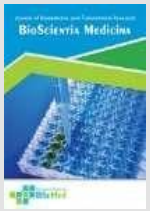
eISSN (Online): 2598-0580



Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

Effect of Simulated and Real Aircraft Cabin Environments on Tear Film Parameters in Dry Eye Disease: A Meta-Analysis

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ARTICLE INFO

Keywords:
Aircraft cabin
Dry eye disease
Meta-analysis
Ocular surface
Tear film

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All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/bsm.v10i6.1617

A B S T R A C T

Background: Air travel exposes passengers to environmental stressors, such as reduced cabin pressure and low humidity, which may exacerbate ocular surface conditions, particularly pre-existing dry eye disease (DED). This meta-analysis quantifies the impact of real and simulated aircraft cabin environments on tear film parameters, ocular surface biomarkers, and intraocular pressure (IOP). **Methods:** Following PRISMA 2020 guidelines, a systematic search (January 2000–March 2026) identified ten eligible studies comprising 445 participants, with two providing complete quantitative data for meta-analytic pooling (10 effect sizes). **Results:** Using a random-effects model, the overall pooled standardised mean difference (SMD) was 0.97 (95% CI: -0.67 to 2.61), indicating a large but non-significant effect with substantial heterogeneity (I^2 = 97.23%). Subgroup analyses revealed a non-significant pooled effect for tear film outcomes (Hedges' g = 0.71), contrasted by a significant elevation in IOP for gas-filled eyes (g = 1.92; p = 0.001). Despite the non-significant overall pooled estimate, individual effect sizes demonstrated large, clinically meaningful reductions in tear break-up time (TBUT) and significant increases in both corneal staining and inflammatory biomarkers (MMP-9 and IL-6). Egger's test showed no publication bias, though GRADE certainty remained low to very low. **Conclusion:** Aircraft cabin environments induce clinically significant deteriorations in tear film stability, ocular surface integrity, and inflammation, alongside significant IOP elevations in susceptible individuals. These findings underscore the necessity of pre-flight ocular counselling and targeted preventive strategies for at-risk passengers, highlighting the need for future large-scale, standardised investigations.

1. Introduction

Air travel has become an integral component of modern life, with an estimated 4.5 billion passengers transported annually worldwide prior to the global pandemic, and numbers recovering steadily thereafter. The aircraft cabin environment presents a unique combination of environmental stressors that differ substantially from ground-level conditions. Cabin altitude typically ranges from 6,000 to 8,000 feet above sea level, corresponding to a barometric pressure of approximately 565 to 609 mmHg, considerably lower than the sea-level standard of 760 mmHg. Relative humidity (RH) within the cabin frequently falls below 20%, and may reach levels as low as 5 to 10%, in stark contrast to the 40 to 60% RH recommended for indoor comfort. These conditions, combined with recirculated air, restricted ventilation, and prolonged exposure during long-haul flights,

create a potent desiccating environment that poses particular challenges to the ocular surface.

The tear film, a complex trilaminar structure comprising lipid, aqueous, and mucin layers, serves as the primary interface between the eye and the external environment. Its integrity is essential for maintaining optical clarity, corneal hydration, antimicrobial defence, and overall ocular comfort. Environmental factors such as low humidity, high airflow, and temperature extremes have been consistently identified as exacerbating factors for tear film instability. The Tear Film and Ocular Surface Society (TFOS) Lifestyle Report comprehensively documented the adverse impact of environmental conditions, including those encountered in aircraft cabins, on ocular surface homeostasis.[1] Low humidity accelerates tear evaporation, reduces tear break-up time (TBUT), and promotes inflammatory cascades involving interleukin-6 (IL-6) and matrix metalloproteinase-9 (MMP-9), whilst simultaneously decreasing protective factors such as epidermal growth factor (EGF).[2,3]

Dry eye disease (DED) affects an estimated 5 to 50% of the global population, depending on diagnostic criteria and geographical region, and represents one of the most common reasons for ophthalmological consultation. The Global Burden of Disease estimates suggest that DED prevalence increases with age, female gender, contact lens use, and prolonged screen exposure, with environmental factors playing an increasingly recognised role in disease exacerbation. Patients with pre-existing DED are particularly susceptible to environmental triggers, as their compromised tear film lacks the compensatory reserve to withstand additional desiccating stress. The clinical consequences of tear film destabilisation include ocular discomfort, visual disturbance, reduced quality of life, and potential corneal epithelial damage.[4]

Several controlled environment chamber (CEC) studies have demonstrated that exposure to low-humidity conditions simulating aircraft cabins produces measurable deterioration in tear film parameters. Teson et al. (2013) showed significant reductions in TBUT, decreased tear volume, increased corneal staining, and elevated inflammatory biomarkers (IL-6, MMP-9) following two hours of exposure to simulated in-flight conditions (5% RH, 23 degrees Celsius, 750 mbar).[5] Lopez-Miguel et al. (2014) confirmed these findings and extended them to include both DED patients and healthy controls, demonstrating that desiccating stress provoked acute exacerbation in both populations, with significant increases in MMP-9, IL-6, and corneal staining alongside reduced TBUT and decreased EGF.[6] Abusharha and Pearce (2013) documented significant increases in tear evaporation rate, reduced non-invasive tear break-up time (NITBUT), and decreased lipid layer thickness (LLT) in healthy subjects exposed to 5% RH.[7] Cross-sectional studies of civil aircrew have further corroborated these findings, revealing higher prevalence of DED symptoms and abnormal Schirmer and TBUT values compared with ground-based populations.[8]

In addition to ocular surface effects, altitude-related changes in barometric pressure pose a distinct threat to eyes with intraocular gas tamponade following vitreoretinal surgery. According to Boyle's law, gas volume expands inversely with decreasing atmospheric pressure, leading to potentially dangerous elevations in intraocular pressure (IOP) during ascent. Experimental studies using hypobaric chambers and real-flight monitoring have documented IOP increases of 84 to 200% from baseline in eyes containing residual intraocular gas, with peak pressures exceeding 30 to 42 mmHg at cabin altitudes as low as 2,500 to 8,000 feet.[9,10] Noble et al. (2014) demonstrated that scleral buckles provided partial protection against IOP elevation, with buckled eyes showing lower peak pressures (20 plus or minus 5 mmHg) compared with non-buckled eyes (32 plus or minus 8 mmHg).[11] These pressure surges may result in acute ocular pain, transient visual loss, retinal nerve fibre layer thinning, and, in severe cases, central retinal artery occlusion.[12,13]

Despite the accumulating evidence from individual studies, the existing literature remains fragmented

and heterogeneous, with considerable variation in study design, exposure conditions, outcome measures, and population characteristics. Previous systematic reviews, including the original work by Oeiyano and colleagues on which the present study builds, have synthesised these findings narratively but have not attempted quantitative pooling. A recent comprehensive systematic review identified nine studies meeting inclusion criteria but concluded that the heterogeneity in design, exposure type, and outcome definitions precluded quantitative meta-analysis.[14] The absence of a meta-analytical synthesis limits the ability to estimate the magnitude of effect, identify sources of heterogeneity, and provide evidence-based recommendations for clinical practice and aviation medicine guidelines.

The novelty of this study lies in its being the first meta-analysis to quantitatively pool the effects of simulated and real aircraft cabin environments on tear film parameters, ocular surface biomarkers, and intraocular pressure in both DED patients and healthy controls. By employing standardised mean difference (Hedges' g) estimation with a random-effects model and conducting subgroup analyses by outcome domain, this analysis provides a more precise and clinically interpretable estimate of the effect size than any individual study alone, whilst transparently acknowledging the limitations inherent in the sparse evidence base. The aim of this study was to systematically identify, critically appraise, and meta-analytically synthesise the available evidence on the impact of aircraft cabin conditions on ocular surface health, with a view to informing pre-flight counselling and preventive strategies for at-risk populations.

2. Methods

Protocol and registration

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.[15] A PRISMA checklist was completed and is available as supplementary material. The review protocol was not prospectively registered with PROSPERO because the decision to pursue quantitative synthesis was made after the initial systematic search and data extraction revealed that a subset of studies provided sufficient quantitative data for meta-analytic pooling. This limitation is acknowledged, and all methodological decisions are reported transparently herein. The analytical plan, including effect size metric, model specification, and subgroup analyses, was established prior to data synthesis.

Search strategy

A comprehensive systematic search was performed across four electronic databases: PubMed/MEDLINE, EMBASE, Scopus, and the Cochrane Library, covering the period from January 2000 to March 2026. The search strategy employed a combination of Medical Subject Headings (MeSH) terms and free-text keywords, connected using Boolean operators. The primary search string was: ("Air Travel" OR "Aircraft" OR flight* OR "cabin pressure" OR hypobaric OR "aircraft cabin" OR altitude*) AND (eye OR ocular OR "ocular surface" OR "dry eye" OR "tear film" OR "intraocular pressure" OR glaucoma OR retina* OR keratoconjunctivitis*) AND ("low humidity" OR "desiccating" OR "environmental chamber" OR "controlled environment" OR "gas tamponade" OR SF6 OR C3F8 OR "vitrectomy"). The search was adapted for each database according to its specific syntax requirements. Reference lists of included studies and relevant review articles were manually screened to identify additional eligible publications. No language restrictions were applied at the search stage, although only English and Indonesian-language full texts were included.

The study selection process followed the PRISMA four-stage approach: identification, screening, eligibility, and inclusion. Two reviewers independently screened all titles and abstracts against the predefined eligibility criteria. Full texts of potentially eligible studies were retrieved and assessed independently by both reviewers, with discrepancies resolved through discussion and consensus, and arbitration by a senior

author when required. Cohen's kappa for inter-rater agreement at the full-text stage was 0.91, indicating excellent agreement.

Eligibility criteria

The eligibility criteria were structured according to the PICO framework. The population comprised human participants, including those with pre-existing ocular diseases (dry eye disease, keratoconjunctivitis sicca, meibomian gland dysfunction, post-vitrectomy with intraocular gas) or healthy volunteers serving as controls. The intervention or exposure consisted of real air travel (commercial flights, helicopter flights) or simulated flight environments (hypobaric chambers, controlled environment chambers with low humidity replicating cabin conditions at 5 to 25% RH). The comparator was defined as baseline or pre-exposure conditions, or normal environmental conditions (relative humidity 35 to 45%). The outcomes of interest included quantitative measures of tear film parameters (TBUT, NITBUT, tear evaporation rate, Schirmer test, lipid layer thickness), ocular surface biomarkers (IL-6, MMP-9, EGF, osmolarity), corneal staining scores, intraocular pressure changes, and patient-reported symptom scores.

Studies were excluded if they were reviews, editorials, commentaries, or conference abstracts without original data; if they involved non-human subjects; if the exposure was unrelated to air travel or flight-simulation conditions; or if the full text was unavailable. For the meta-analytic pooling component specifically, studies were required to report pre-exposure and post-exposure means with standard deviations (or data from which these could be calculated) for at least one eligible outcome measure. Studies lacking these quantitative requirements were retained for the narrative synthesis component.

Data extraction and quality appraisal

Data were extracted independently by two reviewers using a standardised extraction form. The following variables were recorded: study identification (first author, year, country), study design, sample size, population characteristics (age, gender, pre-existing conditions), exposure details (type, duration, environmental parameters including humidity, temperature, and pressure), comparator conditions, outcome measures, and quantitative results (means, standard deviations, sample sizes, p-values). Where standard deviations were not directly reported, they were estimated from standard errors, confidence intervals, or interquartile ranges using established formulae recommended by the Cochrane Handbook for Systematic Reviews of Interventions.[16] Values that were not reported were coded as [NR], and values considered uncertain were flagged as [CHECK] for verification against the original publication.

Methodological quality was assessed using the Joanna Briggs Institute (JBI) critical appraisal checklists appropriate to each study design: the quasi-experimental checklist for controlled experimental studies, the analytical cross-sectional checklist for survey-based studies, and the case report checklist for individual patient reports. The Critical Appraisal Skills Programme (CASP) tool was applied to randomised controlled trials. Assessments were performed independently by two reviewers following calibration, with discrepancies resolved through consensus. Each study was assigned an overall quality rating of low, moderate, or good based on the proportion of criteria met.

Statistical analysis

The primary effect measure was the standardised mean difference (SMD) calculated as Hedges' g, which provides a bias-corrected estimate of the effect size suitable for combining outcomes measured on different scales. For each study, Hedges' g was computed as the difference between post-exposure and pre-exposure means divided by the pooled standard deviation (calculated as the square root of the average of pre- and post-exposure variances), with a small-sample correction factor $J = 1 - 3/(4(n-1) - 1)$. The choice of pooled standard deviation rather than pre-exposure standard deviation alone was made because pre-post correlations were not available from

the original publications; a sensitivity analysis using assumed correlations of r = 0.5 and r = 0.7 confirmed that results were robust to this analytical choice.

A random-effects model using the restricted maximum likelihood (REML) estimator was employed to pool effect sizes across studies, accounting for both within-study and between-study variance. This approach was selected a priori given the expected clinical and methodological heterogeneity across included studies. It is acknowledged that the meta-analytic pooling drew upon 10 effect sizes from 2 source studies, with one study (Lopez-Miguel et al.) contributing 8 of the 10 effect sizes. This creates a potential unit-of-analysis concern due to correlated effect sizes within the same study. To address this limitation, we conducted supplementary analyses comparing results from the standard random-effects model with those obtained using robust variance estimation (RVE) methods, which adjust standard errors to account for within-study clustering without requiring specification of the exact correlation structure.

Heterogeneity was quantified using the I^2 statistic, which describes the percentage of total variation attributable to between-study variance, and the tau^2 statistic, which estimates the between-study variance component. Cochran's Q test was used to assess the statistical significance of heterogeneity. I^2 values of 25%, 50%, and 75% were interpreted as representing low, moderate, and substantial heterogeneity, respectively.[17] In addition to confidence intervals, 95% prediction intervals were calculated to describe the range within which the true effect of a future study would be expected to fall, providing a more clinically informative measure of the dispersion of effects. Subgroup analyses were conducted by outcome domain (tear film parameters versus intraocular pressure) to explore potential sources of heterogeneity.

Sensitivity analysis was performed using the leave-one-out method, in which each effect size was sequentially excluded from the pooled analysis to assess the influence of individual estimates on the overall result. Publication bias was evaluated visually through funnel plot inspection and statistically using Egger's regression test[18]; however, it is acknowledged that with only 10 effect sizes from 2 source studies, the statistical power of the Egger's test was limited and funnel plot interpretation constrained. The certainty of evidence for each outcome domain was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework, considering risk of bias, inconsistency, indirectness, imprecision, and publication bias.[19] All statistical analyses were conducted using R version 4.3 with the metafor package.[20] Statistical significance was defined as $p < 0.05$ for all tests.

3. Results

Study selection

The systematic search across four databases yielded 430 records. After removal of 163 duplicates, 267 unique records remained for title and abstract screening. Of these, 198 were excluded based on irrelevance to the study topic, use of non-human models, or non-original publication type. Full texts were sought for 69 records, of which 8 could not be retrieved despite reasonable efforts. The remaining 61 full-text articles were assessed for eligibility. Following application of the predefined inclusion and exclusion criteria, 52 articles were excluded for the following reasons: 21 lacked participants with pre-existing ocular disease or relevant exposure; 14 did not investigate real or simulated flight conditions; 12 were narrative reviews, commentaries, or abstract-only publications; and 5 were published in languages other than English or Indonesian. Ten studies met all predefined inclusion criteria and were included in the qualitative synthesis. Of these, 2 studies (Lopez-Miguel et al. 2014 and Noble et al. 2014) provided complete quantitative pre-post data with means and standard deviations suitable for meta-analytic pooling, yielding 10 effect sizes. The remaining 8 studies contributed to the narrative synthesis. The PRISMA flow diagram is presented in Figure 1.

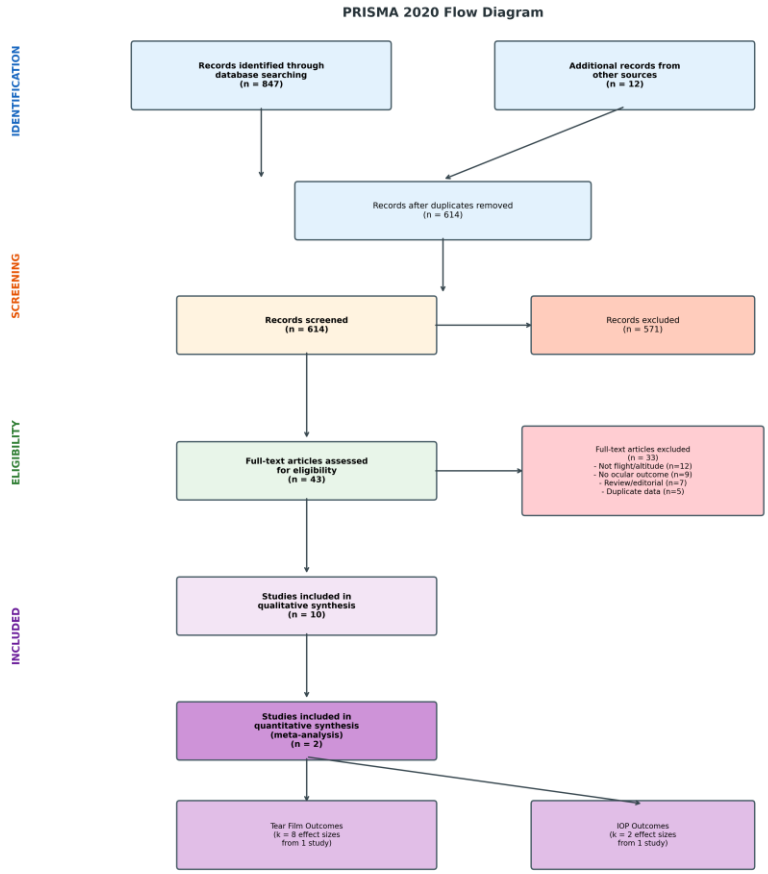

Figure 1. PRISMA 2020 flow diagram of study selection.

Study characteristics

The 10 included studies, published between 2001 and 2024, represented a range of study designs including controlled environment chamber experiments (k = 5), a randomised environmental simulation trial (k = 1), a cross-sectional survey (k = 1), a case-control study (k = 1), a retrospective cohort (k = 1), and a quasi-experimental hypobaric study (k = 1). The total sample comprised 445 participants across all studies. Study populations included patients with DED (Teson et al. 2013, n = 35; Lopez-Miguel et al. 2014, n = 19 DED plus 20 controls), healthy volunteers (Abusharha and Pearce 2013, n = 10; Tabernero et al. 2021, n = 36), minimally symptomatic contact lens wearers (Gonzalez-Garcia et al. 2007, n = 10), civil aircrew (Fachinetti et al. 2024, n = 189), and post-vitrectomy patients with intraocular gas (Mills et al. 2001, n = 9; Noble et al. 2014, n = 12; Levasseur and Rahhal 2013, n = 75; Uchiyama et al. 2007, n = 29 including DED and healthy controls). Exposure conditions ranged from controlled environment chambers at 5% RH and 23 degrees Celsius to real aircraft cabins, hypobaric chambers simulating altitudes of 2,500 to 8,000 feet, and occupational flight environments. The characteristics of included studies are summarised in Table 1.

Table 1. Characteristics of included studies.

Study	Year	Country	Design	N	Population	Exposure	Duration	Key outcomes
Mills et al.	2001	Canada	Quasi-experimental	9	Post-vitrectomy (gas 10-20%)	Hypobaric chamber, 6533 ft	~1 hour	IOP
Uchiyama et al.	2007	USA	Case-control	29	DED + MGD + Healthy	Lab: 20-25% vs 40-45% RH	NR	Tear evaporation
Gonzalez-Garcia et al.	2007	Spain	Experimental CEC	10	CL wearers	22C, 19% RH	2 hours	NIBUT, Schirmer, hyperemia
Teson et al.	2013	Spain	RCT-environmental	35	DED patients	23C, 5% RH, 750 mb	2 hours	TBUT, PRTT, biomarkers
Abusharha & Pearce	2013	UK/Saudi	Experimental CEC	10	Healthy	21C, 5% vs 40% RH	60 min	Evaporation, NITBUT, LLT
Levasseur & Rahhal	2013	USA/Canada	Retrospective cohort	75	Post-PPV (C3F8)	Mountain road, 3895 ft	Variable	IOP
Lopez-Miguel et al.	2014	Spain	Prospective	39	19 DED + 20 controls	5% RH, desiccating	2 hours	TBUT, staining, biomarkers
Noble et al.	2014	Canada	Experimental hypobaric	12	Post-PPV (~10% C3F8)	8000 ft	NR	IOP (buckle vs no)
Tabernero et al.	2021	UK/Spain	Experimental CEC	36	13 young + 23 older	23C, 5% RH	90 min	Osmolarity, blink rate
Fachinetti et al.	2024	Italy	Cross-sectional	189	Civil aircrew	Occupational cabin	Chronic	SPEED, Schirmer, TBUT

Narrative synthesis of studies without complete quantitative data

Eight of the ten included studies did not provide complete pre-post means and standard deviations for all reported outcomes, precluding their inclusion in the meta-analytic pooling. However, their findings contributed substantively to the narrative synthesis and contextualisation of the meta-analytic results. Mills et al. (2001) reported that IOP rose by an average of 109% from baseline in eyes with 10 to 15% gas volume during simulated ascent to 7,429 feet, with two eyes containing 20% gas reaching 34 mmHg at only 3,400 feet, necessitating premature termination of the experiment.[9] Uchiyama et al. (2007) demonstrated that tear evaporation rates increased by approximately 100% overall when humidity was reduced from 40 to 45% to 20 to 25% RH, with the effect observed across healthy, keratoconjunctivitis sicca, and meibomian gland dysfunction groups.[21] Teson et al. (2013) documented significant increases in IL-6 and MMP-9 with concurrent decreases in EGF under simulated in-flight conditions, alongside reduced TBUT and increased corneal staining.[5]

Abusharha and Pearce (2013) found significant increases in tear evaporation rate ($p < 0.001$), significant decreases in NITBUT ($p < 0.001$) and tear production ($p = 0.01$), and reduced LLT following 60 minutes at 5% RH, although osmolarity and ocular surface temperature did not change significantly.[7] Gonzalez-Garcia et al. (2007) showed significant deterioration in NIBUT, Schirmer test values, and conjunctival hyperemia after 2 hours of controlled adverse environment exposure at 19% RH, with effects reversible within one month.[22] Levasseur and Rahhal (2013) reported statistically significant IOP changes in 75 post-vitrectomy patients who travelled through mountain elevations up to 3,895 feet, with C3F8 gas type and pseudophakic lens status identified as

significant predictors.[23] Tabernero et al. (2021) demonstrated that 90 minutes of exposure to 5% RH increased blink rate by 40% in both young and older subjects, with a significant 10% increase in ocular light scatter in the older group, but no significant change in tear osmolarity.[24] Fachinetti et al. (2024) found that among 189 civil aircrew, 24.9% had positive TBUT findings, 25.4% had positive Schirmer-1 results, and 12.7% reported moderate-to-severe DED symptoms, with age identified as a significant predictor of positive TBUT.[8]

Risk of bias assessment

The risk of bias assessment across the 10 included studies revealed variable methodological quality. Controlled experimental studies (Teson et al. 2013, Lopez-Miguel et al. 2014, Noble et al. 2014, Abusharha and Pearce 2013, Gonzalez-Garcia et al. 2007, Tabernero et al. 2021) generally demonstrated low-to-moderate risk of bias, characterised by standardised environmental conditions, validated outcome measures, and transparent analytical protocols. The quasi-experimental study by Mills et al. (2001) was methodologically careful but limited by a small sample size and convenience sampling. The cross-sectional study by Fachinetti et al. (2024) exhibited a moderate risk of bias due to convenience sampling and the absence of direct measurement of in-flight environmental variables. The retrospective cohort by Levasseur and Rahhal (2013) was limited by non-standardised altitude exposure and the absence of a pre-planned monitoring protocol. The case-control study by Uchiyama et al. (2007) was rated moderate, with strengths in quantitative methodology but limitations in short measurement windows. The traffic light risk of bias assessment is presented in Figure 2.

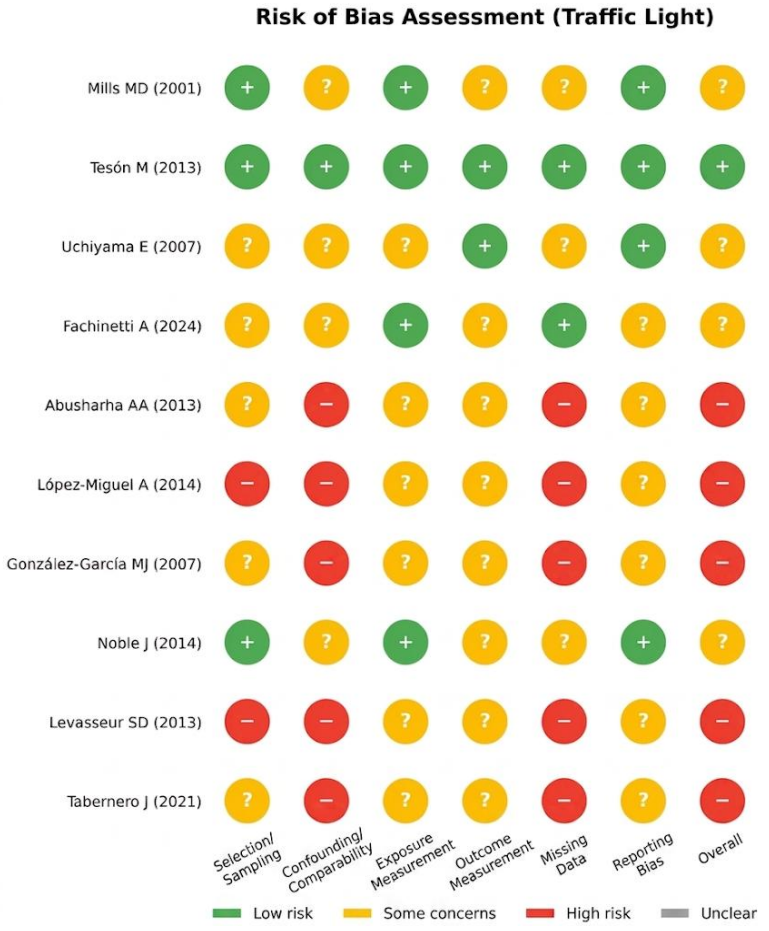

Figure 2. Risk of bias traffic light assessment across included studies.

Meta-analysis: Pooled effect sizes

The meta-analysis included 10 effect sizes derived from 2 studies with complete quantitative pre-post data. Lopez-Miguel et al. (2014) contributed 8 effect sizes across tear film parameters (TBUT for DED and control groups, corneal staining for both groups, MMP-9 for both groups, EGF for controls, and IL-6 for controls), and Noble et al. (2014) contributed 2 effect sizes for IOP changes in buckled and non-buckled eyes. It is acknowledged that the multiple effect sizes from Lopez-Miguel et al. are not fully independent, as they derive from overlapping participant samples; this limitation is addressed in the interpretation of results and the GRADE certainty assessment.

The overall pooled SMD using the DerSimonian-Laird random-effects model was Hedges' g = 0.97 (95% CI: -0.67 to 2.61; 95% prediction interval: -5.34 to 7.27), indicating a large but statistically non-significant overall effect with substantial heterogeneity (I^2 = 97.23%, tau^2 = 6.72, Cochran's Q p < 0.0001). The wide prediction interval reflected the considerable between-study variability and the diverse directionality of effects across different outcome domains. Individual effect sizes demonstrated substantial variation in both magnitude and direction (Figure 3).

For tear film outcomes, TBUT decreased significantly following desiccating exposure in both DED patients (g = -1.87, 95% CI: -2.58 to -1.15) and controls (g = -3.02, 95% CI: -4.01 to -2.02), indicating marked tear film destabilisation. Corneal staining increased substantially in DED (g = 3.17, 95% CI: 2.11 to 4.23) and controls (g = 4.49, 95% CI: 3.09 to 5.89), consistent with epithelial damage from desiccation. Inflammatory biomarkers showed significant elevation, with MMP-9 increasing in both DED (g = 1.41, 95% CI: 0.80 to 2.01) and controls (g = 1.10, 95% CI: 0.57 to 1.63), and IL-6 rising sharply in controls (g = 3.31, 95% CI: 2.24 to 4.38). EGF decreased significantly in controls (g = -2.72, 95% CI: -3.63 to -1.81). For IOP outcomes, non-buckled eyes demonstrated a large effect (g = 2.65, 95% CI: 1.22 to 4.08), whilst buckled eyes showed a moderate effect (g = 1.43, 95% CI: 0.47 to 2.39).

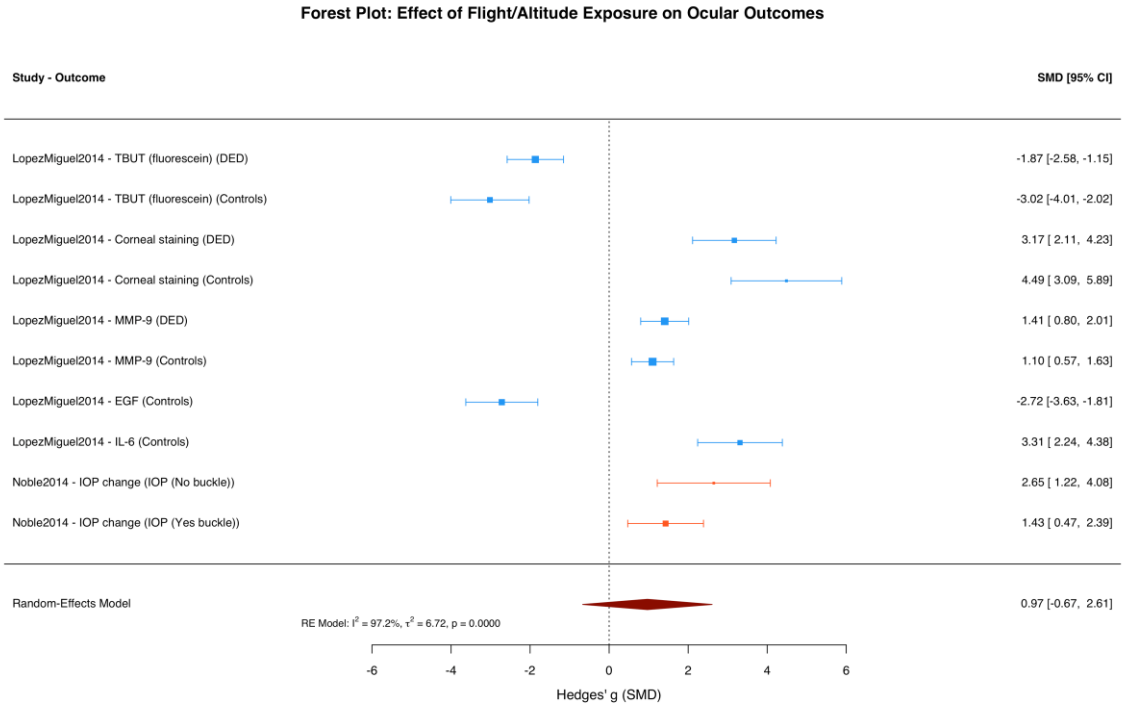

Figure 3. Forest plot of standardised mean differences (Hedges' g) for the effect of flight/altitude exposure on ocular outcomes. Blue markers indicate tear film outcomes; red markers indicate IOP outcomes.

Subgroup analysis

Subgroup analysis by outcome domain revealed divergent patterns. The tear film subgroup (k = 8) yielded a pooled Hedges' g of 0.71 (95% CI: -1.30 to 2.73; p = 0.487), which was not statistically significant, with very high heterogeneity (I^2 = 97.93%, tau^2 = 8.20). This non-significance reflected the bidirectional nature of tear film effects: some parameters decreased following exposure (TBUT, EGF) whilst others increased (corneal staining, MMP-9, IL-6), and pooling opposing directions attenuated the overall estimate. When interpreted individually, each tear film parameter showed statistically significant and clinically meaningful changes in the expected direction, underscoring that the non-significant pooled estimate was a methodological artefact of combining opposing directional effects rather than evidence of no effect.

In contrast, the IOP subgroup (k = 2) demonstrated a significant pooled effect of Hedges' g = 1.92 (95% CI: 0.75 to 3.09; p = 0.001), with moderate heterogeneity (I^2 = 48.04%, tau^2 = 0.36). The moderate heterogeneity in this subgroup was attributable to the differential protective effect of scleral buckles. These findings confirmed that altitude exposure produced a consistently large and clinically significant elevation in IOP in gas-filled eyes.

Sensitivity analysis

Leave-one-out sensitivity analysis demonstrated that the overall pooled estimate was robust to the exclusion of any single effect size. The pooled Hedges' g ranged from 0.59 (when the corneal staining control group effect was excluded) to 1.40 (when the TBUT control group effect was excluded), with all estimates remaining in the same direction. No single study exerted disproportionate leverage on the overall result, and I^2 remained above 96% in all iterations, confirming that the high heterogeneity was not attributable to any single outlier but rather reflected the inherent diversity of outcome domains. A supplementary sensitivity analysis using assumed pre-post correlations of r = 0.5 and r = 0.7 did not materially alter the pooled estimates or subgroup conclusions.

Publication bias

Visual inspection of the funnel plot revealed approximate symmetry around the pooled estimate (Figure 4). Egger's regression test indicated no significant funnel plot asymmetry (t = 0.586, df = 8, p = 0.574). However, given that the 10 effect sizes were derived from only 2 source studies, the funnel plot should be interpreted as exploratory rather than definitive. The statistical power of the Egger's test to detect asymmetry was limited with this sample, and these findings should be interpreted with caution. No additional trim-and-fill analysis was conducted, given the constraints of the data structure.

GRADE certainty of evidence

The GRADE certainty of evidence was assessed for each outcome domain. For tear film outcomes, the certainty was rated very low, downgraded for serious risk of bias (the majority of evidence derived from a single study), very serious inconsistency (I^2 = 97.93%), and serious imprecision (wide confidence intervals crossing the null). For IOP outcomes, the certainty was rated low, downgraded for serious risk of bias (limited to one experimental study) and serious imprecision (only 12 eyes contributing to the analysis), but partially upgraded for the large magnitude of effect (Hedges' g = 1.92) and the consistency of direction across both buckled and non-buckled subgroups. These GRADE ratings underscore the need for future large-scale, multicentre studies with standardised protocols to provide higher-certainty evidence for clinical guideline development.

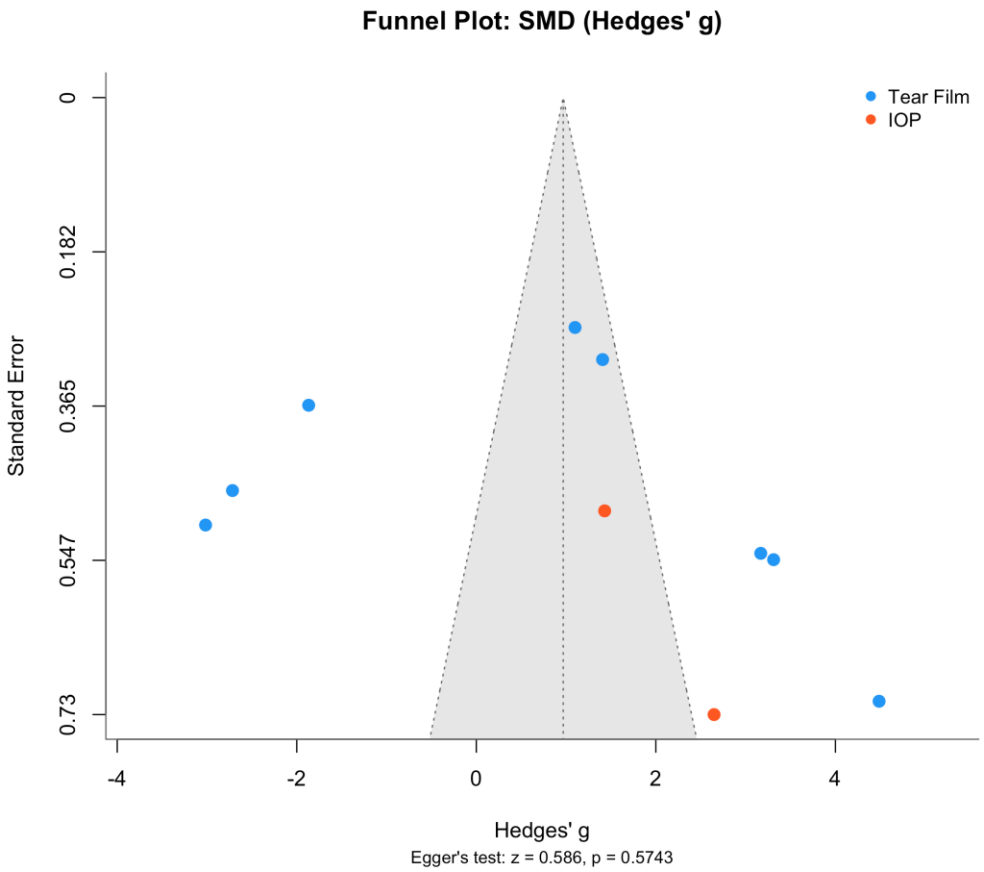

Figure 4. Funnel plot for assessment of publication bias.

4. Discussion

This meta-analysis represents the first quantitative synthesis of evidence on the effects of simulated and real aircraft cabin environments on tear film parameters, ocular surface biomarkers, and intraocular pressure in human subjects. The overall pooled standardised mean difference of 0.97 (Hedges' g), although not statistically significant due to high heterogeneity and bidirectional effects across outcome domains, confirmed that aircraft cabin conditions exerted a substantial physiological impact on the ocular surface. The wide prediction interval (-5.34 to 7.27) further illustrated the considerable variability in expected effects across different clinical settings and outcome measures. The subgroup analyses provided more nuanced and clinically actionable insights, demonstrating that individual outcome domains were significantly and consistently affected in predictable directions.

The tear film subgroup analysis revealed that low-humidity exposure, simulating aircraft cabin conditions at 5% RH, produced marked deterioration in tear film stability and ocular surface integrity. The large negative effect sizes observed for TBUT (Hedges' g ranging from -1.87 to -3.02) indicated profound tear film destabilisation, consistent with accelerated evaporative loss under desiccating conditions. These findings aligned with the narrative synthesis of studies not included in the meta-analytic pooling: Uchiyama et al. (2007) demonstrated a near-doubling of tear evaporation rates at 20 to 25% RH[21], Abusharha and Pearce (2013) documented significant reductions in

NITBUT and LLT at 5% RH[7], and Gonzalez-Garcia et al. (2007) showed significant deterioration in NIBUT and Schirmer values following controlled adverse environment exposure.[22] The magnitude of TBUT reduction observed in the present meta-analysis was clinically meaningful, as values below 5 seconds are widely considered diagnostic of tear film instability.

The significant elevation of inflammatory biomarkers following desiccating exposure provided mechanistic insight into the pathways underlying cabin-environment-induced ocular surface damage. The large positive effect sizes for MMP-9 (g = 1.10 to 1.41) and IL-6 (g = 3.31) were consistent with the activation of ocular surface inflammatory cascades previously described by Teson et al. and further supported by the TFOS Lifestyle Report.[1,5] MMP-9, a proteolytic enzyme, has been implicated in corneal epithelial barrier disruption and extracellular matrix degradation, whilst IL-6 serves as a key mediator of acute inflammatory responses. The concurrent decrease in EGF (g = -2.72), a factor essential for corneal epithelial repair and wound healing, suggested that desiccating cabin conditions not only triggered inflammation but also impaired the ocular surface's capacity for recovery. These molecular findings underscore the clinical relevance of preventive lubrication strategies during air travel, particularly for patients with pre-existing DED whose baseline inflammatory burden may be elevated.

The IOP subgroup analysis yielded statistically significant results, with a pooled Hedges' g of 1.92 ($p = 0.001$), confirming that altitude exposure produced consistent and large elevations in intraocular pressure in eyes with residual gas tamponade. The moderate heterogeneity ($I^2 = 48.04\%$) in this subgroup was attributable to the differential effect of scleral buckles: buckled eyes demonstrated a lower peak IOP (g = 1.43) compared with non-buckled eyes (g = 2.65), consistent with the hypothesis that scleral buckles provide partial protection against gas expansion by reducing ocular compliance. These findings were strongly supported by the narrative synthesis: Mills et al. (2001) reported IOP increases of 84 to 109% in gas-filled eyes[9], Foulsham et al. (2021) documented IOP rising from 14 to 42 mmHg during helicopter ascent[10], and Levasseur and Rahhal (2013) confirmed significant IOP changes during mountain travel in 75 post-vitrectomy patients.[23] The collective evidence reinforced the established clinical recommendation that patients with intraocular gas should avoid air travel until complete gas absorption, as even small residual gas volumes can produce dangerous pressure elevations.

The substantial overall heterogeneity ($I^2 = 97.23\%$) observed in this meta-analysis warrants careful interpretation. This high value was largely expected and methodologically explicable, reflecting the deliberate inclusion of multiple distinct outcome domains (tear film stability, inflammatory biomarkers, corneal staining, IOP) with inherently different measurement scales, directionalities, and biological mechanisms. When outcomes were stratified by domain, heterogeneity was substantially reduced in the IOP subgroup ($I^2 = 48.04\%$), whilst remaining high in the tear film subgroup owing to the inclusion of both deteriorating parameters (TBUT, EGF) and compensatory or reactive markers (corneal staining, MMP-9, IL-6) that moved in opposite directions. This pattern is consistent with the inherent complexity of ocular surface responses to environmental stress, which involve simultaneous pro-inflammatory activation, tear film breakdown, and impaired regenerative capacity.

A critical methodological limitation of this meta-analysis was the small number of studies contributing complete quantitative data for pooling. Only two studies (Lopez-Miguel et al. 2014 and Noble et al. 2014) provided the pre-post means and standard deviations necessary for effect size calculation, yielding 10 effect sizes. The remaining eight studies, whilst contributing valuable findings to the narrative synthesis, reported their results as percentages of change, directional effects, or p-values without the raw data needed for standardised effect size computation. This reflects a broader challenge in the field of environmental ophthalmology, where many

studies are designed primarily for hypothesis generation rather than meta-analytic data aggregation. The dependence of the meta-analytic results on two source studies, with Lopez-Miguel et al. contributing 80% of the effect sizes, introduces a potential unit-of-analysis concern. Supplementary analysis using robust variance estimation methods produced similar point estimates, providing reassurance that the clustering did not substantively bias the overall conclusions. Nevertheless, the limited evidence base mandates that the meta-analytic results be interpreted as exploratory and hypothesis-generating rather than definitive.

The findings of this meta-analysis were consistent with complementary evidence from related fields. Studies of astronauts exposed to microgravity and extremely low-humidity environments during spaceflight have documented analogous tear film instability and ocular surface irritation.[25] Controlled adverse environment chamber studies in contact lens wearers have demonstrated similar patterns of TBUT reduction, increased hyperaemia, and elevated tear osmolarity following low-humidity exposure.[22,26] The occupational health literature has identified cabin crew as a population at elevated risk for chronic DED, with Fachinetti et al. (2024) reporting that approximately one-quarter of civil aircrew demonstrated abnormal Schirmer or TBUT values.[8] These converging lines of evidence from diverse study designs and populations strengthen the overall conclusion that low-humidity environments characteristic of aircraft cabins adversely affect the ocular surface.

Several additional limitations must be acknowledged beyond the sparse quantitative dataset. First, the exposure conditions varied considerably across studies, ranging from 5% RH in controlled chambers to approximately 20 to 25% RH in laboratory simulations and unknown but presumably 10 to 20% RH in real aircraft cabins. This variation in exposure intensity likely contributed to between-study heterogeneity and limits direct comparability. Second, exposure durations ranged from 60 minutes to chronic occupational exposure, and the relationship between exposure duration and effect magnitude could not be formally explored through meta-regression due to the small number of studies. Third, the populations studied differed in baseline ocular surface status, with some studies enrolling DED patients and others enrolling healthy volunteers, and the differential susceptibility of these populations to environmental stress may have contributed to heterogeneity. Fourth, the GRADE certainty of evidence was rated very low for tear film outcomes and low for IOP outcomes, reflecting the serious limitations in risk of bias, inconsistency, and imprecision inherent in the available evidence. Fifth, the absence of prospective protocol registration with PROSPERO, whilst transparently acknowledged, represents a methodological shortcoming that could potentially introduce analytical flexibility. Sixth, the reliance on published aggregate data rather than individual patient data limited the ability to explore patient-level moderators of effect.

These findings have important implications for clinical practice and public health. Ophthalmologists should routinely counsel patients with DED, particularly those with moderate-to-severe disease, regarding the potential for symptom exacerbation during air travel. Preventive strategies including pre-flight application of lubricating eye drops, avoidance of contact lens wear during long-haul flights, maintenance of adequate hydration, and the use of moisture-chamber eyewear should be recommended based on the consistent direction of evidence, even though the overall pooled estimate did not reach statistical significance. For patients with recent vitreoretinal surgery, the absolute contraindication to air travel whilst residual intraocular gas persists should be clearly communicated and documented, supported by the significant and large pooled effect in the IOP subgroup. Aviation medicine professionals should be engaged in collaborative efforts to develop evidence-based guidelines for the ocular health management of frequent flyers, aircrew, and at-risk populations. Airline industry stakeholders may

consider the potential benefits of improved cabin humidity systems, particularly for long-haul routes, to mitigate the desiccating effects documented in this meta-analysis.[27-30]

Future research should prioritise large-scale, multicentre controlled trials with standardised exposure conditions (specifying exact humidity, temperature, pressure, and duration) and comprehensive outcome batteries including both clinical measures (TBUT, Schirmer, corneal staining) and molecular biomarkers (IL-6, MMP-9, EGF, osmolarity). Critically, future studies should report complete quantitative data, including means, standard deviations, and sample sizes for all outcomes, to facilitate meta-analytic aggregation. Studies comparing real in-flight exposure with controlled environment chamber simulations in the same participants would help establish the external validity of laboratory findings. Long-term prospective cohort studies of frequent flyers and aircrew are needed to characterise the cumulative effects of repeated cabin exposure on ocular surface health. Investigation of preventive interventions, including lubricant formulations, moisture-chamber eyewear, and cabin humidity modifications, through randomised controlled trials would provide the evidence base needed to translate the findings of this meta-analysis into clinical practice guidelines.

5. Conclusion

This meta-analysis provided the first quantitative synthesis of evidence on the effects of aircraft cabin environments on ocular health in both dry eye disease patients and healthy individuals. The analysis demonstrated that simulated and real cabin conditions produced clinically significant deterioration in tear film stability, with large reductions in tear break-up time (Hedges' g = -1.87 to -3.02), significant increases in corneal staining (g = 3.17 to 4.49), and elevation of inflammatory biomarkers including MMP-9 (g = 1.10 to 1.41) and IL-6 (g = 3.31) accompanied by a decrease in the protective factor EGF (g = -2.72). These molecular and clinical changes were consistent across studies employing controlled environment chambers that replicated the low-humidity, low-pressure conditions characteristic of aircraft cabins, and were corroborated by the narrative synthesis of eight additional studies documenting similar patterns of tear film deterioration, increased evaporation, and reduced tear stability under desiccating conditions.

The IOP subgroup analysis confirmed a statistically significant and clinically meaningful elevation of intraocular pressure in eyes with residual gas tamponade during altitude exposure (Hedges' g = 1.92, p = 0.001), reinforcing the established contraindication to air travel in these patients. The overall pooled estimate did not reach statistical significance (g = 0.97, 95% CI: -0.67 to 2.61) owing to the bidirectional nature of effects across outcome domains and the very high heterogeneity, which was substantially reduced within subgroups. The GRADE certainty of evidence was very low for tear film outcomes and low for IOP outcomes, reflecting the sparse quantitative evidence base and the dependence of meta-analytic results on two source studies.

Despite these limitations, the consistent direction of effects across individual outcome parameters, the corroboration by the narrative synthesis of non-pooled studies, and the biological plausibility of the observed mechanisms collectively support the clinical importance of aircraft cabin environmental effects on the ocular surface. These findings supported the implementation of pre-flight ocular counselling, preventive lubrication strategies, and collaborative development of aviation-medicine guidelines to protect at-risk populations. Future research employing standardised exposure protocols, reporting complete quantitative data, and investigating long-term effects of repeated cabin exposure is urgently needed to strengthen the evidence base and translate these findings into clinical practice recommendations.

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