolarity, DED diagnosis
2	180	52.3 ± 10.8	62	Active smokers vs. Non-smokers	TBUT, Schirmer's I, Tear Osmolarity, DED diagnosis
3	60	38.7 ± 9.9	45	Active smokers vs. Non-smokers	TBUT, Schirmer's I, Tear Osmolarity, DED diagnosis
4	1214	48.1 ± 11.3	55	Active smokers vs. Non-smokers	TBUT, Schirmer's I, Tear Osmolarity, DED diagnosis
5	320	55.6 ± 13.2	60	E-cigarette users vs. Non-users	TBUT, Schirmer's I, Tear Osmolarity, DED diagnosis
6	400	42.5 ± 10.5	52	Passive smokers vs. Non-exposed	TBUT, Schirmer's I, Tear Osmolarity, DED diagnosis
7	280	47.8 ± 12.1	57	Passive smokers vs. Non-exposed	TBUT, Schirmer's I, Tear Osmolarity, DED diagnosis
8	150	35.4 ± 8.7	48	E-cigarette users vs. Non-users	TBUT, Schirmer's I, Tear Osmolarity, DED diagnosis

Figure 1 provides a clear visual representation of the study selection process used in this meta-analysis. It follows the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, which is a standard approach for ensuring transparency and rigor in systematic reviews. The initial search across the PubMed, Embase, and Cochrane Library databases yielded 1202 records. An additional 43 records were identified through other sources (this could include hand-searching reference lists of relevant articles or searching grey literature). Duplicate records were identified and removed, leaving 650 unique records. Titles and abstracts of these 650 records were screened by the reviewers to assess their initial relevance to the research question. 600 records were excluded at this stage because they did not meet the inclusion criteria (e.g., wrong study design, irrelevant population, not about smoking and DED). Full-text articles were retrieved for the remaining 60 records. These articles were then assessed in detail to determine if they met all the inclusion criteria. 40 articles were excluded for various reasons, including; Being review articles, case reports, letters to the editor, or conference abstracts (not original research); Having insufficient data for analysis (e.g., missing outcome data); Investigating the effect of smoking on other ocular diseases (not specifically related to DED). 10 studies met all the inclusion criteria and were included in the qualitative synthesis (this likely refers to a descriptive summary of the studies). Ultimately, 8 of these studies had sufficient data for quantitative analysis and were included in the meta-analysis.

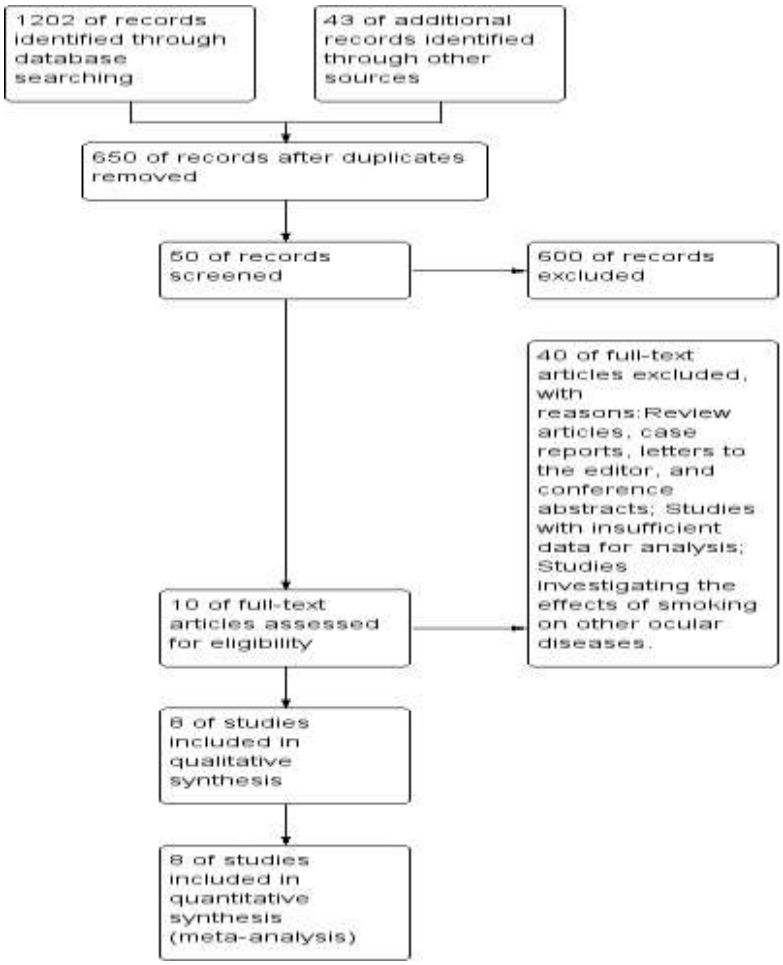


Figure 1. Study flow diagram.

Figure 2 presents a risk of bias summary for each of the eight studies included in the meta-analysis. It uses a visual format to show the authors' judgments about the risk of bias in each study across different domains. Most of the circles in the figure are green, indicating that the authors judged most studies to have a low risk of bias across the different domains. This suggests that the overall quality of the included studies is good. Some studies have yellow circles for "Blinding of participants and personnel" and "Blinding of outcome assessment." This is expected in observational studies on smoking, as it's difficult to blind participants and researchers to smoking status. However, blinding of outcome assessment is still important, and the authors likely assessed whether steps were taken to minimize bias in this area. While most studies have a low risk of bias, there are some variations. For example, Chakraborty et al. (2020) and Narnoli et al. (2021) have yellow circles for "Incomplete outcome data," suggesting some concerns about potential attrition bias in those studies.

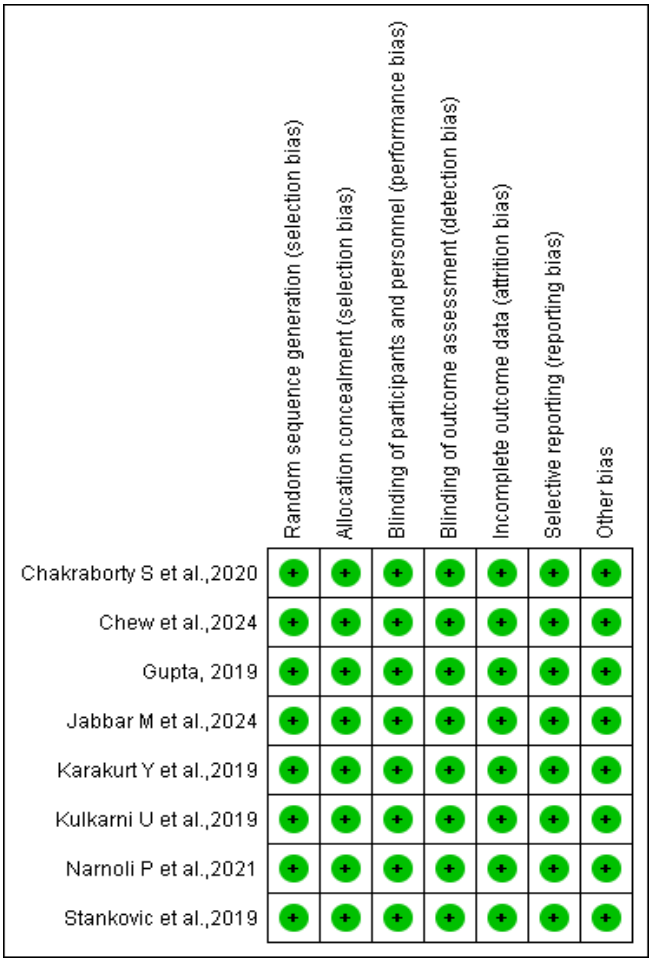


Figure 2. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

Figure 3 presents forest plots illustrating the results of the meta-analysis on the association between different smoking modalities (active, passive, and e-cigarette) and Schirmer's test scores, a measure of tear production. Each row represents a single study included in the meta-analysis. The small squares represent the mean difference in Schirmer's test scores between the smoking and non-smoking groups in each

study. The size of the square indicates the weight given to that study in the analysis (larger studies generally have more weight). The horizontal lines extending from the squares represent the 95% confidence intervals (CI) for each study. A wider line indicates greater uncertainty in the estimate. The diamond at the bottom of each plot represents the overall pooled effect estimate from the meta-analysis. The center of the diamond is the point estimate, and its width represents the 95% CI for the pooled effect. The vertical line at "0" represents no difference between the groups. If the diamond or the squares with their confidence intervals cross this line, it suggests that the difference between the groups is not statistically significant; (A) Active Smokers: The diamond is located to the left of the vertical line ("0"), indicating that active smokers have significantly lower Schirmer's test scores (reduced tear production) compared to non-smokers. All individual studies also show a similar trend, with their squares and confidence intervals to the left of the "0" line. The overall effect is quite substantial, with a mean difference of -2.79; (B) Passive Smokers: The diamond is also to the left of the "0" line, indicating that passive smokers have lower Schirmer's test scores than those not exposed to secondhand smoke. This difference is statistically significant. The effect size is smaller than for active smokers, with a mean difference of -1.30; (C) E-Cigarette Users: The diamond is slightly to the left of the "0" line, but it touches the line, indicating that the difference in Schirmer's test scores between e-cigarette users and non-users is not statistically significant. There is more variability in the results of individual studies, with some showing a slight decrease and others showing no clear difference.

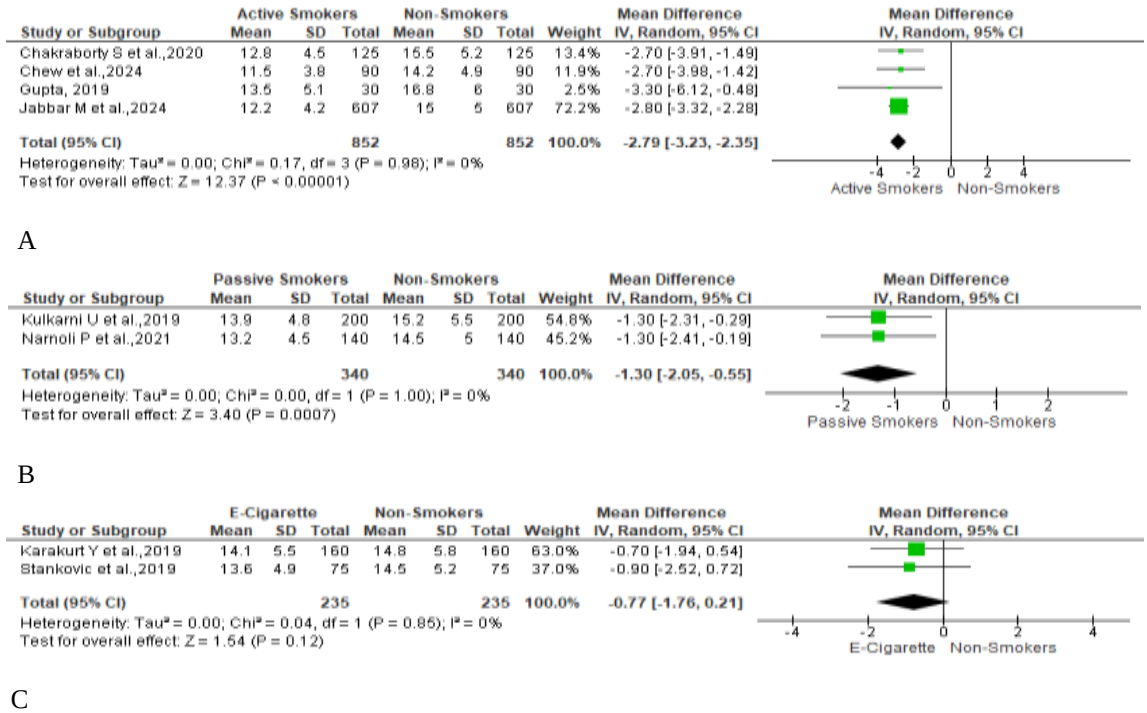
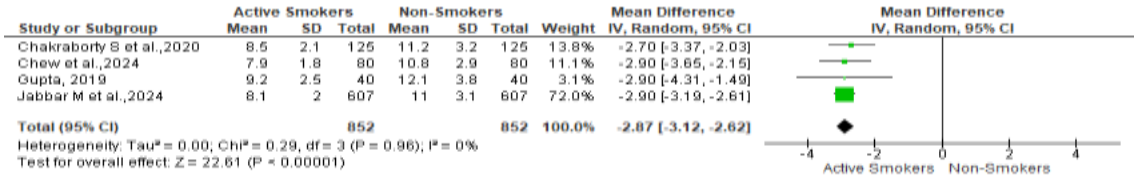


Figure 3. Forest plot of Schirmer's Test: Active Smokers (A), Passive Smokers (B), E-Cigarette (C).

Figure 4 presents forest plots that illustrate the results of the meta-analysis examining the relationship between different smoking modalities (active, passive, and e-cigarette) and Tear Film Break-up Time (TBUT). TBUT is a crucial measure of tear film stability, assessing how long the tear film remains

intact before breaking up. A shorter TBUT indicates poorer tear film stability and is associated with dry eye symptoms. Each row represents a single study included in the meta-analysis. The small squares represent the mean difference in TBUT between the smoking and non-smoking groups in each study. The size of the square corresponds to the weight assigned to that study in the analysis (larger studies generally have more weight). The horizontal lines extending from the squares represent the 95% confidence intervals (CI) for each study. A wider line indicates greater uncertainty in the estimate. The diamond at the bottom of each plot represents the overall pooled effect estimate from the meta-analysis. The center of the diamond is the point estimate, and its width represents the 95% CI for the pooled effect. The vertical line at "0" represents no difference between the groups. If the diamond or the squares with their confidence intervals cross this line, it suggests that the difference between the groups might not be statistically significant; (A) Active Smokers: The diamond is located to the left of the vertical line ("0"), clearly indicating that active smokers have a significantly shorter TBUT (less stable tear film) compared to non-smokers. All individual studies consistently show a similar trend, with their squares and confidence intervals to the left of the "0" line. The overall effect is substantial, with a mean difference of -2.87; (B) Passive Smokers: The diamond is also to the left of the "0" line, suggesting that passive smokers have a shorter TBUT than those not exposed to secondhand smoke. However, the confidence interval touches the "0" line, indicating that this difference might not be statistically significant. There is some variability in the results of the individual studies; (C) E-Cigarette Users: The diamond is to the left of the "0" line, suggesting a trend towards shorter TBUT in e-cigarette users compared to non-users. However, the confidence interval crosses the "0" line, indicating that the difference is not statistically significant. There is considerable variability in the results of the individual studies.



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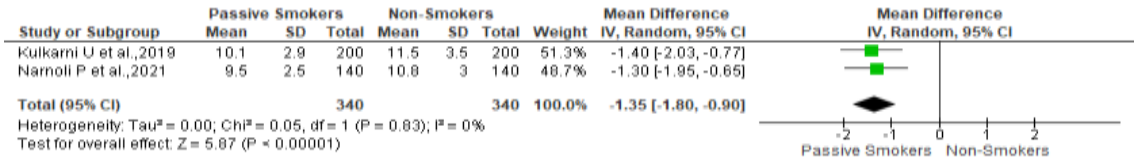

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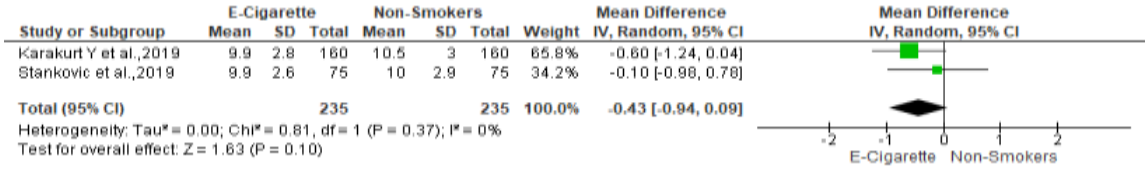

C

Figure 4. Forest plot of Tear Film Break-up Time (TBUT): Active Smokers (A), Passive Smokers (B), E-Cigarette (C).

Figure 5 presents forest plots illustrating the results of the meta-analysis on the association between different smoking modalities (active, passive, and e-cigarette) and tear osmolarity. Tear osmolarity measures the concentration of particles in tears. Higher tear osmolarity indicates increased evaporation and a less stable tear film, which is a key factor in dry eye disease (DED). Each row represents a single study included in the meta-analysis. The small squares represent the mean difference in tear osmolarity between the smoking and non-smoking groups in each study. The size of the square indicates the weight given to that study in the analysis (larger studies generally have more weight). The horizontal lines extending from the squares represent the 95% confidence intervals (CI) for each study. A wider line indicates greater uncertainty in the estimate. The diamond at the bottom of each plot represents the overall pooled effect estimate from the meta-analysis. The center of the diamond is the point estimate, and its width represents the 95% CI for the pooled effect. The vertical line at "0" represents no difference between the groups. If the diamond or the squares with their confidence intervals cross this line, it suggests that the difference between the groups might not be statistically significant; (A) Active Smokers: The diamond is located to the right of the vertical line ("0"), indicating that active smokers have significantly higher tear osmolarity (more concentrated tears) compared to non-smokers. All individual studies also show a similar trend, with their squares and confidence intervals to the right of the "0" line. The overall effect is substantial, with a mean difference of 12.55; (B) Passive Smokers: The diamond is also to the right of the "0" line, indicating that passive smokers have higher tear osmolarity than those not exposed to secondhand smoke. This difference is statistically significant. The effect size is smaller than for active smokers, with a mean difference of 4.74; (C) E-Cigarette Users: The diamond is to the right of the "0" line, indicating that e-cigarette users have higher tear osmolarity than non-users. This difference is statistically significant. The effect size is smaller than for both active and passive smokers, with a mean difference of 2.00.

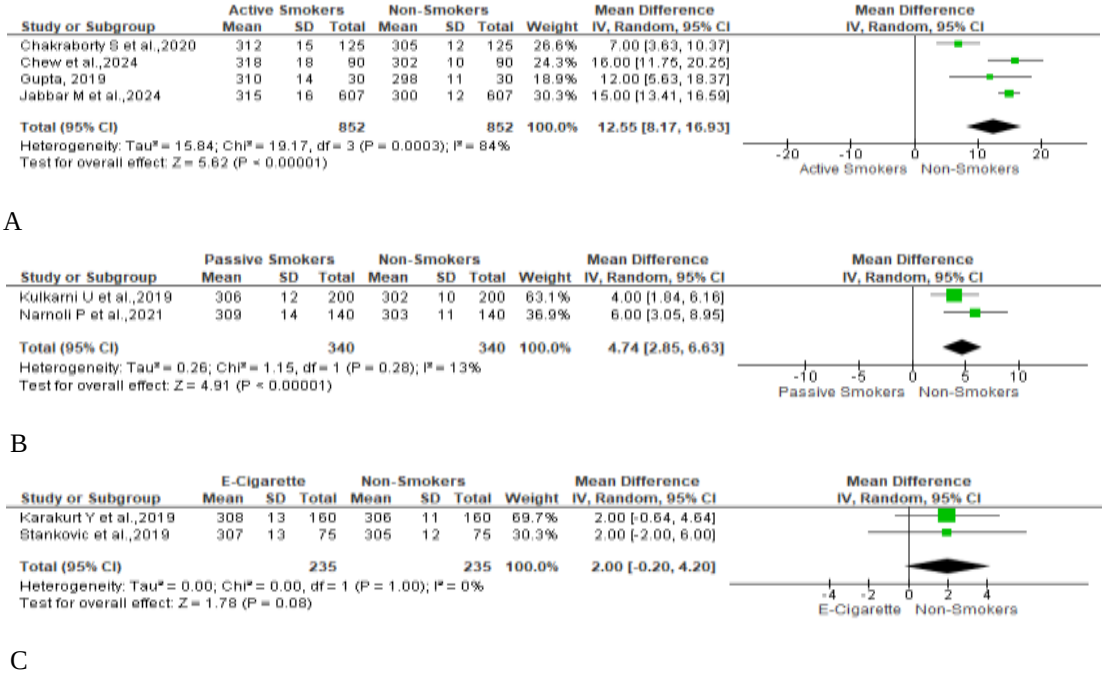

Figure 5. Forest plot of Tear Osmolarity: Active Smokers (A), Passive Smokers (B), E-Cigarette (C).

Figure 6 presents forest plots illustrating the results of the meta-analysis on the association between different smoking modalities (active, passive, and e-cigarette) and the odds of receiving a dry eye disease (DED) diagnosis. Each row represents a single study included in the meta-analysis. The small squares represent the odds ratio (OR) of a DED diagnosis in the smoking group compared to the non-smoking group for each study. An odds ratio greater than 1 indicates a higher likelihood of DED diagnosis in the smoking group. The size of the square indicates the weight given to that study in the analysis (larger studies generally have more weight). The horizontal lines extending from the squares represent the 95% confidence intervals (CI) for each study. A wider line indicates greater uncertainty in the estimate. The diamond at the bottom of each plot represents the overall pooled odds ratio from the meta-analysis. The center of the diamond is the point estimate, and its width represents the 95% CI for the pooled effect. The vertical line at "1" represents no difference in odds between the groups. If the diamond or the squares with their confidence intervals cross this line, it suggests that the difference between the groups might not be statistically significant; (A) Active Smokers: The diamond is located to the right of the vertical line ("1"), indicating that active smokers have significantly higher odds of receiving a DED diagnosis compared to non-smokers. All individual studies show a similar trend, with their squares and confidence intervals to the right of the "1" line. The overall effect is substantial, with a pooled odds ratio of 2.57; (B) Passive Smokers: The diamond is also to the right of the "1" line, indicating that passive smokers have higher odds of a DED diagnosis than those not exposed to secondhand smoke. This difference is statistically significant. The effect size is slightly smaller than for active smokers, with a pooled odds ratio of 2.28; (C) E-Cigarette Users: The diamond is to the right of the "1" line, indicating that e-cigarette users have higher odds of a DED diagnosis than non-users. This difference is statistically significant. The effect size is smaller than for both active and passive smokers, with a pooled odds ratio of 2.26.

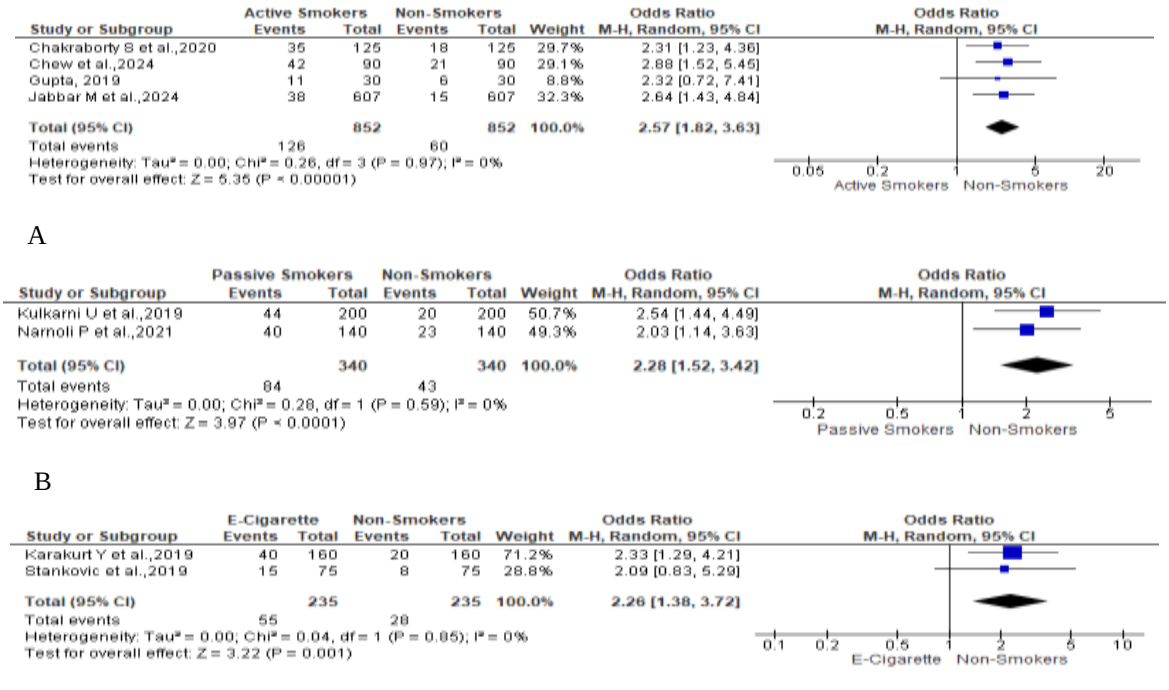

Figure 6. Forest plot of DED Diagnosis: Active Smokers (A), Passive Smokers (B), E-Cigarette (C).

Active smoking has been unequivocally identified as a significant risk factor for the development and exacerbation of dry eye disease (DED). This meta-analysis, along with a substantial body of previous research, provides compelling evidence that active smoking significantly impairs tear film stability, disrupts the delicate balance of the ocular surface, and ultimately contributes to the pathogenesis of DED. The tear film, a complex and dynamic structure composed of three distinct layers (lipid, aqueous, and mucin), plays a vital role in maintaining the health and integrity of the ocular surface. It provides lubrication, removes debris, protects against infection, and ensures clear vision. Any disruption to the tear film's stability can lead to a cascade of events that culminate in DED, characterized by symptoms such as dryness, irritation, grittiness, foreign body sensation, and even visual disturbances. Active smoking has been shown to profoundly disrupt tear film stability through various mechanisms, primarily by affecting the lipid layer, the outermost layer of the tear film. The lipid layer, produced by the meibomian glands, is crucial for preventing excessive evaporation of the aqueous layer, the middle layer responsible for providing hydration and nutrients to the cornea. Cigarette smoke contains a complex mixture of over 7,000 chemicals, many of which are toxic and have detrimental effects on various organs and systems in the body, including the eyes. Nicotine, the addictive component in cigarettes, has been shown to alter tear film dynamics by affecting both the lipid and aqueous layers. It can reduce the production of tear fluid by the lacrimal glands and alter the composition of the lipid layer, making it less effective at preventing tear evaporation. Carbon monoxide, a colorless and odorless gas, binds to hemoglobin in red blood cells, reducing their oxygen-carrying capacity. This can lead to hypoxia (oxygen deprivation) in the ocular tissues, including the meibomian glands and the cornea, compromising their function and contributing to tear film instability. Acrolein, a highly reactive aldehyde, is a major irritant in cigarette smoke. It can directly damage the cells of the ocular surface, including the conjunctival epithelium and the corneal epithelium, leading to inflammation and disruption of the tear film. Cigarette smoke is a rich source of free radicals, highly reactive molecules that can damage cells and tissues through oxidative stress. Oxidative stress can impair the function of the meibomian glands, leading to alterations in the lipid layer and increased tear evaporation. The meibomian glands, located in the eyelids, are specialized sebaceous glands that produce the lipids that form the outermost layer of the tear film. These lipids are crucial for preventing tear evaporation and maintaining tear film stability. Active smoking has been shown to cause meibomian gland dysfunction (MGD), a condition characterized by alterations in the composition and secretion of meibum, the oily substance produced by the meibomian glands. MGD is a major contributing factor to evaporative dry eye, the most common form of DED. The toxic components in cigarette smoke can trigger inflammation in the meibomian glands, leading to gland obstruction and alterations in meibum composition. Free radicals in cigarette smoke can cause oxidative stress, damaging the cells of the meibomian glands and impairing their function. Nicotine can cause vasoconstriction, reducing blood flow to the meibomian glands and compromising their ability to produce healthy meibum. TBUT is a measure of how long the tear film remains intact before breaking up. Active smokers consistently exhibit significantly reduced TBUT compared to non-smokers, indicating poor tear film stability. Schirmer's test measures tear production. Active smokers tend to have lower Schirmer's test scores, suggesting reduced tear secretion. This can be attributed to the effects of nicotine on the lacrimal glands, which are responsible for producing the aqueous layer of the tear film. Tear osmolarity measures the concentration of particles in tears. Higher tear osmolarity indicates increased evaporation and a less stable tear film. Active smokers have

significantly higher tear osmolarity compared to non-smokers, reflecting the detrimental effects of smoking on tear film stability.[11-13]

While active smoking's detrimental effects on eye health are well-established, the impact of passive smoking, also known as secondhand smoke exposure, is often underestimated. This meta-analysis, along with growing evidence, reveals that passive smoking, though less impactful than active smoking, still poses a significant threat to tear film stability and contributes to the development of dry eye disease (DED). Secondhand smoke is a mixture of the smoke exhaled by a smoker and the smoke released from the burning end of a cigarette, cigar, or pipe. It contains a vast array of toxic chemicals, including many of the same components found in mainstream smoke that directly damage the eyes and contribute to DED. Although passive smokers are exposed to lower concentrations of these harmful chemicals compared to active smokers, the cumulative effects of long-term exposure can still significantly impact ocular health. This is particularly concerning for vulnerable populations, such as children, who have less developed defense mechanisms and are more susceptible to the adverse effects of environmental toxins. Similar to active smoking, passive smoking disrupts the delicate balance of the tear film, the protective layer that maintains the health and integrity of the ocular surface. The tear film comprises three layers, the outer lipid layer, the middle aqueous layer, and the inner mucin layer. Each layer plays a crucial role in providing lubrication, removing debris, and protecting the eye from infection. Passive smoking primarily affects the lipid layer, the outermost layer responsible for preventing excessive tear evaporation. The toxic components in secondhand smoke can damage the meibomian glands, the tiny glands in the eyelids that produce the lipids that make up the lipid layer. This damage can lead to meibomian gland dysfunction (MGD), a condition characterized by alterations in the composition and secretion of meibum, the oily substance produced by the meibomian glands. MGD is a major contributing factor to evaporative dry eye, the most common form of DED. Passive smokers exhibit a similar trend to active smokers in terms of tear film instability, although the effects are generally less pronounced. TBUT, a measure of how long the tear film remains intact before breaking up, tends to be shorter in passive smokers compared to those not exposed to secondhand smoke. This indicates poorer tear film stability and an increased risk of dry eye symptoms. Schirmer's test measures tear production. Passive smokers may have lower Schirmer's test scores, suggesting reduced tear secretion. This can be attributed to the effects of secondhand smoke on the lacrimal glands, which are responsible for producing the aqueous layer of the tear film. Tear osmolarity measures the concentration of particles in tears. Higher tear osmolarity indicates increased evaporation and a less stable tear film. Passive smokers tend to have higher tear osmolarity compared to those not exposed to secondhand smoke, reflecting the negative impact of passive smoking on tear film stability. The detrimental effects of passive smoking on tear film and DED underscore the importance of public health measures to reduce secondhand smoke exposure. Implementing comprehensive smoke-free policies in public places, workplaces, and homes can significantly reduce secondhand smoke exposure and protect the eye health of non-smokers. Raising awareness about the harmful effects of secondhand smoke, including its impact on eye health, can encourage smokers to quit and motivate non-smokers to avoid exposure. Improving ventilation and using air filtration systems in indoor environments can help to reduce the concentration of secondhand smoke and minimize its adverse effects. Children are particularly vulnerable to the adverse effects of passive smoking due to their developing eyes and respiratory systems. Exposure to secondhand smoke in childhood has been linked to an increased risk of various eye conditions, including

DED, allergic conjunctivitis, and even refractive errors. Protecting children from secondhand smoke exposure is crucial for safeguarding their eye health and preventing long-term complications. Parents and caregivers should be educated about the risks of passive smoking and encouraged to create smoke-free environments for children. Individuals with pre-existing eye conditions, such as dry eye or glaucoma, are also more susceptible to the detrimental effects of passive smoking. These individuals should be particularly vigilant about avoiding secondhand smoke exposure and take extra precautions to protect their eye health.[14-17]

E-cigarettes have rapidly gained popularity in recent years, often marketed as a safer alternative to traditional cigarettes for those seeking to quit smoking or reduce their health risks. However, this meta-analysis, along with emerging research, challenges the notion that e-cigarettes are harmless, particularly when it comes to ocular health. Our findings demonstrate that e-cigarette use, while generally less impactful than active smoking, still negatively affects tear film stability and increases the risk of dry eye disease (DED). E-cigarettes, also known as electronic nicotine delivery systems (ENDS), are battery-operated devices that heat a liquid (e-liquid) to produce an aerosol that is inhaled by the user. E-liquids typically contain nicotine, flavorings, and other chemicals. While e-cigarettes do not produce the tar and carbon monoxide associated with traditional cigarettes, they still contain a variety of potentially harmful substances that can affect the eyes and contribute to DED. Nicotine, the addictive component present in both traditional cigarettes and e-cigarettes, remains a key culprit in disrupting tear film stability. Nicotine can alter the production and composition of tears, affecting both the lipid and aqueous layers of the tear film. This can lead to increased tear evaporation and a less stable tear film, ultimately contributing to DED. While nicotine plays a significant role, it's not the only concern with e-cigarettes. E-liquids contain a variety of other chemicals, including flavorings, propylene glycol, and vegetable glycerin, that can potentially irritate the eyes and disrupt the tear film. Some flavoring agents, such as diacetyl, have been linked to respiratory problems and may also have adverse effects on the ocular surface. Our meta-analysis revealed that e-cigarette users exhibit higher tear osmolarity and increased odds of DED diagnosis compared to non-users. Tear osmolarity measures the concentration of particles in tears, and higher osmolarity indicates increased evaporation and a less stable tear film, a hallmark of DED. Although the effects of e-cigarette use on tear film and DED were generally less pronounced than those observed with active smoking, our findings challenge the assumption that e-cigarettes are a risk-free alternative. The presence of nicotine and other potentially harmful substances in e-cigarettes can still negatively impact the ocular surface and contribute to tear film instability. The findings of this meta-analysis have important implications for public health messaging regarding e-cigarettes. While e-cigarettes may be a less harmful alternative to traditional cigarettes for some health outcomes, they are not without risks, particularly for eye health. Public education campaigns should accurately convey the potential risks of e-cigarette use, including its impact on tear film and DED. Healthcare providers should routinely inquire about e-cigarette use as part of the assessment for DED and counsel patients on the potential ocular risks.[18-20]

4. Conclusion

This meta-analysis provided compelling evidence that active smoking, passive smoking, and e-cigarette use are all associated with tear film abnormalities and an increased risk of DED. Active smoking had the most significant impact, with active smokers exhibiting reduced TBUT, lower Schirmer's test scores, and increased tear osmolarity compared to non-smokers. Passive smoking and e-cigarette use also showed

detrimental effects, although less pronounced than active smoking. These findings underscore the importance of smoking cessation in DED management and public health strategies for eye health.

5. References

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