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Impact of particulate matter and air pollution on ocular surface disease: A systematic review of preclinical and clinical evidence

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ABSTRACT

Purpose: Exposure to particulate matter (PM) and air pollution has been implicated in the etiology of ocular surface diseases (OSD). The purpose of this systematic review is to evaluate and synthesize peer-reviewed literature on the impact of PM exposure on the ocular surface, integrating results from preclinical *in vitro* and *in vivo* studies with clinical findings to provide a comprehensive understanding of molecular mechanisms, physiological effects, clinical implications, and potential therapies to target acute and chronic PM-induced ocular toxicity.

Methods: A systematic literature search was performed using PubMed and EMBASE over the period from 2009 to 2024 following the recommendations for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines. 102 studies were identified that met the inclusion/exclusion criteria. All studies were assessed for the risk of bias and qualitative data were analyzed.

Results: Preclinical studies using models of corneal and conjunctival cells found that exposure to PM and similar air pollutants resulted in apoptosis, primarily via inflammatory and oxidative stress pathways as well as allergic and immune responses. Animal models resulted in phenotypes reminiscent of that of dry eye disease, presenting with reduced tear volumes and ocular surface damage. These results were corroborated by clinical studies, which reported that patients commonly presented with symptoms of itching, burning, and irritation, and ocular surface signs correlated with a diagnosis of dry eye disease, conjunctivitis, and allergic eye disease.

Conclusions: This systematic review provides a comprehensive summary of our current understanding of PM exposure on the ocular surface, highlighting the correlation between exposure to PM and ocular surface dysfunction.

1. Introduction

Exposure to particulate matter (PM) as one of the major air pollutants has emerged as a significant public health concern in recent years due to its pervasive presence and wide-ranging adverse health effects. According to the World Health Organization, household air pollution alone was responsible for 3.2 million deaths globally per year in 2020, and the combined effects of ambient air pollution and household air pollution are associated with 6.7 million premature deaths annually [1]. Among the many organs affected by PM, the eyes are particularly vulnerable because they are directly exposed to the environment. The ocular surface, which serves as the interface between the eye and our surrounding environment, is the primary barrier against external pollutants. The ocular surface is comprised of the cornea, conjunctiva, eyelids and eyelashes, the lacrimal and meibomian glands, and the tears [2]. Exposure to PM can lead to a variety of acute and chronic ocular surface diseases (OSD) [3,4]. Acute OSD typically includes allergic and irritant-induced conjunctivitis, while chronic sequelae present as dry eye syndrome, allergic conjunctivitis, and meibomian gland dysfunction [5–7]. Thus, there is an urgent need to develop a comprehensive understanding of the etiology of PM-induced OSD and strategies for developing novel targeted therapeutics.

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PM is a heterogeneous mixture of toxic pollutants that may be solid particles and liquid droplets suspended in the air. These particles vary in size, composition, and origin. They are frequently characterized by their diameter, where $PM_{2.5}$ refers to particles with a diameter of 2.5 μm or less, and PM_{10} refers to particles with a diameter of 10 μm or less. Together, $PM_{2.5}$ and PM_{10} are widely referenced as "fine atmospheric PM". Carbon black is a component of PM composed primarily of elemental carbon in the form of fine particles. PM exposure can be from combustion processes such as vehicle emissions, diesel exhaust fumes, biomass combustion, military burn pits, and other industrial activities, natural sources like wildfires and volcanic eruption, or manmade sources like cigarette smoke and indoor fuel burning for cooking and heating.

In vitro studies provide crucial insights into the molecular mechanisms underlying the detrimental effects of PM exposure on the ocular surface and can identify cell-type specific responses following PM exposure. In contrast, preclinical *in vivo* studies allow for rigorous and standardized experimental designs to determine local effects on the ocular surface as a whole, including histopathological assessments, not possible in living organisms. Together, *in vitro* and *in vivo* preclinical studies can support the translation of novel therapeutic strategies to first-in-human trials.

Given the significant and growing body of evidence linking particulate matter to ocular surface diseases, the objective of the present study was to conduct a systematic review of preclinical and clinical studies of the effects of PM and air pollution exposure to the ocular surface. This comprehensive approach is crucial for identifying gaps in current knowledge, guiding future research directions, and informing clinical practices and public health policies aimed at protecting ocular health from the adverse effects of air pollution and toxic exposures.

2. Methods

2.1. Literature search

This systematic review followed a comprehensive search strategy to retrieve published articles following the recommendations for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines [8]. Two major databases, PubMed and EMBASE, were searched to identify peer-reviewed original articles on PM and OSD in the past 15 years, from January 01, 2009 to January 19, 2024. The following search items were used: particulate matter AND ocular OR particulate matter AND ocular surface OR pollution AND ocular OR pollution AND ocular surface. Search terms were queried in both databases. This review was not registered.

2.2. Inclusion and exclusion criteria

Articles were included in this systematic review if they met the following inclusion criteria: (1) studies in English, (2) published in the last 15 years (starting 2009), (3) articles in peer-reviewed scientific journals, and (4) preclinical studies in human and non-human models and clinical studies (interventional and observational).

The following articles and article types were excluded: (1) meta-analysis, review, and systematic review, and (2) studies in languages other than English.

2.3. Data collection

Two reviewers (S.I. and A.R.) independently conducted the literature search based on the predetermined search terms. Records were imported into Excel and duplicates were removed. Titles and abstracts were searched manually, and relevant articles had to meet the above inclusion/exclusion criteria and address the objectives of this systematic review. Any discrepancies were resolved by discussion and if needed, consultation with a third reviewer (S.K.). Full text versions of all potential studies were retrieved.

2.4. Data extraction and synthesis

The following data were extracted: (1) study characteristics and (2) study outcomes. Data were tabulated and compared with other preclinical or clinical studies.

2.5. Risk of bias

To assess bias in the included studies, the SYRCLE risk of bias tool was used for *in vivo* studies based on the Cochrane Collaboration's tool for assessing risk bias in randomized trials [9,10]. For *in vitro* studies, a modified SYRCLE risk of bias tool was used [11]. For non-randomized clinical studies, the Risk-of-Bias In Non-Randomized Studies of Exposure (ROBINS-E) tool was used for observational studies [12]. Finally, the Cochrane Risk-of-bias tool 2.0 (RoB 2.0) was used for the single interventional study [13]. Bias assessments were carried out by 2 independent reviewers (S.I. and A.R.) and any discrepancies were resolved after discussion. All risk of bias assessments were plotted using the robvis visualization tool [14].

2.6. Statistical analysis

Descriptive statistics were used to characterize the studies included in the analysis. Due to insufficient quantitative data, conducting a meta-analysis was not feasible. Therefore, a qualitative comparison between studies was performed.

3. Results

3.1. Study selection

A systematic search initially identified 946 records, of which 426 were from PubMed and 520 were from EMBASE (Fig. 1). 231 duplicate records were removed, and the remaining 715 records were screened for inclusion and exclusion criteria. Finally, 194 records were sought for retrieval and assessment. 92 studies were excluded after full-text screening. Ultimately, 102 studies were included in the qualitative systematic review and analyzed based on their classification type of (1) *in vitro*, (2) *in vivo*, or (3) clinical.

3.2. Preclinical models

Preclinical studies originated from around the world and used various types of air pollutants. The primary type of pollutant used for the included studies was particulate matter of varying sizes, as described in 25 out of 44 (57%) studies [15–39]. Other types of pollutants included carbon black, urban dust, cigarette smoke, wood smoke, diesel exhaust fumes, and volcanic ash. These pollutants were sourced from a variety of locations, including self-collected from the site of research or commercially purchased. Given the varying composition of the PM and related pollutants used, varying doses and routes were implemented to model exposure in these preclinical models. The characteristics of these studies are summarized in Table 1.

In vitro models primarily consisted of corneal epithelial cells exposed to PM or similar pollutants in 20 out of 25 (80%) *in vitro* studies [16,18,19,22–25,30–32,35,36,38–45]. 7 of 25 (28%) *in vitro* studies used conjunctival epithelial cells [21,30,42,45–48]. Additional models included both corneal and conjunctival epithelial cells [30,42,45] and a reconstructed 3D human corneal epithelial tissue model with stratified corneal epithelial cells [25]. For almost all studies, *in vitro* exposure consisted of adding PM or similar pollutants directly into the cell culture medium, except for Karakoçak et al. who performed both a liquid and gas phase exposure [40].

In vivo models primarily consisted of C57BL/6 J and BALB/c mice in

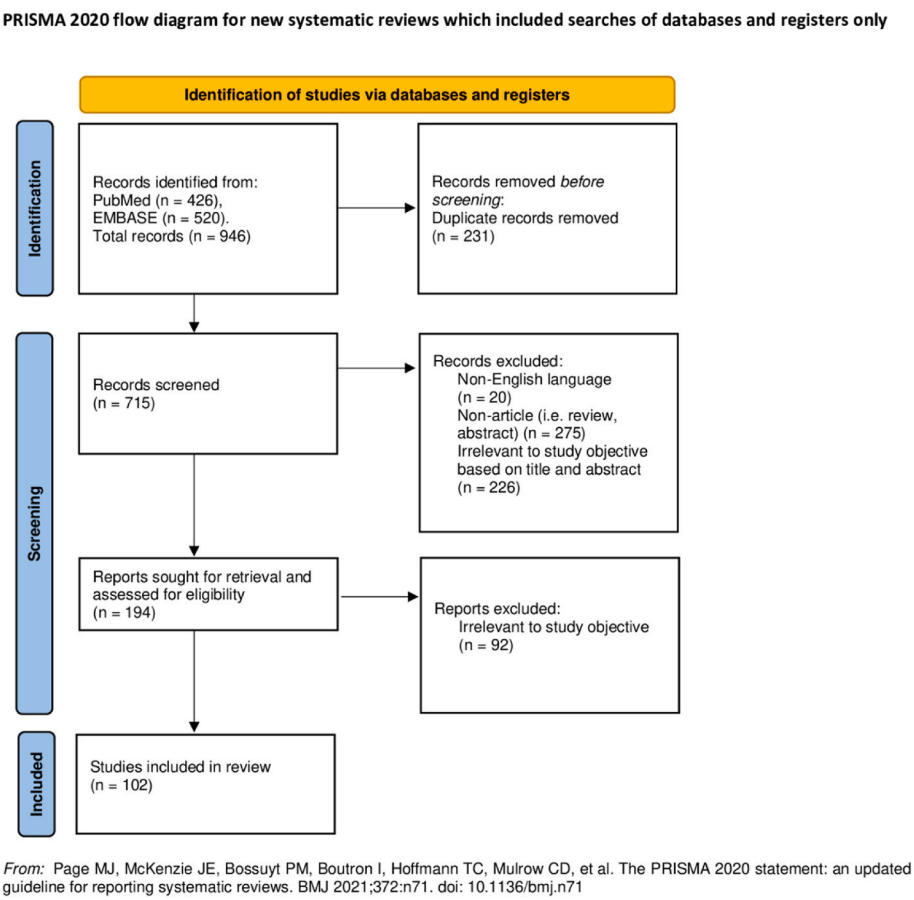

Fig. 1. PRISMA 2020 flow diagram of included studies.

11 out of 31 (35%) [17,26,32,38,39,41,43,44,49–51] and 7 out of 31 (23%) [20,28,36,52–55] *in vivo* studies respectively. Sprague-Dawley rats were also commonly used in 8 out of 31 (26%) *in vivo* studies [21,22,27,29,31,33,34,56]. Almost all studies used rodent models, except single zebrafish study [57], and a study by Ghosh et al. who were the first to describe the toxic effects of PM on the ocular surface and therapeutic efficacy of drug candidates and therapeutics in New Zealand White rabbits [18]. 20 out of 31 (65%) *in vivo* studies applied PM or other pollutants directly into the eye [17,18,20–22,26–28,31–34,36–38,44,49,51,52,57], whereas the remaining 11 out of 31 (35%) used air-forced chambers [15,29,39,41,43,50,53–56,58].

3.3. Molecular mechanisms and phenotypes identified following exposure to preclinical models

Most selected articles identified oxidative stress, inflammatory pathways, and apoptosis implicated in PM-induced ocular pathophysiology (Table 1, Suppl. Table 2). Further mechanisms identified included changes to mucin expression [44,45,53,57] and allergic and immune responses [17,20,26,37,54].

Upon exposure to PM, *in vivo* models recapitulated varying degrees of OSD phenotypes manifesting as, most commonly, a decrease in tear volume and tear film stability, and increases in corneal fluorescein staining, inflammation, and the overall presence of dry eye symptoms (Table 1, Suppl. Table 3).

3.4. Pharmacological targeting of PM-induced ocular toxicity

13 out of the 44 preclinical articles (30%) tested a drug candidate or therapeutic for PM-induced ocular toxicity in both *in vitro* and *in vivo* models either concurrently or following discontinuation of PM exposure (Table 2). The therapies tested targeted proteins or genes implicated in PM-induced toxicity, such as a sirtuin 1 (SIRT1) activator [30], granulocyte-macrophage colony-stimulating factor (GM-CSF) inhibitor [23], or necrostatin-1 (Nec-1), a specific inhibitor of necroptosis [44]. Several therapies were derived from medicinal herbs [15,21,33,34,57], and all treatments had evidence of some antioxidant and anti-inflammatory properties. Furthermore, all therapies demonstrated some level of protective effects and mitigated PM-induced toxicity to some extent.

3.5. Preclinical risk of bias assessment

The risk of bias assessments is presented in Suppl. Table 4 and Fig. 2a–b for *in vitro* studies. Across all categories, the overall quality was considered high, with a median ± interquartile range of 16 (2). All studies clearly defined the type of environmental pollutant used and the context of its use. Furthermore, all studies clearly defined *in vitro* methodology, including the cell material and specification of materials and media used. Some studies did not clearly indicate exposure or exposure modeling, and several studies demonstrated medium or no compliance with experimental robustness and randomization or blinding (Fig. 2a). Overall, the *in vitro* studies detailed full or medium compliance for criteria of robustness and downstream application; however, nearly 33% and 24% showed no compliance or medium compliance respectively for reproducibility (Fig. 2b).

The risk bias assessments are presented in Fig. 3 for *in vivo* studies. Most studies (65%) detailed randomization and baseline characteristics of the cohort. Only 23% and 26% of the studies stated blinding of participants and blinding of outcomes assessments, respectively, in their methodology. Most studies were high risk for or did not state details about allocation concealment, random housing, random outcome

Table 1
Characteristics of preclinical studies.

Study	Type of pollutant studied	Source of pollutant	Type of ocular surface disease studied	Acute or chronic exposure	Study type	Study model	Exposure dose	Exposure route	Key Results
Particulate Matter ($PM_{2.5}$, PM_4, PM_{10}, PM, Urban PM, Other PM)									
Ko et al. [25]	$PM_{0.3\text{-}2.4}$, $PM_{>2.4}$,	Fukuoka, Japan	Not specified	Not specified	*in vitro*	Reconstructed human corneal epithelium model			Decreased HCE viability and ZO-1 expression
Fu et al. [16]	$PM_{2.5}$	Hanghzou, China	Not specified	Acute	*in vitro*	HCECs	0–100 μg/mL for 24 h	Added to cell culture media	Significant decrease in cell viability
Hwang et al. [20]	$PM_{2.5}$	Road dust from Seoul, Korea	Ocular allergic inflammation	Not specified	*in vivo*	BALB/C mice	0.1–1 mg/mL b.i.d for 7 days	Topical	Th2-dominant immune response, leading to exacerbation of ocular allergic inflammation and enhanced dendritic cell maturation at 5 mg/mL
Kashiwagi et al. [23]	$PM_{2.5}$	NIES CRM No. 28 and No. 30	Ocular surface damage	Not specified	*in vitro*	HCECs	5–200 μg/mL for 48 h	Added to cell culture medium	Reduced HCEC survival and inflammatory cytokine release
Kim et al. [24]	$PM_{2.5}$	NIST SRM 1650b	Ocular surface damage	Not specified	*in vitro*	Rat CECs	25–300 μg/mL for 24h	Added to cell culture medium	$PM_{2.5}$ exposure leads to ROS/p38 MAPK/NF-κB signaling pathway and leads to mitochondrial damage and DNA double-strand break
Lee et al. [26]	$PM_{2.5}$	Road dust from Seoul, Korea	Dry eye disease or allergies	Not specified	*in vivo*	C57BL/6 mice	0.5 mg/mL b.i.d 14 days	Topical	Increase in CFS, proinflammatory cytokines, serum IgE, Th2, epithelium toxicity
Lee et al. [27]	$PM_{2.5}$	NIST SRM 1650b	Dry eye disease	Not specified	*in vivo*	Sprague-Dawley rats	5 mg/mL q.i.d for 2 weeks	Topical	Reduction of tear secretion, corneal epithelial damage, over-expression of pro-inflammatory cytokines
Lyu et al. [31]	$PM_{2.5}$	Center for Disease Control and Prevention of Zhejiang Province, Hangzhou, Zhejiang, China	Dry eye disease	Acute	*in vitro* and *in vivo*	HCECs and Sprague-Dawley rats	25–100 μg/mL for 24 h *in vitro*, 1 mg/mL q.i.d. for 21 days *in vivo*	Added to cell culture medium, topical	Upregulation of PAI-2 expression. Increased CFS and reduced tear secretion
Niu et al. [32]	$PM_{2.5}$	Chengguan Distrcit, Lanzhou, China	Ocular surface damage	Not specified	*in vitro* and *in vivo*	HCECs and C67BL/6 mice	25–400 μg/mL for 48 h *in vitro*, 1 mg/mL t.i.d. 3 months *in vivo*	Added to cell culture medium, topical	ROS formation and NLRP3 inflammasome-mediated pyroptosis axis
Yu et al. [39]	$PM_{2.5}$	Beijing	Dry eye disease	Not specified	*in vitro* and *in vivo*	HCE-T and C57/BL	Increasing doses (40–200 mg/mL) *in vitro* for 24–48 h, 200 μg/mL up to 10 weeks *in vivo*.	Added to cell culture medium, air forced chambers	Mitochondrial dysfunction, inhibition of Nrf2, activation of P65
Song et al. [35]	$PM_{2.5}$	Hanghzou	Ocular surface damage	Not specified	*in vitro*	HCECs	50–200 μg/mL for 24 h	Added to cell culture medium	Long noncoding RNAs RP3-406P24.3 and RP11-285E9.5 are involved in the biological processes and pathogenic pathways of PM-induced ocular surface damage

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Table 1 (*continued*)

Study	Type of pollutant studied	Source of pollutant	Type of ocular surface disease studied	Acute or chronic exposure	Study type	Study model	Exposure dose	Exposure route	Key Results
Tan et al. [36]	$PM_{2.5}$	Xi'an environmental monitoring station	Dry eye syndrome	Not specified	*in vitro* and *in vivo*	HCEC and BALB/c mice	5 mg/ml $PM_{2.4}$ for up to 8 h *in vitro*, 5 mg/mL q.i.d. for 14 days *in vivo*.	Added to cell culture medium, topical	Significant decrease in tear volume, TBUT, corneal epithelial microvilli and corneal desmosomes. Apoptosis and increased expression of proinflammatory cytokines.
Tang et al. [37]	$PM_{2.5}$	Taichung city, Taiwan	Allergic conjunctivitis	Chronic	*in vivo*	ICR mice	3.2–12.8 mg/mL, t.i.d. for 19 days	Topical	More eyelid edema, tearing, and scratching behaviors, with increased TBUT, higher goblet cell density and eosinophil infiltration ≥3.2 mg/mL
Ghosh et al. [18]	PM_4	NIST SRM 2786	Dry eye disease	Not specified	*in vitro* and *in vivo*	SIRC and New Zealand White Rabbits	1–300 μg/mL for 24 h *in vitro*, 5 mg/mL *in vivo* t.i.d. for up to 10 days	Added to cell culture media, topical.	Dose-dependent cell death and impaired cell motility, hyperemia, increased CFS, and decreased tear volume
Yang et al. [38]	PM_4	NIST SRM 2786	Ocular surface damage	Not specified	*in vitro* and *in vivo*	HCECs and C57BL/6 mice	0.1 mg/mL and 0.2 mg/mL for 12 or 14 h *in vitro*, 0.5–5 mg/mL q.i.d for 6 months *in vivo*	Added to cell culture medium, topical	Increased inflammatory cytokines, elevated ROS generation, and cellular apoptosis, reduced TBUT, damage to conjunctiva ≥0.5 mg/mL
Li et al. [28]	PM_{10}		Dry eye disease	Not specified	*in vivo*	BALB/c mice	5 mg/mL q.i.d. for 14 days	topical	Increased CFS, decreased tear volume, corneal epithelial microvilli, corneal chondriosome/desmosome. Apoptosis and increased levels of proinflammatory cytokines.
Guerra-Flórez et al. [19]	PM	Medellin, Colombia	Not specified	Not specified	*in vitro*	Rabbit corneal epithelial cells (SIRC) and a microphysiologic two-cell layer system.	1–5 mg/mL for 24 h	Added to cell culture medium	Multilayer models are more resistant to PM exposure than monolayer models. Fine PM is more cytotoxic than coarse PM.
Fukase et al. [17]	PM, Asian dust	NIES, Japan	Allergic conjunctivits	Not specified	*in vivo*	C57BL/6 mice	0.5 mg suspended in 2.5 μL	Topical	Increased eosinophil infiltration, no change in neutrophil infiltration
Hyun et al. [21]	Urban PM	NIST SRM 1648a	Keratoconjunctivitis Sicca	Not specified	*in vitro* and *in vivo*	Conjunctival epithelial cells and Sprague-Dawley rats	100 μg/mL for 24 *h in vitro* and 20 mg/mL t.i.d for 5 days *in vivo*	Added to cell culture media, topical	Increased release and expression of TNF-α and IL-6, reduction of tear secretion, corneal epithelial damage, disruption of mucin-4
Hyun et al. [57]	Urban PM	NIES No. 28	Ocular surface damage	Not specified	*in vitro* and *in vivo*	zebrafish, EA.hy926 cells	0.001–0.1 % PM in water, 3–100 μg/mL PM in cell culture medium	Added to cell culture medium, added to water of zebrafish embryo	Fatal malformation in the integuments of zebrafish, increased vascular diameter, increased cell migration and capillary-like structure formation, and angiogenesis
Kang et al. [22]	Urban PM	NIST SRM 1648a	Ocular surface damage	Chronic	*in vitro* and *in vivo*	HCE cells and Sprague-Dawley rats	0–1000 μg/mL for 24 h *in vitro*, 5 mg/mL q.i.d.	Topical, added to cell	Decreased cell migration and survival, and

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Table 1 (*continued*)

Study	Type of pollutant studied	Source of pollutant	Type of ocular surface disease studied	Acute or chronic exposure	Study type	Study model	Exposure dose	Exposure route	Key Results
							for 16 weeks *in vivo*	culture media	consistently increased fluorescein scores
Li et al. [30]	Urban PM	NIST 1648a	Ocular surface damage	Acute	*in vitro*	HCEC and HCjECs	100–1000 μg/mL for 24 h	Added to cell culture medium	ROS production, decreased SIRT1 expression.
Park et al. [33]	Urban PM	NIST SRM 1648a	Dry eye disease	Not specified	*in vivo*	Sprague-Dawley rats	20 mg/mL t.i.d for 5 days	Topical	Tear hyposecretion, corneal irregularity, apoptotic injury of lacrimal gland
Shi et al. [44]	Urban PM	NIST 1649b	Ocular surface damage	Not specified	*in vitro* and *in vivo*	HCECs and C57BL/6 mice	50–150 μg/mL for 16 h *in vitro*, and 2 mg/mL q.i.d *in vivo*.	Added to cell culture medium, topical	PM-induced necroptosis, inducing corneal inflammation and decreased mucin production.
Song et al. [34]	Urban PM	NIST SRM 1648a	Dry eye syndrome	Not specified	*in vivo*	Sprague-Dawley rats	1 mg/mL - 10 mg/mL t.i.d for 10 days	Topical	Decreased tear volume, corneal epithelial irregularity and damage, disruption of corneal mucin-4 layer ≥1 mg/mL
Maglione et al. [53]	Urban air	Buenos Aires City	Ocular mucosa	Chronic	*in vivo*	BALB/c mice	5 L/min for up to 12 months	Air forced chambers	Alterations in mucin-positive cells and increased IL-6 levels
Sendra et al. [54]	Urban airflow and indoor airflow	Buenos Aires city	Immune responses	Not specified	*in vivo*	BALB/c mice	8 h per day	Air forced chambers	Development of a severe form of herpes simplex keratitis with increased corneal opacity, neovascularization, HSV-1 DNA and production of proinflammatory cytokines. Activation of dendritic cells.
Vitar et al. [55]	Urban air	Buenos Aires city	Ocular surface damage	Not specified	*in vivo*	BALB/c mice	Urban air for 8 h/day, 5 days/week up to 12 weeks	Air forced chambers	Increase in antioxidant enzymes after 1 week, redox imbalance, proinflammatory cytokines
PM from combustion									
Akintunde et al. [15]	Wood smoke and PM_{10}	Melina wood	Ocular surface damage	Subchronic	*in vivo*	Albino rats	441.2 μg/m^3 PM_{10} from wood smoke, 20 min, q.d. for 21 days	Air forced chambers	Inflammation, alterations in antioxidant enzyme concentration, and cell damage
Karakoçak et al. [40]	Applewood and coal combustion	Commercially available sources	Toxicity on ocular cells	Acute	*in vitro*	Corneal, lens, and retinal epithelial cells	3 L per minute or 10–1000 μg/mL for 1 h	Gas phase exposure and liquid phase exposure.	Coal emission had more toxic effect than applewood emission on ocular cells, with decreased cell viability and increased ROS generation.
Cigarette and tobacco smoke									
Jin et al. [49]	Cigarette smoke extract	Commercial cigarette	Ocular surface damage	Not specified	*in vivo*	C57/BL6J mice	1–5 % V/V q.d. for 1 week	Topical	Disruption of the structural integrity of the superficial epithelium, decreased the density of microvilli, and compromised the corneal epithelial barrier intactness ≥1 % V/V
Kojima et al. [50]	Sidestream cigarette smoke	Seven Stars	Ocular surface damage	acute	*in vivo*	C57BL/6 Wildtype and Nrf2 knockout mice	1 lit cigarette every 30 min, 6 times in 3 h for 5 days	Air forced chamber	Decreased tear stability, ocular surface damage, and altered conjunctival phenotype for Nrf2

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Table 1 (*continued*)

Study	Type of pollutant studied	Source of pollutant	Type of ocular surface disease studied	Acute or chronic exposure	Study type	Study model	Exposure dose	Exposure route	Key Results
									knockout over wildtype
Li et al. [41]	Cigarette smoke	Marlboro cigarettes	Dry eye disease	Chronic	*in vitro* and *in vivo*	HCECs and c57BL mice	Dilutions of DMSO lipid-soluble cigarette smoke particles equivalent of 3 cigarettes *in vitro*, equivalent of 8 cigarettes for 4 or 12 weeks *in vivo*	Added to cell culture medium, air forced chambers	Presence of dry eye symptoms, corneal and conjunctival damage, increase of apoptosis and Ki67. Proinflammatory cytokine release
Miao et al. [43]	Cigarette smoke extract	Marlboro cigarettes	Ocular surface damage	Not specified	*in vitro* and *in vivo*	HCECs and C57BL/6 mice	1.5 % cigarette smoke extract up to 6 h *in vitro*, 50 mL smoke every 30 min, 6 times for up to 3 days *in vivo*.	Added to cell culture medium, air forced chambers	Reduced cell viability, increased apoptotic cells, elevated intracellular oxidative stress and loss of mitochondrial transmembrane potential, autophagy
Xiao et al. [58]	Tobacco smoke	Malboro	Corneal wounds	Acute	*in vivo*	NFκB1 mutated mice	3 lit cigarettes in 90 min, twice 12 h apart	Air forced chamber	Increased levels of epinephrine and norepinephrine, enhanced inflammatory responses, delayed wound healing, and altered immune cell populations in the cornea
Carbon black									
Jiao et al. [52]	Carbon black	Extracted from $PM_{2.5}$ from Beijing	Dry eye disease	Not specified	*in vivo*	BALB/C mice	0.5 mg/mL - 5 mg/mL t.i.d for 2 weeks	Topical	Decreased tear film stability, reduced tear secretion, ocular surface damage ≥0.5 mg/mL
Li et al. [56]	Carbon black	Orion Engineered Carbons	Ocular injury	Not specified	*in vivo*	Sprague-Dawley rats	160 μg/m^3 for 2 h b.i.d. for 5 days	Air forced chambers	Increased CFS, LDH activity, serum IgG and IgE, cervical lymph nodes, IK-4, IFN-γ
Li et al. [29]	Carbon black, PM_{10}	Orion Engineered Carbons	Ocular surface damage	Not specified	*in vivo*	Sprague-Dawley rats	160 μg/m^3 for 5 days	Air forced chambers	Increase in ocular surface staining scores, tear LDH activity, tear MMP-9, histamine, and lactoferrin concentrations, and the expression of IL-4 and IFN-γ
Diesel exhaust particles									
Tau et al. [45]	Diesel exhaust particles	Sao Paulo, Brazil	Not specified	Not specified	*in vitro*	corneal epithelial cells (HCLE) and conjunctiva epithelial cells (IOBA-NHC)	10–500 μg/mL for 24 h	Added to cell culture medium	Cytotoxicity and inflammatory response, increase in mucin expression in cornea and conjunctiva
Vitar et al. [47]	Diesel exhaust particles	Sao Paulo, Brazil	Not specified	Not specified	*in vitro*	Human conjunctival epithelium cell line	10–100 μg/mL for 24 h	Added to cell culture media	Increased levels of reactive oxygen species (ROS), reactive nitrogen species (RNS), hydrogen peroxide
Vitar et al. [48]	Diesel exhaust particles	Sao Paulo, Brazil	Not specified	Not specified	*in vitro*	Conjunctival epithelial cells	100 μg/mL for up to 24 h	Added to cell culture medium	Early redox imbalance followed by an IL-6 mediated inflammatory response, with

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Table 1 (*continued*)

Study	Type of pollutant studied	Source of pollutant	Type of ocular surface disease studied	Acute or chronic exposure	Study type	Study model	Exposure dose	Exposure route	Key Results
									involvement of mitochondrial superoxide anion and NADPH oxidase-4
Yang et al. [51]	Diesel exhaust particles	NIST SRM 2975	Ocular surface damage	Not specified	*In vivo*	C57BL/6 mice	100 and 1000 μg/mL b.i.d. for up to 28 days	Topical	Increased corneal epithelial permeability, alterations in corneal epithelial cell layers, Ki67 expression. Reduced goblet cells in the conjunctival fornix, and apoptotic cells in the corneal and conjunctival epithelium. Increased $CD4^+$ cells and NFκB expression in conjunctiva ≥100 μg/mL
Other PM sources									
Li et al. [42]	Titanium dioxide (TiO_2) NPs, carbon black (CB) NPs, and silicon dioxide (SiO_2)	Commercial suppliers	Ocular surface damage	Not specified	*in vitro*	HCECs and HCjECs	12.5–400 μg/mL for 24 h	Added to cell culture medium	Toxic effects were more severe in HCECs than HCjECs, increased ROS, leading to apoptosis and mitochondrial damage
Tesone et al. [46]	Volcanic ash	Puyehue-Cordon Caulle Volcanic Complex	Not specified	Not specified	*in vitro*	Conjunctival epithelial cells	50–1000 μg/mL for 24 h	Added to cell culture medium	Reduced cell proliferation, increased pro-inflammatory cytokines

Table 1 Abbreviations: HCEC: Human corneal epithelial cells, h: hours, NIES: National Institute for Environmental Studies, NIST: National Institute for Standards and Technology, SRM: Standard Reference Materials, t.i.d.: ter in die (three times a day), b.i.d,: bis in die (two times a day), q.d.: quaque die (once a day), q.i.d.: quater in die (four times a day), CRM: Certified Reference Materials, Nrf2: Nuclear factor (erythroid-derived 2)-like 2, HCjECs: Human Conjunctival Epithelial Cells, NFκB1: Nuclear Factor Kappa B Subunit 1.

assessment, and selective outcome reporting (Fig. 3).

3.6. Clinical studies

A summary of key characteristics (geographic location, study population, type of pollutant(s) studied, method of pollutant exposure measurement, type of ocular surface disease studied/symptoms, method of ocular surface disease/symptoms diagnosis or evaluation) of all clinical studies assessed in this review are represented in Table 3.

The results of the studies assessed are briefly summarized below.

3.7. Ocular surface signs and symptoms

Several studies in school children investigated general ocular symptoms, such as itching, burning, irritation, and tearing in response to $PM_{2.5}$ and PM_{10} [59–62], as well as other airborne irritants [63,64]. Generally, exposure to PM was positively correlated with ocular surface symptoms. Similar findings were obtained in various studies in adult populations across differing geographical locations and social or occupational exposures [65–74]. Overall, most studies demonstrated that levels of PM and other airborne pollutants such as NO_2, O_3, SO_2 were significantly correlated with incidence and/or severity of varying ocular surface symptoms.

Presence of DED has been found to significantly associated with NO_2 [75,76] and O_3 but not with SO_2 or PM_{10} [76], supported by significant correlations between $PM_{2.5}$, PM_{10}, and NO_2 and biomarkers for meibomian gland disease and inflammation [77–81]. Similarly, ocular surface signs such as tear break-up time (TBUT), lipid layer thickness (LLT), mucus quality and composition, Schirmer's test, were associated positively with PM levels and other airborne pollutants [82–85]. Pollutants had similar effects in patients with Sjögren's disease and those with MGD [83].

While Matsuda et al. reported that air pollutants including $PM_{2.5}$ alter the ocular surface through perturbations in mucus quality [84], Toricelli et al. did not observe any significant correlation between levels of NO_2 or $PM_{2.5}$ and OSDI scores or MUC5AC mRNA expression [86]. The same group observed a negative correlation between tear osmolarity level and $PM_{2.5}$ levels but not NO_2; similarly OSDI, TBUT, Schirmer test, and vital staining scores were not significantly correlated with $PM_{2.5}$ or NO_2 levels [87]. Blepharitis-associated eyelid debris was significantly correlated CO, NO_2, and PM_{10} exposure, while NO_2 exposure was linked to increased MG secretion [88].

Several studies reported paradoxical findings, while others demonstrated that associations between particulate matter exposure and ocular surface signs and symptoms were notably affected by confounding variables, including temperature and humidity [89,90], consistent with studies that evaluated the impact of indoor environment [91,92].

3.8. Conjunctivitis and allergic eye disease

Several studies found differential associations between CO, $PM_{2.5}$, PM_{10}, NO, NO_2, O_3, and SO_2 with incidence of conjunctivitis, vernal keratoconjunctivitis, diagnosis and outpatient visits for allergic conjunctivitis, and acute microsporidial keratoconjunctivitis (MKC) [93–102]. Nucci et al. reported the association between pediatric conjunctivitis of unknown origin and higher levels of PM_{10}, but did not

Table 2
Preclinical studies testing therapies to mitigate PM-induced toxicities.

Study	Type of pollutant studied	Study model	Exposure dose	Therapy tested	Therapy dose and route	Description of therapy	Effects of therapy
Akintunde et al. [15]	Wood smoke and PM_{10}	Albino rats	441.2 μg/m^3 PM_{10} from wood smoke, 20 min, q.d. for 21 days	Naringin	80 mg/kg/d oral, cotreated with exposure for 21 days	Naturally-derived bioactive flavanone glycoside	Protective against wood smoke-induced ocular damage
Ghosh et al. [18]	PM_4	SIRC and New Zealand White Rabbits	1–300 μg/mL for 24 h *in vitro*, 5 mg/mL *in vivo* t.i.d. for up to 10 days	Two separate treatments: Mn-TM-2-PyP or lifitegrast	0.05 % w/v Mn-TM-2-PyP or 5 % ophthalmic lifitegrast, topical, for 10 days after discontinuation of PM exposure	Mn-TM-2-PyP, a synthetic antioxidant, and lifitegrast.	Both treatments improved hyperemia and CFS. Efficacy of Mn-TM-2-PyP was greater compared with lifitegrast.
Hyun et al. [21]	Urban PM	Conjunctival epithelial cells and Sprague-Dawley rats	100 μg/mL for 24 *h in vitro* and 20 mg/mL t.i.d for 5 days *in vivo*	Apricot kernel extract and amygdalin	0.5 or 1 mg/mL topical q.d. for 5 days after exposure	Extract from the seed of *Prunus armeniaca* (apricot)	Attenuate corneal epithelial damage and reduction of tear secretion, and prevention of MMP9 and proinflammatory cytokines
Hyun et al. [57]	Fine dust	zebrafish, EA.hy926 cells	0.001–0.1 % PM in water, 3–100 μg/mL PM in cell culture medium	α/β adenosine	0.3–3 μg/mL added to water or cell culture medium	Isolated from the anti-angiogenic brown algae *Ishige okamurae* extract	Protective against angiogenesis
Kashiwagi et al. [23]	$PM_{2.5}$	HCECs	5–200 μg/mL for 48 h	Suramin	1 or 5 μM added to cell culture medium simultaneously	Suramin, a GM-CSF inhibitor	Alleviated HCEC impairment
Lee et al. [27]	$PM_{2.5}$	Sprague-Dawley rats	5 mg/mL q.i.d for 2 weeks	Spermidine, cyclosporin A	0.2 % and 0.5 %, topical, q.i.d. 30 mins after PM exposure for Spermidine. 0.05 % Cyporin N.	Spermidine, cyclosporine A	Attenuated reduction of tear secretion and corneal epithelial damage
Li et al. [56]	Carbon black	Sprague-Dawley rats	160 μg/m^3 for 2 h b.i.d. for 5 days	diquafosol	3 % topical 6 times a day during exposure	Diquafosol, a mucin secretagogue	Protective effect, increased tear MUC5AC concentration and decreased tear LDH activity.
Li et al. [29]	carbon black, PM_{10}	Sprague-Dawley rats	160 μg/m^3 for 5 days	Eyebon-W eye wash	1 mL irrigation for 30 s after exposure (twice daily)	Commercial eye wash solution containing anti-inflammatory and antihistamine agents.	Reversed elevation of IL4, IFNγ, ocular staining scores, tear LDH activity, histamine and MMP-concentrations in tear fluid
Li et al. [30]	Urban PM	HCEC and HCjECs	100–1000 μg/mL for 24 h	SRT1720	2.5 μM for 24 h with PM exposure	SRT1720, a SIRT1 activator	Upregulated SIRT1 expression and inhibited ROS production
Miao et al. [43]	Cigarette smoke extract	HCECs and C57BL/6 mice	1.5 % cigarette smoke extract up to 6 h *in vitro*, 50 mL smoke every 30 min, 6 times for up to 3 days *in vivo*.	cysteamine	250 μM *in vitro*, 0.55 % in PBS topical pretreatment *in vivo*	Cysteamine, an anti-oxidant and inducer of autophagy	Attenuated cell damage, oxidative stress and mitochondrial dysfunction; rescued *in vivo* phenotype.
Park et al. [33]	Urban PM	Sprague-Dawley rats	20 mg/mL t.i.d for 5 days	Aucubin	0.1 % and 0.2 %, topical t.i.d. 30 mins after exposure for an additional 5 days	Aucubin, isolated from a traditional medicinal herb, *Aucuba japonica*	Attenuated tear hyposecretion, corneal irregularity, and apoptotic injury of lacrimal glands
Shi et al. [44]	Urban PM	HCECs and C57BL/6 mice	50–150 μg/mL for 16 h *in vitro*, and 2 mg/mL q.i.d *in vivo*.	Nec-1	5 mg/kg intraperitoneally q.d. with PM exposure	Necrostatin-1, specific inhibitor of necroptosis	Inhibition of the increased inflammatory cytokines and the decreased mucin expression. Reduced corneal inflammation and mucin underproduction in mouse ocular surface
Song et al. [34]	Urban PM	Sprague-Dawley rats	1 mg/mL - 10 mg/mL t.i.d for 10 days	*Liriope platyphylla* extract	10 mg/mL topical t.i.d. for 9 days with exposure. On final day, administered once.	Extract from *Liriope platyphylla,* a perennial herbaceous evergreen of the lily family.	Attenuated decrease in tear volume and reduced corneal epithelial irregularity and damage; protected against disruption of the corneal mucin-4 layer and reduction in the conjunctival goblet cell density

Table 2 Abbreviations: q.d.: quaque die (once a day), h: hours, t.i.d.: ter in die (three times a day), Mn-TM-2-PyP: Manganese(III) tetrakis(1-methyl-4-pyridyl) porphyrin, CFS: Corneal Fluorescein Staining, MMP: Matrix metalloproteinases, HCEC: Human corneal epithelial cells, GM-CSF: Granulocyte-macrophage colony-stimulating factor, q.i.d.: quater in die (four times a day), ROS: Reactive Oxygen Species, b.i.d.: bis in die (two times a day), MUC5AC: Mucin-5AC, HCjECs: Human Conjunctival Epithelial Cells, SIRT1: Sirtuin 1.

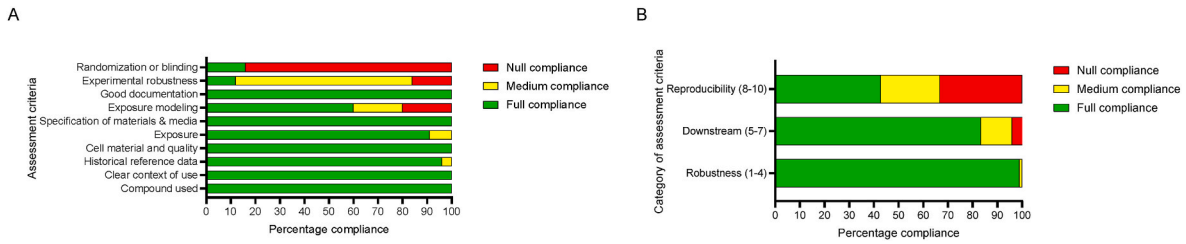

Fig. 2. Risk of bias assessment of *in vitro* studies. (A) Study compliance with validation metrics as evaluated in Suppl. Table 4 using a modified SYRCLE risk of bias tool. (B) Study compliance with validation criteria categorically presented. The following domains were assessed: 1) Does the study use (an) appropriate compound(s) to stimulate the desired outcome(s)? 2) Is there a clear definition of the relevance of the test method, making clear the relationship of the test method to the outcome(s) of interest? 3) Does the study make use of data for the outcome(s) for defined reference compounds (positive and negative controls). Are the concentration ranges tested included? 4) Is there a full description of cell or tissue source(s), are quality checks included? (e.g., viability, functional performance tests, metabolic activity). 5) Does the study detail drug stability data and determination of exposure? (total/unbound, ideally also intracellular concentrations). 6) Is there a detailed description of materials with regards to drug interactions? 7) Has there been an attempt to model the in vitro-in vivo extrapolation of the drug response? 8) Was the study carried out according to clear protocols? Is there available documentation suitable for a GLP-style environment i.e. commercial assay? 9) Is there a demonstration of intra-lab or multi researcher repeatability? (There would also ideally be demonstration of inter-laboratory comparative data). 10) Is there mention of attempts to reduce investigator bias including randomization and/or blinding.?.

observe any association with $PM_{2.5}$ levels [103].

3.9. Associations between particulate matter exposure and ocular disease

Three studies evaluated the possible association between toxic particulate exposure and ocular disease. Zambrano et al. demonstrated significantly higher odds for the presence and increased severity of trachoma when exposed to indoor pollution secondary to cooking fires [104]. Ramirez et al. did not observe any significant association between PM exposure and pterygium [105], while Lee et al. noted a weak yet significant association with PM_{10} [106]. No significant association of new pterygium or pterygium recurrence was found with O_3, NO_2, or SO_2 [106].

3.10. Studies with therapeutic interventions

Only one clinical study assessed in this review was focused on therapeutic management. Antonini et al. investigated the safety and efficacy of daily three times a day administration of topical glycophosphoinositol (GPI) eye drops for the treatment of urban syndrome, a mixed condition with features of DED thought to be caused by poor air conditions and the urban environment [107]. Results noted that OSDI score, TBUT, and Schirmer's tear test showed an improvement from patient enrollment to the 1-month endpoint. Of note, the open interventional study only had a treatment arm with no controls nor healthy patients with no history of urban syndrome.

3.11. Clinical risk of bias assessment

Risk of bias was assessed using the ROBINS-E tool for observational clinical studies and the RoB 2.0 tool for the single interventional study (Suppl. Tables 5 and 6). Summary findings are reported through the Traffic Light Plots and Summary Plot as represented in Fig. 4a–c. Per ROBINS-E parameters of overall risk of bias assessment, 42% of studies were classified as low, 25% as some concerns, and 33% as high. Domain three had the highest number of risk assessments evaluated as high risk of bias. This is notable as domain three evaluates risk of bias in selection of participants into the study (or analysis); many studies assessed in this review focused on a subsect of patients, which may have existing underlying ocular surface dysfunction, distinct from the general population. For the one interventional study evaluated using the RoB 2.0 tool, the overall risk assessment was high.

4. Discussion

Overall, this systematic review of both preclinical and clinical studies demonstrates evidence of ocular surface dysfunction resulting from air pollution consisting of a mixture of gaseous substances such as NO_2, O_3 as well as different types of PM ($PM_{2.5}$, PM_4, PM_{10}, urban PM), diesel exhaust particles, cigarette smoke, and carbon black. While studies varied in their findings of significance, correlation between ocular surface disease and exposure to air pollutants in both normal daily living and environmental disasters is of increased significance. In addition, studies reviewed suggest that exposure to PM and air pollution is not only detrimental during acute environmental disasters or occupational exposures but also from every day exposure given increases in the levels of air pollution parameters measured throughout the years and worsening AQI in some parts of the world [108–111].

One open question that remains is to what extent acute and subchronic PM exposures contribute to an increased risk for developing chronic ocular surface disease. Whole body exposure chambers are best suited to model real world exposure and systemic effects of PM exposure that include inflammation, allergic responses, and organ toxicity. Such systemic effects may confound the investigation of ocular effects, which can occur due to local and systemic exposure. Therefore, topical instillation of PM allows for the investigation of mechanism of ocular PM toxicity in the absence of systemic exposure in the preclinical setting. In contrast, whole body exposure could investigate the possible link between neurotoxicity and ocular surface toxicity. Notably, to our knowledge there have been no studies investigating the effects of PM-mediated neurotoxicity on the postganglionic parasympathetic pathway which could result in impaired tear secretion from the lacrimal gland, thereby contributing to ocular surface disease.

Although the exact mechanisms behind the correlation are not fully elucidated, preclinical models implicate pathways related to oxidative stress, inflammation, and apoptosis in PM-induced ocular pathophysiology. Current hypotheses suggest the perturbations may lead to a combination of exaggerated inflammatory response, impaired oxidative stress handling, changes to mucin expression, and allergic and immune responses ultimately leading to ocular surface dysfunction. Given the differences in the composition, type, and origin of PM, the possibility cannot be excluded that different molecular and cellular mechanisms contribute to ocular toxicity. Furthermore, several preclinical studies that reported efficacy of test articles also noted that only limited information was available pertaining to the exact mechanisms of action. Investigation of molecular mechanisms and/or targets of tested interventions can improve the translatability of the studies as well as inform future drug development efforts of targeted therapeutics for PM-

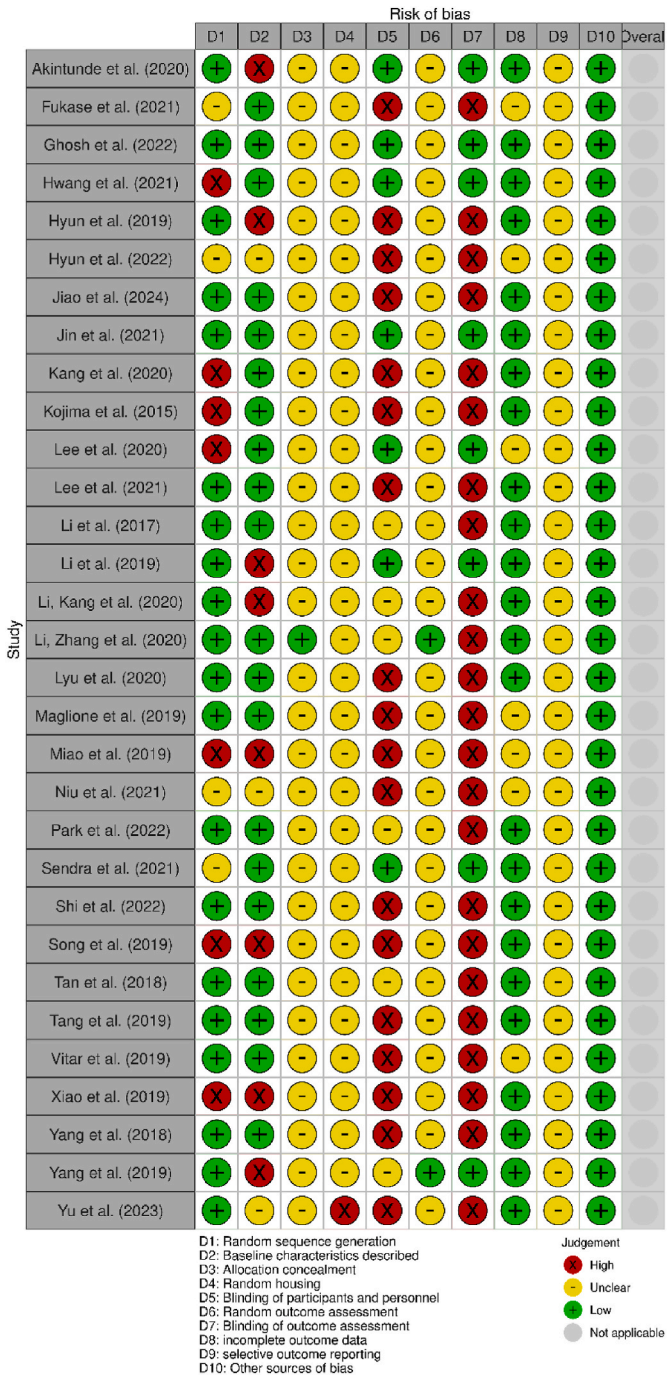

Fig. 3. Risk of bias assessment of *in vivo* studies. The SYRCLE's RoB tool was used to evaluate all *in vivo* studies. The following domains were assessed: 1) Was the allocation sequence adequately generated and applied? 2) Were the groups similar at baseline, or were they adjusted for confounders in the analysis? 3) Was the allocation to the different groups adequately concealed? 4) Were the animals randomly housed during the experiment? 5) Were the caregivers and/or investigators blinded from knowledge of which intervention each animal received during the experiment? 6) Were animals selected at random for outcome assessment? 7) Was the outcome assessor-blinded? 8) Were incomplete outcome data adequately addressed? 9) Are reports of the study free of selective outcome reporting? 10) Was the study apparently free of other problems that could result in high risk of bias.?.

induced ocular toxicity.

There are several important factors that some studies have in common while others vary and must be taken into careful consideration. *In vitro* and *in vivo* studies utilized different models of environmental pollution exposure that differed in the composition and method/route of administration. For example, the authors obtained environmental pollutants either locally, e.g. by collecting PM from a nearby building, or from commercial vendors. However, different amounts of characterization are publicly available even for commercially sourced PM, further complicating the interpretation of studies. Similarly, the administration model and dosing route had significant heterogeneity between studies, varying from whole-body exposure to topical instillation. For this reason, most studies received medium to low compliance scores for reproducibility in the risk assessment (Fig. 2b). By nature, articles that investigated specific chemicals present in environmental pollutants are more reproducible. However, due to the heterogeneity between sources of pollutants, their use, and the readouts in each study, this systematic review offers a comprehensive overview of models that replicate aspects of the real-world exposure to PM on the ocular surface.

In clinical studies, one major factor that limits comparisons between studies is the method of measuring air pollution exposure. Some studies utilized individualized measurements that provided real-time exposure levels, while others focused on national air quality/meteorological station data. A few studies even built models to combine various data to predict the likely exposure. As expected, the primary concern with national air quality/meteorological data and survey/sociodemographic variables is the potential for misclassification of exposure, which is why the ROBINS-E tool was utilized to compare studies' potential misclassification.

Interestingly, only one study specifically investigated the effect of PM associated with desert sources and at the time of desert storms, but linked the effect of symptoms to the air quality data [112], Another study reported that participants from the mediterranean climates in the US *vs.* participants from the subtropical desert climates in the US had better ocular surface health and identified a positive correlation between TBUT measurements and air temperature, humidity, and dewpoint [81]. The effects of environmental conditions on the ocular surface and ocular health in general have recently been reviewed in a scoping review [113]and in the TFOS Lifestyle Report [114], respectively.

In vitro models primarily employed corneal epithelial or conjunctival epithelial cells as they represent the outermost layers of the eye and the first to come in contact with exposure to the environment; furthermore, they are frequently used in preclinical drug discovery [115,116]. *In vivo* models primarily utilized rodents, because of their low cost and the extensive availability of molecular tools [117]. Ghosh et al. was the singular study to use New Zealand White rabbits [18]. Rabbit models have a larger eye, which allows for a larger exposed ocular surface and the ability to perform more standardized veterinary ophthalmic exams, which are challenging to impossible in rodents. Similarly, Hyun et al. used zebrafish embryos [57]. Zebrafish models have many advantages in providing insights into developmental biology, however, the zebrafish model is not a preferred species for translatability of the ocular surface. The transparent larva allows for sublocalization of any deformations, as seen in the results with severe deformation on epithelial and ocular regions following exposure to fine dust [57,118].

There was also a notable variability in clinical studies assessing the ocular surface disease. Approaches ranged from assessing symptoms per self-report to more detailed and specific clinical examinations. Another consideration is the method of analysis given the wide range of statistical analysis options studies utilized ranging from simple correlation analysis to more complex regression models. While these varying factors provide a unique diversity of studies to assess, they also demonstrate the significant challenge of synthesizing the findings of multiple studies.

Table 3
Clinical studies.

Study	Geographic Location	Study population	Type of Pollutant (s) studied	Method of pollutant exposure measurement	Type of ocular surface disease studied/ symptoms	Method of ocular surface disease/symptoms diagnosis or evaluation
Aik et al. [102]	Singapore	Patients diagnosed with conjunctivitis in governmental polyclinics	SO2, NO_2, $PM_{2.5}$, PM_{10}, O_3, CO	Air quality monitoring station data	Acute conjunctivitis	EMR
Almeida et al. [61]	Uberaba, Brazil	Schoolchildren	PM_{10}, NO_2, O_3	Particle monitor, passive sampling	Tearing, itchy eyes	Questionnaire
Antonini et al. [107]	USA	Patients affected by urban syndrome	N/A (assessed safety and efficacy of GPI topical ophthalmic treatment)	N/A	Urban failure	OSDI, TBUT, Schirmer, fluorescein vital staining according to Oxford score, conjunctival hyperemia score, ocular discomfort symptoms assessed as a score
Arikan et al. [59]	Kutahya, Turkey	Students at a primary school	PM_{10}, $PM_{2.5}$	Particles Plus 8306 Handheld Particle Counter	Redness-itching-watering of eyes	Questionnaire
Ashraf et al. [74]	Lahore, Pakistan	Patients presenting with chief complaints of redness, burning, FBS at tertiary care hospitals	Lahore smog: CO, NO_x, SO_2, O_3, VOC, PM_{10}, $PM_{2.5}$, TSP	Air quality monitoring station data	Dry eyes, irritation, lid erosion, corneal disease, conjunctival disease	Slit lamp examination and diagnosis by ophthalmologist
Bao et al. [97]	Heifei, China	Patients diagnosed with conjunctivitis in an outpatient setting	NO_2	Air quality monitoring station data	Conjunctivitis	EMR
Berg et al. [81]	USA	Adults with ocular dryness for at least 6 consecutive months with moderate to severe symptoms	O_3, CO, NO_2, NO_x, NO_y, SO_2, $PM_{2.5}$	Air quality monitoring station data	DED	OSDI, TBUT, corneal and conjunctival staining, Schirmer's test
Berra et al. [72]	Buenos Aires, Argentina	Patients with ocular complaints and healthy volunteers	Wildfire smoke, CO, NO_2, PM	Air quality monitoring station data	Ocular burning, dryness, foreign body sensation, irritation, itching	Questionnaire, ophthalmic examination: bulbar conjunctival hyperemia, corneal fluorescein staining, conjunctival Rose Bengal vital staining, TBUT, Schirmer's test, tear lysozyme concentration, impression cytology
Blinn et al. [66]	Pennsylvania, USA	Residents living in proximity to unconventional oil and gas development	$PM_{2.5}$, CO, NOx, VOC, CH_4, XO_2	Air quality monitoring station data	Itchy or burning eyes	Questionnaire
Camara et al. [69]	O'ahu, Hawaii	Patients presenting with chief complaint of eye irritation	SO_2, $PM_{2.5}$, volcanic fog	Air quality monitoring station data	Eye itchiness, foreign body sensation, tearing, burning sensation	Self-reported symptoms, Slit lamp examination findings
Chang et al. [96]	Taiwan	Patients diagnosed with conjunctivitis in an outpatient setting	PM_{10}, $PM_{2.5}$, NO_2, SO_2, O_3, CO	Air quality monitoring station data	Conjunctivitis	EMR/ICD-9 codes
Cilluffo et al. [62]	Palermo, Italy	Schoolchildren aged 8-10	NO_2	Estimated from land use regression model	Burning, itching, dry, red eyes, swollen eyes, sandy feeling in the eyes	Questionnaire
Das et al. [95]	Hyderabad, India	Patients diagnosed with microsporidial keratoconjunctivitis	PM_{10}, $PM_{2.5}$, SO_2, NO_2, O_3, CO	Air quality monitoring station data	Microsporidial keratoconjunctivitis	EMR, assessed by ophthalmologist
Das, Basu [101].	Hyderabad, India	Patients <21 newly diagnosed with allergic eye disease and acute exacerbation of recent onset of symptoms <3 months	PM_{10}, $PM_{2.5}$, SO_2, NO_2, O_3, CO	Air quality monitoring station data	Allergic eye disease	EMR, assessed by ophthalmologist
Galperin et al. [82]	Buenos Aires, Argentina	Sjogren's syndrome patients and healthy volunteers	NO_2	Individual passive sampler	Sjogren's syndrome, worsening ocular surface disease	OSDI, biomicroscopy, TBUT, Schirmer test, corneal and conjunctival staining, tear lysozyme concentration, impression cytology
Guo et al. [98]	Jinan, China	Patients diagnosed with conjunctivitis in an outpatient setting	NO_2	Air quality monitoring station data	Conjunctivitis	EMR/ICD-10
Hao et al. [119]	China	DED patients	$PM_{2.5}$, SO_2, NO_2, O_3	Air quality monitoring station data	DED	OSDI, Schirmer's I test, TMH, TBUT, corneal fluorescein staining, MGD, tear cytokines
Hao, Wan et al. [78]	China	Healthy volunteers aged 20–80 across different regions (coal, steel, oil, urban living)	AQI, PM_{10}, $PM_{2.5}$, SO_2, NO_2, O_3	Air quality monitoring station data	General ocular surface dysfunction	OSDI, lid margin morphology, MG morphology/function, tear meniscus height, Schirmer's test, TBUT, CFS, slit lamp examination of MG; tear film cytokines including IL-1B, IL-6,

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Table 3 (*continued*)

Study	Geographic Location	Study population	Type of Pollutant (s) studied	Method of pollutant exposure measurement	Type of ocular surface disease studied/ symptoms	Method of ocular surface disease/symptoms diagnosis or evaluation
						IL-8, IL-10, Il-17, TNF-a, IFN-y, VEGF, BAFF
Ho et al. [90]	Taipei City, Taiwan	First time DED patients	PM_{10}, $PM_{2.5}$, SO_2, O3, CO, CH_4, NO, NO_2, Total hydrocarbon, nonmethane hydrocarbon, AQI	Air quality monitoring station data	DED	OSDI, SPEED questionnaire, TBUT, lipid layer thickness, MG morphology, amount of expressive meibomian glands, Schirmer test
Huang et al. [91]	Miami, USA	Veterans	$PM_{2.5}$, PM_{10}	Individual passive sampler	DED	OSDI, tear osmolarity, InflammaDry, TBUT, corneal epithelial cell disruption, Schirmer test, eyelid parameters, meibomian gland atrophy, meibum quality
Hwang, Choi et al. [76]	South Korea	Adults	PM_{10}, O_3, NO_2, SO_2	Air quality monitoring station data	DED	Questionnaire
Jing et al. [77]	Beijing, China	Healthy elderly volunteers	AQI, PM_{10}, $PM_{2.5}$, SO_2, NO_2, O_3	Air quality monitoring station data	General ocular surface dysfunction/DED	OSDI, slit lamp examination, conjunctival congestion score, conjunctivochalasis grade, TMH, TBUT, corneal fluorescein staining, Schirmer I test, conjunctival impression cytology; VEGF, IL-1B, IL-6, IL-8 in tears
Kaplan et al. [92]	South Florida	Healthy veterans	PM	Collected from Schirmer strips	Ocular surface dysfunction	DEQ5, OSDI, tear osmolarity, InflammaDry®, TBUT, corneal staining, Schirmer test
Khalaila et al. [120]	Beersheba, Israel	Patients diagnosed with conjunctivitis in ophthalmology ER	PM_{10}, $PM_{2.5}$	Hybrid model using monitoring station data and mixed model regression	Conjunctivitis	EMR
Kim, Choi et al. [79]	South Korea	DED patients utilizing eye drops	PM_{10}, $PM_{2.5}$, O_3	Air quality monitoring station data	DED	OSDI, TBUT, CFS, Schirmer test
Lai [99].	Taiwan	Patients diagnosed with conjunctivitis in an outpatient setting	CO, NO_2, SO_2, O_3, $PM_{2.5}$, PM_{10}	Air quality monitoring station data	Conjunctivitis	EMR/ICD-9 coding
Lee, Choi et al. [106]	South Korea	Adults	PM_{10}, O_3, NO_2, SO_2	Air quality monitoring station data	Pterygium	Questionnaire, diagnosis confirmed with history of ocular examination
Levanon et al. [93]	Southern Israel	Patients previously diagnosed with vernal keratoconjunctivitis	NO_2, O_3, PM_{10}, $PM_{2.5}$, SO_2	Air quality monitoring station data based on participants address	Vernal Keratoconjunctivitis exacerbations	ICD-9 codes
Majbauddin et al. [68]	Yonago, Japan	Healthy volunteers	SPM, $PM_{2.5}$, SO_2, NO_x	Air quality monitoring station data	Itchy eyes, teary eyes, bloodshot eyes, bleary eyes	Questionnaire
Malerbi et al. [88]	Sao Paulo, Brazil	Patients presenting to eye clinic	CO, PM_{10}, NO_2	Air quality monitoring station data	Blepharitis	Presence and amount of debris in lid margin, evaluation of meibomian secretion
Matsuda et al. [84]	Sao Paulo, Brazil	Sugarcane workers and residents of neighboring towns	$PM_{2.5}$	Continuous particulate matter lase photometer	Mucus quality and mucin gene expression	MUC5AC, MUC1, MUC16 mRNA levels, goblet cells density from bulbar and tarsal conjunctiva
Matsuda, Bonatti et al. [80]	Sao Paulo, Brazil	Outdoor workers	$PM_{2.5}$	Individual sampler	Lacrimal film alterations	Tear cytokines: IL-2, IL-4, IL-4, IL-10, IFN-y
Miyazaki et al. [100]	Japan	Members of Japan Ophthalmologist Association and their family members	NO, NO_2, NO_x, SO_2, $PM_{2.5}$, PM_{10}	Air quality monitoring station data	Various forms of allergic ocular disease	Questionnaire
Modi et al. [70]	Miami, USA	Veterans who were abroad in either Iraq or Afghanistan	Incinerated waste	Self-reported exposure	Eye dryness/discomfort	Questionnaire, DEQ5
Moen et al. [85]	Norway	Those living or working near an oil tanker explosion site and "unexposed" volunteers	Black smoke (of mixed pollutants)	Not measured	Tear film stability	NIBUT, SBUT
Norback et al. [64]	Johor Bahru, Malaysia	Junior high schools students	VOC, formaldehyde, NO_2, CO_2	Sampling and classroom measurements (not individual)	Eye irritation	Questionnaire

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Table 3 (*continued*)

Study	Geographic Location	Study population	Type of Pollutant (s) studied	Method of pollutant exposure measurement	Type of ocular surface disease studied/ symptoms	Method of ocular surface disease/symptoms diagnosis or evaluation
Novaes et al. [71]	Sao Paulo, Brazil	Healthy volunteers	NO_2	Individual passive sampler	Ocular dryness, irritation, heaviness/ fatigue, and itching	OSDI, Schirmer test, biomicroscopy, TBUT, corneal and conjunctival staining
Nucci et al. [103]	Milan, Italy	Pediatric conjunctivitis patients presenting to ER or outpatient	$PM_{2.5}$, PM_{10}	Air quality monitoring station data	Conjunctivitis of unknown origin	EMR, diagnosis confirmed by ophthalmologist
Prapamontol et al. [63]	Upper Northern Thailand	First grade junior high school students	FeNO, PM_{10}	FeNO levels: portal instrument PM10: Air quality monitoring station data	Itching, burning, or irritation of eyes	Questionnaire
Ramirez et al. [105]	Lima, Peru	Workers involved in production and marketing of toilets and ceramics	Exposed for five years or more to PM in an environment with dosimetry values > 10 mg/m^3 for total/ inhalable dust and > 3 mg/m^3 for respirable dust	Company data	Pterygium	Primary care physician diagnosis
Recchioni et al. [89]	United Kingdom	Patients with severe ocular surface disease	NO_2, NO_x, PM_{10}, $PM_{2.5}$	Air quality monitoring station data	Ocular surface disease	OSDI
Singh et al. [65]	Mumbai, India	Exposed group: those living within 1 km radius of Deonar Dumping site	PM_{10}, $PM_{2.5}$, CO, O_3, NO_2, SO_2, NH3	Air quality monitoring station data	Eye soreness/redness, watering of eyes, itching of eyes	Questionnaire
Sugiyama et al. [60]	Fukoka, Japan	Schoolchildren aged 9-12	$PM_{2.5}$	Air quality monitoring station data	Itchy eyes, watery eyes, sore eyes	Questionnaire
Sundram et al. [121]	Malaysia	Outdoor workers	$PM_{2.5}$	DustTrak DRX Aerosol Monitor installed 1 km radius from each sampling location	Itchy, redness, tearing, swelling of eyes	TOSS
Torricelli et al. [87]	Sao Paulo, Brazil	Healthy male taxi drivers or traffic controllers	NO_2, $PM_{2.5}$	Individual passive sampler	Ocular dryness, irritation, heaviness, fatigue, and itching	OSDI, Schirmer test, TBUT, vital staining of cornea and conjunctiva, tear osmolarity
Torricelli, Matsuda et al. [86]	Sao Paulo, Brazil	Healthy male taxi drivers or traffic controllers	NO_2, $PM_{2.5}$	Individual passive sampler	Ocular dryness, irritation, heaviness, fatigue, and itching	OSDI, conjunctival goblet cell assays, MUC5AC mRNA expression, tarsal GC density
Tzortzi et al. [73]	Athens, Greece	Healthy non-smoking adults	$PM_{2.5}$, PM_{10}	Continuous measurement during exposure periods	Ocular itchiness, burning, watery eyes, dryness	Questionnaire
Vehof et al. [75]	Netherlands	Healthy volunteers	NO2, PM_{10}, $PM_{2.5}$	Standardized land-use regression model approach from air quality monitoring station data	DED	Women's Health Study dry eye questionnaire
Wang et al. [83]	Xuzhou, China	Sjogren's syndrome patients and healthy volunteers	AQI	Air quality monitoring station data	Meibomian gland dysfunction	Tear film lipid layer thickness
Watanabe et al. [112]	Japan	Asthma patients	SPM, SO_2, NO, NO_2	Air quality monitoring station data	Tearing, itching, mucus, pain	Telephone survey
Zambrano et al. [104]	Kongwa, Tanzania	Children aged 1-9	Indoor cooking fire	Survey/recording of exposure status	Trachoma	Ophthalmic evaluation
Zhang et al. [67]	Beijing, China	Respiratory clinic patients, visitors, graduate students (all naturally exposed to haze)	$PM_{2.5}$	Air quality monitoring station data	Dry eyes, itchy eyes	Questionnaire
Zhou et al. [94]	Guangzhou, China	Children	PM_{10}, $PM_{2.5}$, SO_2, NO_2, O_3	Air quality monitoring station data	Allergic conjunctivitis	ICD-10 codes

Table 3 Abbreviations: EMR: electronic medical record; OSDI: Ocular Surface Disease Index; TBUT: tear break-up time; FBS: foreign body sensation; TMH: tear meniscus height; MG: meibomian gland; MGD: meibomian gland dysfunction; CFS: corneal fluorescein staining; SPEED: Standardized Patient Evaluation of Eye Dryness; DEQ5: Dry Eye Questionnaire-5; NIBUT: non-invasive tear break-up time; SBUT: symptomatic break-up time; VOC: volatile organic compound; DED: dry eye disease.

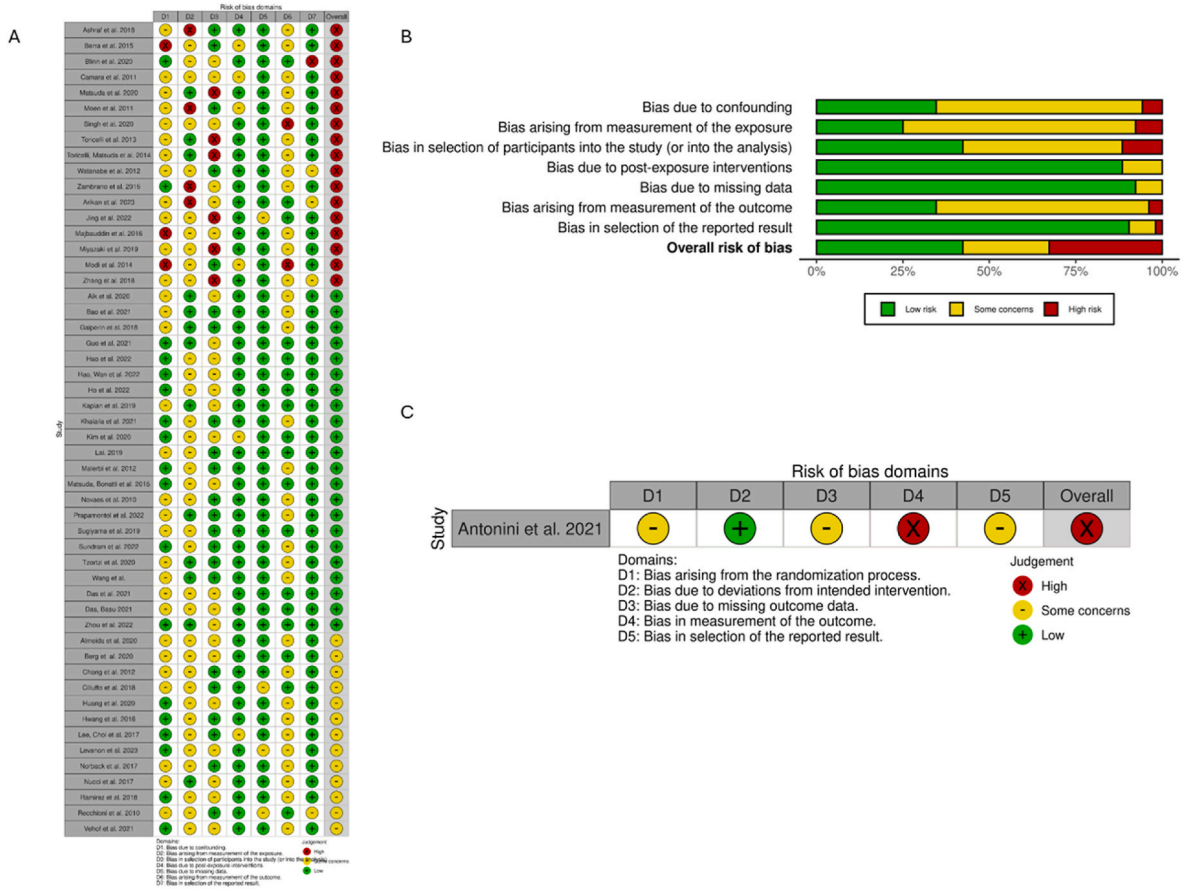

Fig. 4. Risk of bias assessment of clinical studies. (A) For non-randomized clinical studies, the Risk-of-Bias In Non-Randomized Studies of Exposure (ROBINS-E) tool was used for observational studies and (B) the summary plot is provided. (C) The Cochrane Risk-of-bias tool 2.0 (RoB 2.0) was used for randomized controlled trials.

5. Conclusion

This systematic review provides a synthesis of preclinical and clinical studies on the effects of PM and air pollution exposure on the ocular surface. Preclinical studies strongly suggest a correlation between PM exposure and ocular surface dysfunction, primarily due to oxidative stress and inflammatory pathways. Clinical studies have corroborated these findings, demonstrating signs and symptoms similar to those of dry eye disease, conjunctivitis, and allergic eye disease. Though only a few studies have investigated therapeutics for mitigating PM-induced ocular surface damage, there remains an unmet need for the development of future treatments. Collectively, these studies highlight the need for future studies elucidating the multiple molecular mechanisms and targeted therapies for PM-induced ocular toxicity.

CRediT authorship contribution statement

Sana Iqbal: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation. **Abhishek Ramini:** Writing – review & editing, Writing – original draft, Investigation, Data curation. **Simon Kaja:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of interest statement

The authors report that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jtos.2024.12.003.

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