Exposome for Ocular Diseases: From Exposure Evidence to Causality and Actionable Prevention

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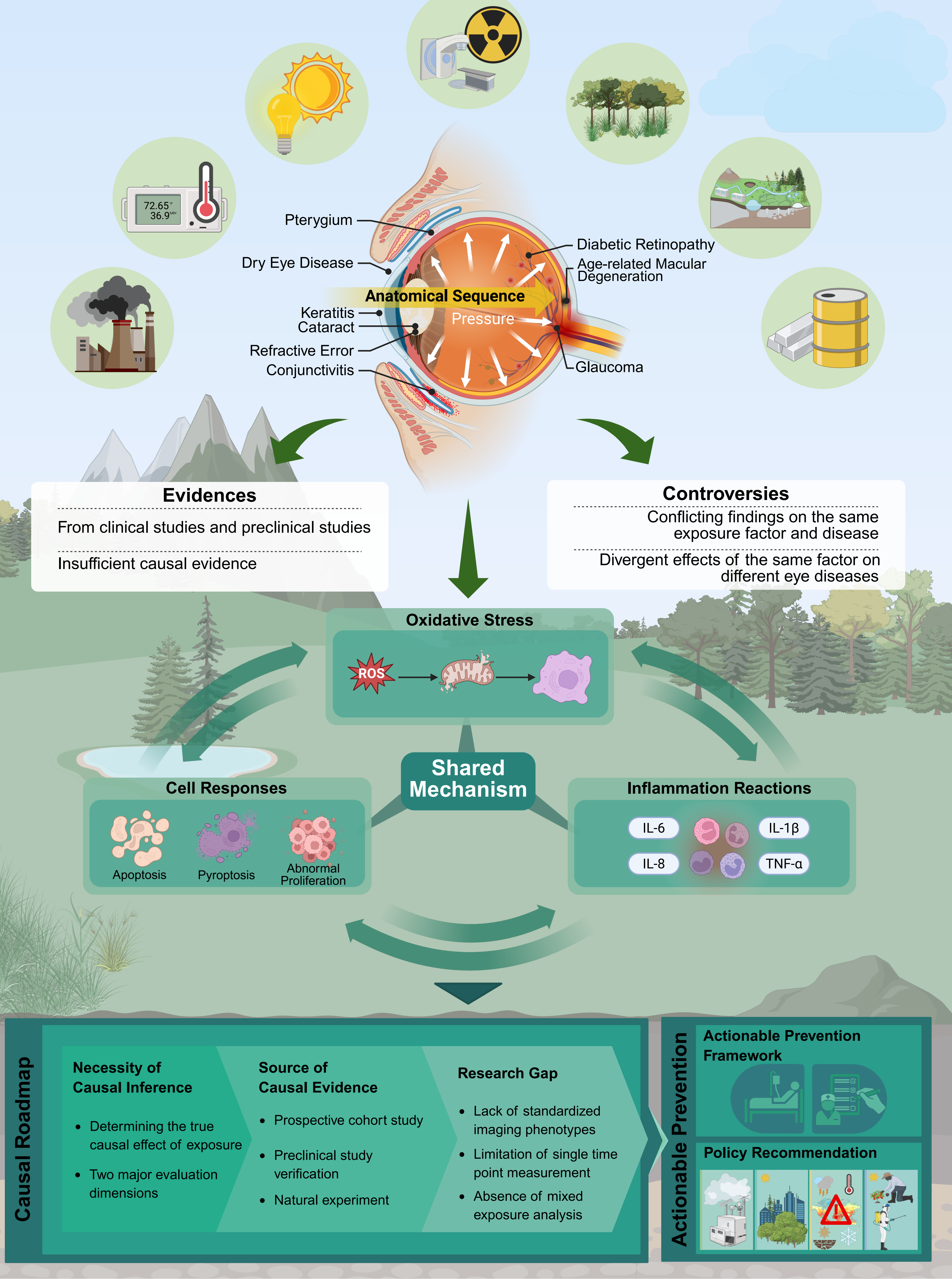

72.65
36.9
Pterygium
Dry Eye Disease
Keratitis
Cataract
Refractive Error
Conjunctivitis
Anatomical Sequence
Pressure
Diabetic Retinopathy
Age-related Macular Degeneration
Glaucoma
Evidences
From clinical studies and preclinical studies
Insufficient causal evidence
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Conflicting findings on the same exposure factor and disease
Divergent effects of the same factor on different eye diseases
Oxidative Stress
ROS
Shared Mechanism
Cell Responses
Apoptosis
Pyroptosis
Abnormal Proliferation
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IL-8
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Determining the true causal effect of exposure
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Source of Causal Evidence
Prospective cohort study
Preclinical study verification
Natural experiment
Research Gap
Lack of standardized imaging phenotypes
Limitation of single time point measurement
Absence of mixed exposure analysis
Actionable Prevention
Actionable Prevention Framework
Policy Recommendation

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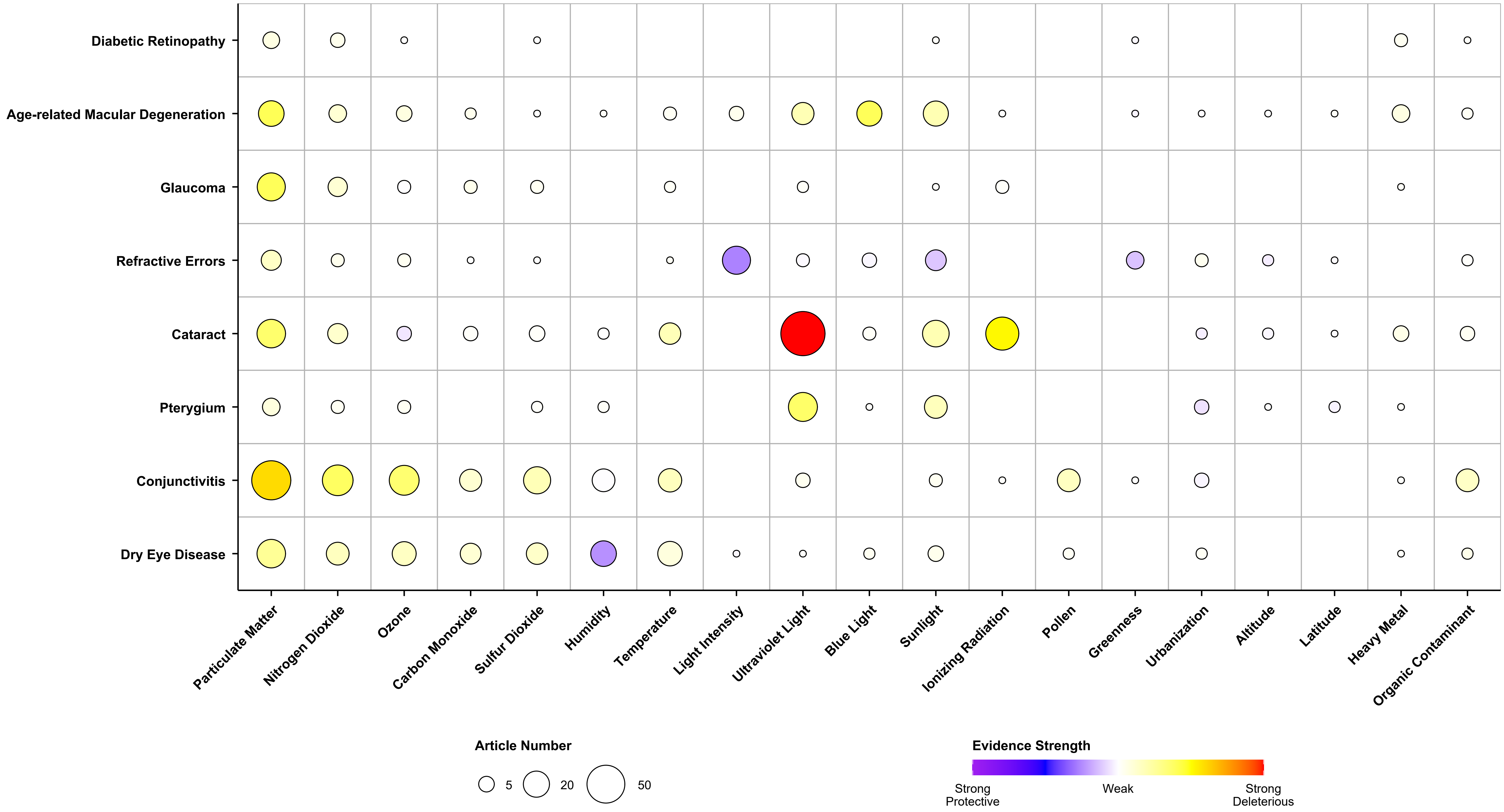

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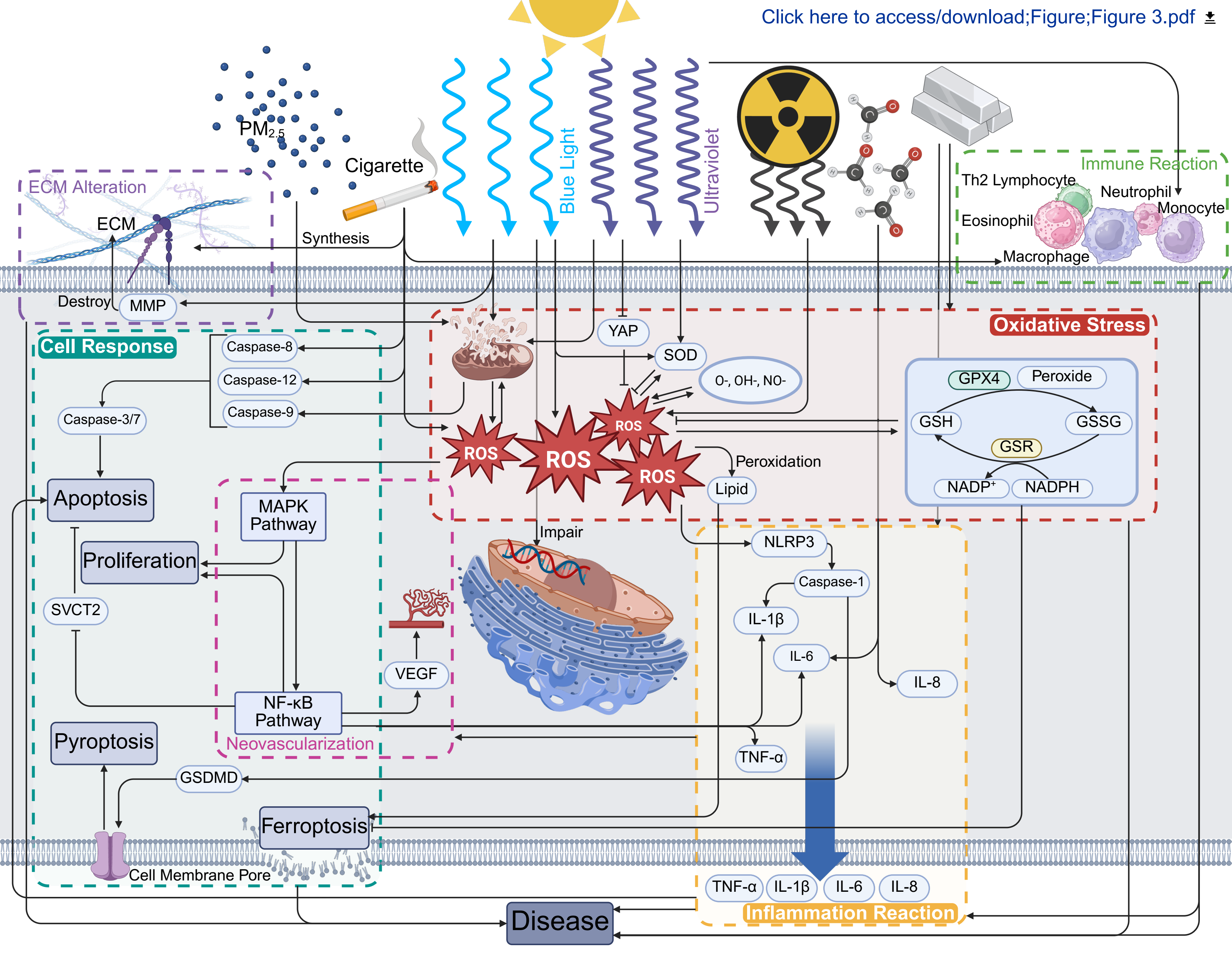

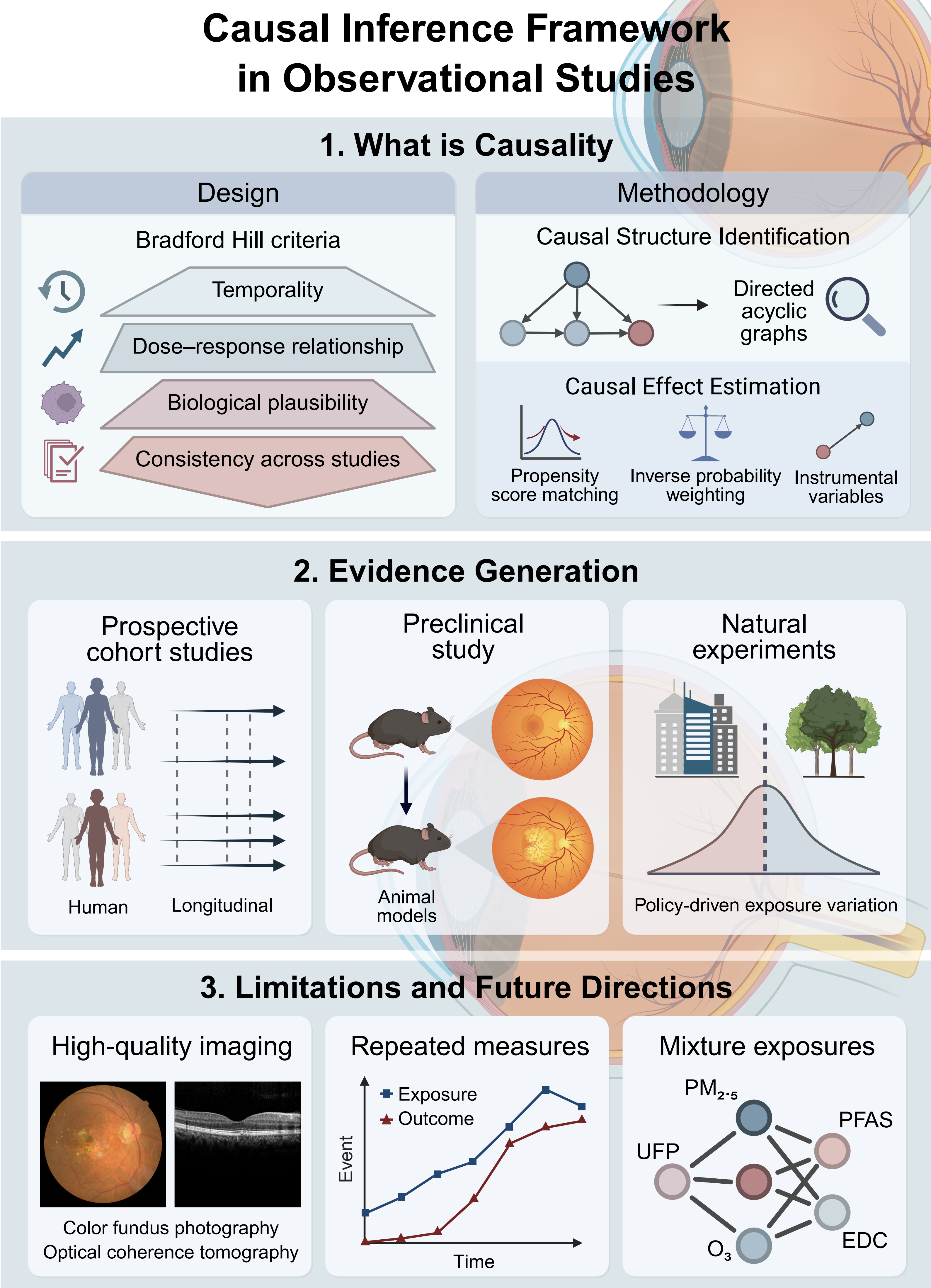
Causal Inference Framework
in Observational Studies
1. What is Causality
Design
Bradford Hill criteria
Temporality
Dose–response relationship
Biological plausibility
Consistency across studies
Methodology
Causal Structure Identification
Directed
acyclic
graphs
Causal Effect Estimation
Propensity
score matching
Inverse probability
weighting
Instrumental
variables
2. Evidence Generation
Prospective
cohort studies
Human
Longitudinal
Preclinical
study
Animal
models
Natural
experiments
Policy-driven exposure variation
3. Limitations and Future Directions
High-quality imaging
Color fundus photography
Optical coherence tomography
Repeated measures
Exposure
Outcome
Event
Time
Mixture exposures
PM2·5
PFAS
UFP
O3
EDC

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Abstract

The exposome, defined as the totality of external exposures individuals experience throughout the lifespan and the internal biological responses they trigger, is increasingly recognized as a major, modifiable determinant of health. The eye is uniquely vulnerable to exposome risk factors because it comprises an external interface directly exposed to the environment, a transparent lens highly sensitive to cumulative oxidative injury, and metabolically active retina prone to inflammation and vascular dysregulation. Research linking ocular diseases to air pollution, climate and weather factors, heavy metals, persistent organic pollutants, and emerging threats such as micro-/nanoplastics has expanded rapidly, yet the evidence remains fragmented and lacks systematic integration. In this review, we propose an anatomy-informed ocular exposome atlas along the visual axis to comprehensively evaluate evidence from clinical studies, pathological mechanisms, and intervention strategies across major disease groups-including ocular surface diseases, cataract, refractive errors, glaucoma, and retinal diseases. We further integrate cross-disease mechanistic pathways (oxidative stress, cellular responses, inflammation, immune reactions) and discuss causality. Finally, we identify priority research directions and provide actionable recommendations for prevention and policy.

Keywords: Eye diseases, Exposome, Pollution, Ultraviolet, Climate, Dry eye disease, Cataract, Refractive error, Age-related macular degeneration

1. Introduction

Disease pathogenesis arises from the intricate interplay between exposomes and genetic susceptibility (Vermeulen, et al., 2020). Given the limited malleability of the human genome, research priorities and public health strategies have increasingly pivoted toward modifiable exposure-related factors (Münzel, et al., 2023). In 2005, Wild introduced the concept of the exposome as the counterpart to the genome, encompassing the cumulative external exposures and accompanying internal biological responses throughout the life course (Miller, 2025; Miller, 2021; Miller, Jones, 2014; Rappaport, 2011; Rappaport, Smith, 2010; Vineis, Dagnino, 2024; Wild, 2005; Wild, 2012). The Global Burden of Disease (GBD) study has confirmed the pivotal contribution of exposome in mortality burden and disability-adjusted life years (DALYs) (Lelieveld, et al., 2020). The impact of the exposome on disease burden intensifies with advancing age, driven by biological senescence, multimorbidity, and the accumulation of lifelong exposures. This escalating burden is particularly conspicuous in the eye, an organ uniquely vulnerable to exposome owing to its direct and continuous interface with the external exposome. According to GBD estimates, in 2020, 33.6 million adults aged ≥ 50 years were blind, and 206 million had moderate-to-severe visual impairment (Collaborators., Study, 2021), underscoring the urgent need to understand how exposome shape ocular health.

As the primary sensory organ, the eye mediates approximately 80% of all sensory input (Yu, et al., 2025) and, by virtue of its anatomical and functional attributes, stands at the forefront of exposome (Iqbal, et al., 2025). Various exposure factors can directly perturb the immune microenvironment, disrupt the epithelial barrier and tear film integrity, damage the ocular surface (Kim, et al., 2020), and inflict cumulative damage to the transparent lens through inflammatory pathways (Meyer, et al., 2013; Söderberg, 1990). Furthermore, via oxidative stress, chronic inflammation, and vascular dysregulation, these factors may injure non-regenerative retinal ganglion cells, disrupt the blood–retinal barrier, and impair retinal pigment epithelium (RPE) mitochondrial function (Dai, et al., 2021), thereby contribute to retinal diseases, potentially accompanied by vascular endothelial growth factor (VEGF)-related angiogenesis (Kozulin, et al., 2011). Beyond direct effects, exposome indirectly regulate ocular nutrient supply and neural transmission by influencing the neuroendocrine system, forming a multi-level regulatory network (Torii, et al., 2017; Torii, et al., 2017).

A substantial body of research has examined the associations between exposome and ocular diseases, encompassing air pollution, climatic and meteorological conditions, heavy metals, persistent organic pollutants, and emerging contaminants such as micro- and nanoplastics. Although this field has expanded rapidly, the integration and translational application of existing evidence remain fragmented. Notably examples include light exposure, a key modifiable exposure factor can cause refractive errors that affect nearly the entire global population (Torii, et al., 2017; Torii, et al., 2017), nitrogen dioxide (NO_2), which contributes to approximately 10.98% of emergency visits for eye diseases in China (Wang, et al., 2022), and fine particulate matter < 2.5 μm in diameter ($PM_{2.5}$), to which about 60.63% of ophthalmic disease cases in India are attributed (Sahu, et al., 2025). Despite these insights, current evidence on the exposome–ocular disease nexus remains highly siloed, with the majority of studies reporting single-exposure, single-outcome associations (Cheng, et al., 2025). Controversies persist due to ecological complexity, conceptual ambiguity, and inadequate confounding control. Therefore, a review is urgently needed to integrate these scattered findings, resolve inconsistencies, and identify shared pathophysiological mechanisms across diseases.

This review comprehensively consolidates the scientific evidence linking the exposome to major ophthalmic conditions, including ocular surface diseases (dry eye disease, keratitis, conjunctivitis, and pterygium), cataract, refractive error, glaucoma, and retinal diseases (age-related macular degeneration and diabetic retinopathy). Integrating clinical practice with preclinical research, we propose an anatomy-informed ocular exposome atlas along the visual axis (Supplementary Figure S1). This review progresses logically from evidence of association and current controversies to pathological mechanisms and intervention strategies, integrates cross-disease mechanistic pathways (oxidative stress, cell responses, inflammation, and immune reactions), identifies priority directions for future research, and provides actionable prevention and policy recommendations (Figure 1).

2. Methodology

Because the scope of the exposome is too broad, encompassing nearly the entire life course, this review focuses on air pollution (e.g., $PM_{2.5}$, NO_2), climatic and geographical conditions (temperature, humidity, altitude), living environments (indoor microenvironment, occupational environment), physical factors (light, electromagnetic radiation), and chemical pollutants (heavy metals, organic compounds), while excluding socioeconomic, psychosocial, and behavioral factors, as well as integrated omics data (e.g., metabolomics, proteomics, epigenomics) and their associated biomarkers. We excluded studies in which these factors were the primary exposure of interest, and studies that adjusted for these factors were not excluded and remain included in our synthesis.

We searched PubMed, Embase, and Web of Science databases for literature published from database inception to April 2025. Included studies were restricted to original research published in English, with primary diseases or core pathological processes located within the eye, confirmed by International Classification of Diseases (ICD) codes or physician diagnosis, and involving ocular diseases within our defined scope of exposome. We excluded duplicate records, retracted articles, studies for which the full text or data was unavailable, studies unrelated to the primary topic, and articles with unclear disease diagnoses or poorly defined exposome measures (Supplementary Figure S2).

Regarding the "exposome", the key words mainly used for retrieval include: "pollution" or "exposure" or "particulate matter" or "climate" or "weather" or "altitude" or "air pressure" or "carbon dioxide" or "nitrogen dioxide" or "ozone" or "mercury" or "lead" or "arsenic" or "greenness" or "urbanization" or "formaldehyde" or "smoke" or "spatial frequency" or "internal exposure" or "microplastics". Regarding the "eye disease", the key words mainly used for retrieval include: "eye diseases" or "ophthalmology" or "blindness" or "ophthalmic disease" or "glaucoma" or "uveitis" or "macular degeneration" or "graves ophthalmopathy" or "dry eye disease" or "cataract" or "retinopathy" or "retinitis pigmentosa" or "retinal vascular disease" or "diabetic retinopathy" or "refractive errors" or "keratitis" or "blepharitis" or "conjunctivitis" or "pterygium" or "eye neoplasms". The terms "climate" and "weather" in accordance with the National Center for Biotechnology Information (NCBI) Medical Subject Headings (MeSH) classification. Regarding the “organic contaminants”, the key words mainly used for retrieval include: "total hydrocarbons" or "nonmethane hydrocarbons" or "Formaldehyde" or "Polychlorinated Biphenyls" or "Organophosphates" or "pyrethroid pesticide" or "Bisphenol A Compounds" or "phthalate" or "per- and poly-fluoroalkyl substance" or "disinfection by-products" or "haloacetic acids" or "Trihalomethanes". The complete search terms and the full screening process are provided in Supplementary Table S1.

We have applied the Bradford Hill criteria to evaluate the associations for each exposure–disease pair, and in the summary for each disease, we provide a critical appraisal of the main findings based on the accuracy of the exposome assessment and the robustness of outcome definitions (e.g., self-reported versus physician-diagnosed), while cautioning readers to interpret with care those single-pollutant associations that have not been adjusted for multiple comparisons.

The clinical evidence scoring was informed by evidence pyramid that consistently rank prospective cohort designs above retrospective or cross-sectional designs, and larger sample sizes above smaller ones. Elucidation of a full biological pathway makes a greater contribution to establishing biological plausibility. The total score in Figure 2 is intended as a summary of relative evidence quality based on uniformly applied criteria across all exposure–disease pairs, and should be interpreted as such rather than as an absolute quantitative metric.

3. Anatomy-informed exposome atlas along the visual axis

3.1 Ocular surface diseases

The ocular surface constitutes a sophisticated and functionally integrated system that coats the anterior segment of the globe. Anatomically, it encompasses the cornea, limbus, conjunctiva, eyelids, and lacrimal apparatus, which collectively establish a critical physiological barrier (Galor, et al., 2023). This barrier is essential for maintaining ocular surface moisture and safeguarding the eye against diverse exposome (Hong, et al., 2023). Disruptions to this delicate equilibrium—manifesting as ocular surface disorders such as dry eye disease (DED), keratitis, conjunctivitis, and pterygium—are frequently etiologically linked to a spectrum of exogenous exposures.

3.1.1 Dry eye disease

Based on extensive evidence, air pollutants, climate, weather, light, heavy metals, and other exposomes conspire to aggravate DED. Among these, air pollutants play a critical role. Particulate matters (PM), including both $PM_{2.5}$ and particulate matter < 10 μm in diameter (PM_{10}), have been identified as risk factors. Notably, their effects are more pronounced during the cold season, with young adults (aged 21–40 years) emerging as the most susceptible group—a finding that challenges the traditional view of DED as a condition predominantly affecting the elderly (Mo, et al., 2019). Although $PM_{2.5}$ and PM_{10} are both implicated (Cao, et al., 2025; Chu, et al., 2025; Hao, et al., 2022; Liang, et al., 2023; Mu, et al., 2021; Yu, et al., 2019), their impacts differ. $PM_{2.5}$ has been associated with increased tear secretion and exacerbated ocular discomfort, whereas PM_{10} compromises tear film stability without a strong link to subjective discomfort (Kim, et al., 2020). Certain occupations with greater exposure to air pollutants are associated with a significantly elevated risk of DED. For instance, outdoor cleaners have twice the risk of developing the disease compared to indoor cleaners who have less exposure to dust (Echieh, et al., 2021). Emerging studies have also identified coal dust (Sun, et al., 2007), indoor smoke (Tandon, et al., 2020), black smoke (Stankovic, et al., 2019), and sulfur dioxide (SO_2) (Cao, et al., 2025; Chu, et al., 2025; Hao, et al., 2022; Liang, et al., 2023; Mo, et al., 2019; Um, et al., 2014; Xia, et al., 2024) as potential risks for DED.

Climate has an important impact on the progression of DED. The Mediterranean and plateau climates have a protective effect (Berg, et al., 2020), while extreme climates, such as cold desert climates, are associated with significantly higher prevalence rates (Chaturvedi, et al., 2023). Plenty of studies have shown that DED exhibits distinct seasonal patterns as well. Population-based studies conducted in the United States (Kumar, et al., 2015), China (Zhong, et al., 2018), and Japan (Kabata, et al., 2024) have all indicated that winter and spring are the peak seasons. This finding is further supported by the observation that user searches for DED on Google are highest during spring (Azzam, et al., 2021). Meteorological factors—namely humidity and atmospheric pressure—represent an essential status. High humidity is a protective factor for DED (Hwang, et al., 2016; Kabata, et al., 2024; Um, et al., 2014; Youn, et al., 2020), mitigating the occurrence and progression by reducing tear evaporation and maintaining tear film stability (Berg, et al., 2020; Calonge, et al., 2014; Galor, et al., 2014; Madden, et al., 2013; Shen, et al., 2018; Zhong, et al., 2018). In studies by Song et al., decreased humidity exacerbated subjective symptoms but showed no significant correlation with objective clinical signs, suggesting a dissociation between patient perception and physiological measures in some contexts (Song, et al., 2024; Song, et al., 2023). Elevated air pressure has been linked to increased disease prevalence (Galor, et al., 2014; Kabata, et al., 2024; Lu, et al., 2023), while extremely low pressure—often accompanied by extreme weather events such as dust storms or cold surges—may also elevate risk, potentially due to impaired tear drainage and reduced tear film stability (Gui, et al., 2023). Studies have identified sun exposure as an independent risk factor for DED (Sahai, Malik, 2005; Tandon, et al., 2020), whose effect appears dose-dependent (Tandon, et al., 2020; Um, et al., 2014). Ultraviolet (UV) is likely the primary pathogenic component of sunlight in this context (Rocha, et al., 2023). More recently, Kaido et al. proposed that short-wavelength blue light may exacerbate visual dysfunction in DED patients with unstable tear film, speculating that scattering of blue light due to tear film disruption could impair visual performance (Kaido, et al., 2016).

The relationship between exposome and DED is further complicated by allergen exposure and geographic variability. The DREAM study published two consecutive reports indicating that while pollen levels are associated with DED symptoms, they show no significant correlation with clinical signs (Shen, et al., 2019; Shen, et al., 2018). The authors propose that this dissociation may reflect underlying allergic phenomena in susceptible individuals, suggesting that during high-pollen seasons, treatment of concomitant allergic conjunctivitis could help alleviate symptom burden. Interestingly, the research group observed a paradoxical increase in tear film breakup time with rising pollen counts, which they attributed to enhanced reflex tearing in response to ocular surface irritation (Shen, et al., 2019). Geographically, the ICMR-EYE SEE study group found that the prevalence of DED in hilly and coastal areas is significantly lower than that in plain areas, especially the risk in coastal areas reduced by as much as 80% (Tandon, et al., 2020). This seems somewhat surprising, as many studies mentioned above have pointed out that direct sunlight leads to higher UV doses, which can increase the risk of DED. And sea surface reflection in coastal areas can also increase UV exposure. In this study, the high humidity in coastal areas may have offset the impact of UV. Urbanization has also emerged as a significant risk factor. Two studies from the United States and South Korea have confirmed the significant correlation between urbanization and disease risk from the perspectives of behavioral big data (Azzam, et al., 2021) and epidemiology (Um, et al., 2014) respectively, possibly due to pollution (e.g., industrial waste gases like SO_2), climate deterioration (e.g., urban heat island effect), and lifestyle changes (e.g., screen time, air conditioner use).

Heavy metals entering the human body constitute non-negligible exposomes in DED. Based on the Korea National Health and Nutrition Examination Survey (KNHANES) 2010–2012, Jung et al. systematically analyzed blood heavy metal concentrations. They found no statistically significant relationship between lead or cadmium concentrations and DED, while mercury was significantly associated, especially in women (Jung, Lee, 2019). The authors speculated that mercury may damage the autonomic nervous system, affecting lacrimal gland secretion. It can also trigger conjunctival inflammation, destroy the ocular surface epithelium and increase tear osmolarity, thereby inducing DED.

Despite extensive research, inconsistencies persist, machine learning models show a negative correlation between PM_{10} and tear lactoferrin levels (Hao, et al., 2022; Lu, et al., 2023), but some studies found none (Hwang, et al., 2016; Um, et al., 2014; Xia, et al., 2024; Youn, et al., 2020). Compared to $PM_{2.5}$, PM_{10} has a larger particle size, so while it can irritate the ocular surface and cause damage, it also triggers reflexive tear secretion and blinking, which helps to flush out and remove PM from the ocular surface, thereby reducing the continuous irritation and damage caused. Additionally, PM_{10} is often highly correlated with other air pollutants such as NO_2 and SO_2, making its individual contribution difficult to interpret. In multiple studies conducted in different regions of China, exposure to NO_2 has been found to be significantly associated with an increase in outpatient visits (Cao, et al., 2025; Chu, et al., 2025; Liang, et al., 2023; Mo, et al., 2019; Mu, et al., 2021), and NO_2 is one of the main reasons driving the regional differences in the incidence of DED (Youn, et al., 2020). However, Xia et al. analyzed the impact of it with a 7-day observation and found that only the first two days were significant (Xia, et al., 2024). Moreover, some studies showed that NO_2 is not significantly correlated (Berg, et al., 2020; Um, et al., 2014), and Yu et al. even found that people exposed to NO_2 more than 150 days had a slightly lower risk in the multivariate logistic regression analysis, indicating a weak protective effect (Yu, et al., 2019). The general trend indicates a positive association with carbon monoxide (CO) (Chu, et al., 2025; Mo, et al., 2019), while there are studies that did not observe significance between CO exposure and DED (Liang, et al., 2023; Um, et al., 2014). And Yu's research found that when the exposed days were $\geq$ 124, the risk actually decreased (Yu, et al., 2019). As for ozone (O_3), numerous studies have shown that the exposure is closely related to DED (Lu, et al., 2023; Mu, et al., 2021; Rocha, et al., 2023; Song, et al., 2024; Yu, et al., 2019). It reduces tear secretion and aggravates ocular surface discomfort (Kim, et al., 2020; Kim, et al., 2019). Nonetheless, in the study by Liang, significance was only observed at the cumulative lag 0-7 days in the multi-factor model, with the risk increasing by only 6% (Liang, et al., 2023). According to two studies in Hangzhou, China, the association between O_3 and DED outpatient visits is not significant (Chu, et al., 2025; Mo, et al., 2019). Overall, the association between air pollutants and DED is widely controversial, which may imply that no single air pollutant plays a decisive role, but rather the synergistic action between different pollutants that mainly promotes DED.

Similarly, understandings regarding climate and weather are also not entirely uniform. A study in Urumqi found that for every 10-unit increase in relative humidity, the risk of outpatient visits even increased by approximately 6%, and under extremely high humidity conditions it rose by 35% (Gui, et al., 2023). This is contrary to studies in other regions, and it may be due to Urumqi's unique arid, continental climate. Low humidity may reduce the breeding of irritants in the air, such as mold and dust mites, thereby indirectly alleviating ocular irritation. As for temperature, lower temperature is associated with a higher risk of disease, a finding supported by longitudinal studies in China (Gui, et al., 2023) and Japan (Kabata, et al., 2024), as well as a retrospective cohort study in South Korea (Song, et al., 2024; Song, et al., 2023). Research even suggests that extremely high ambient temperature (> 32 ℃) may have a protective effect (Chaturvedi, et al., 2023). A possible explanation is that low ocular surface temperature induces constriction or obstruction of meibomian gland orifices, reducing lipid secretion and compromising tear film stability, thereby accelerating evaporation. In addition, low temperature may stimulate corneal cold receptors, contributing to discomfort (Ho, et al., 2022). Conversely, other studies have reported contradictory findings, suggesting that higher temperatures may be a risk factor. The evidence includes a cross-sectional study in South Korea (Um, et al., 2014), case–control studies in China (Lu, et al., 2023; Zhong, et al., 2018), and a prospective cohort study in Poland (Chlasta-Twardzik, et al., 2021). Researchers believe that higher temperatures may lead to reduced tear secretion and accelerated evaporation, thereby inducing or exacerbating the disease. From the above discussion, the relationship between temperature and DED appears to be U-shaped. It can be roughly inferred that both low (< 10 ℃) and high temperature (> 25 ℃) may exacerbate DED, with 15–20 ℃ being a relatively low-risk range. It is worth pointing out that there is no "safest temperature range" agreed upon by all studies, which may be related to interactions with other factors such as humidity and wind speed. Excessive wind exposure increases the risk by 2.15 times in India (Sahai, Malik, 2005). While a national study of American veterans found that an increase in wind speed significantly reduced the risk (Galor, et al., 2014). This may be because in this study, the wind speed had not yet reached the threshold to trigger the disease, and in India, where dust storms are frequent, wind is often accompanied by enhanced evaporation and particulate irritation.

Mechanisms are being continuously revealed, but the current understanding is still not sufficient and comprehensive. For air pollutants, exposure to $PM_{2.5}$, in a dose-dependent manner, induces inflammatory responses-activates nuclear factor kappa-B (NF-κB) pathway and promotes the release of interleukin 1 beta (IL-1β) and tumor necrosis factor alpha (TNF-α) and mitochondrial dysfunction (produces reactive oxygen species), corroborated by both *in vivo* and *in vitro* experiments (Yu, et al., 2023). Tear secretion is significantly reduced, corneal epithelial damage occurs, the number of conjunctival goblet cells decreases, and tear film stability is disrupted, ultimately leading to DED in Sprague-Dawley rats (Song, et al., 2020). Besides, DED patients are more susceptible to the effects of particles than normal condition. After exposure to TiO_2 nanoparticles, rats with DED exhibited a significant increase in corneal opacity, inflammatory cell infiltration, and lactate dehydrogenase levels in tears (Han, et al., 2017). The way by which NO_2 affects DED may differ from that of other pollutants. It may contribute to the pathogenesis by inducing meibomian gland inflammation rather than directly disrupting tear film stability (Hao, et al., 2022). O_3 may induce DED through subclinical inflammatory responses (Hwang, et al., 2016). Among meteorological factors, low humidity exacerbates ocular surface damage by upregulating heat shock protein 60 (HSP-60) and matrix metalloproteinases-9 (MMP-9), and it also increases high-mobility group box 1 (HMGB1) levels to mediate inflammatory responses (Alven, et al., 2021). The increased tear osmolarity in patients lowers the threshold of nerve cells and enhances nerve sensitivity, which reveals the mechanism of pain experienced during slight cooling (Hirata, Rosenblatt, 2014). For light, *in vitro* experiments have proven that blue light (especially at 420 nm) significantly reduces the survival rate of corneal and conjunctival epithelial cells, alters cell morphology, and induces excessive production of reactive oxygen species (ROS). Hyperosmotic stress enhances the phototoxicity of blue light, induces inflammation, alters mitochondrial membrane potential, and triggers the cellular antioxidant system (Marek, et al., 2018). In the field of organic pollutants, Vitoux et al. has unveiled the DED pathogenesis mechanisms behind formaldehyde, a major indoor pollutant, indicating that it activates the gene expression and protein secretion of pro-inflammatory factors (IL-6, IL-8), thus inducing inflammation and stress responses with *in vitro* evidence. As the concentration of formaldehyde increases, cell viability continuously decreases, exacerbating the damage caused by low humidity and airflow, and thereby promoting the occurrence of DED (Vitoux, et al., 2016; Vitoux, et al., 2018). The mechanism by which DED is affected by exposome can be seen in Supplementary Figure S3.

In summary, the existing literature is predominantly composed of clinical studies, with preclinical research remaining scarce and the underlying mechanisms still poorly understood. Only two preclinical studies on organic pollutants were identified, and clinical research in this area remains a blank. The primary exposomes associated with DED include air pollutants, humidity, temperature, sunlight, and organic pollutants. Notably, humidity is recognized as an important protective factor. The included clinical studies not only analyzed single exposome but also employed multi-exposome models (Hao, et al., 2022) or covariance analyses (Berg, et al., 2020) to adjust for confounding by exposomes such as PM_{10}, NO_2, and CO (Hao, et al., 2022; Zhong, et al., 2018), while also addressing issues such as multicollinearity. The available evidence is of high quality, characterized by large sample sizes and supported by three prospective cohorts. Exposome data were primarily sourced from local or national environmental databases or monitoring stations (e.g.,the National Centers for Environmental Information (Berg, et al., 2020) and the Taiwan Air Quality Monitoring Network (Zhong, et al., 2018)), ensuring high data quality. However, outcome definitions varied considerably across studies, ranging from diagnostic criteria based on national or international guidelines (Song, et al., 2023) and medical insurance database records (Zhong, et al., 2018) to objective clinical signs and subjective symptom scores (Berg, et al., 2020). Air pollutants such as PM, NO_2, O_3, CO, and SO_2 are considered harmful, and these conclusions have been validated using both single-pollutant and multi-pollutant models (Yu, et al., 2019). Regarding the risk of bias, the main identified sources include exposure misclassification (due to the spatial distance between study locations and meteorological/pollution monitoring stations), small sample sizes, and selection bias (Cao, et al., 2025; Liang, et al., 2023). Exposomes such as UV and heavy metals may be harmful to DED; however, the number of relevant studies is limited, and there is a lack of high-quality, large-scale prospective studies or preclinical studies elucidating the underlying mechanism, warranting caution when interpreting the results. Furthermore, research on the associations between ionizing radiation, greenness, altitude, latitude, and DED remains a blank.

To address the impact of exposomes on DED, systematic measures should be implemented at both the macro level (policy formulation) and the micro level (personal protection). Regarding environmental governance and public health policies, $PM_{2.5}$ and PM_{10} should be prioritized as key targets, and continuous efforts are needed to promote industrial emission reduction and vehicle exhaust control (Liang, et al., 2023; Mo, et al., 2019; Zhong, et al., 2018); to mitigate the urban heat island effect and low humidity caused by urbanization, increasing urban greenness can help regulate the local microclimate and thereby alleviate ocular surface stress. In terms of personal protection and behavioral interventions, precise regulation of the indoor environment is crucial: maintaining optimal humidity reduces tear evaporation (Madden, et al., 2013); selecting eco-friendly building materials during decoration can prevent formaldehyde-induced ocular surface inflammation (Vitoux, et al., 2018); and enhancing ventilation while avoiding indoor smoking or biomass fuel combustion can eliminate harmful smoke exposure (Tandon, et al., 2020). For outdoor protection, it is advisable to avoid prolonged outside activities during extreme weather conditions, and wearing sunglasses to block intense sunlight is recommended (Tandon, et al., 2020), with protective goggles during pollen season can provide additional defense.

3.1.2 Conjunctivitis and keratoconjunctivitis

Plenty of evidence indicates that $PM_{2.5}$ is a significant risk factor in conjunctivitis (Chen, et al., 2022; Chen, et al., 2021; Gui, et al., 2023; Jarernwong, et al., 2023; Lu, et al., 2019; Szyszkowicz, et al., 2016; Wang, et al., 2022; Yan, et al., 2023). It is worth noting that a longitudinal study found that among patients over a period of up to 10 years, approximately 3.02% of cases were due to $PM_{2.5}$ (Aik, et al., 2020). Exposure to PM_{10} can significantly increase the frequency of outpatient visits (Chang, et al., 2012; Gui, et al., 2023; Larrieu, et al., 2009; Lee, et al., 2018; Lu, et al., 2019; Villani, et al., 2015; Wang, et al., 2022; Yan, et al., 2023). Short-term extreme PM_{10} exposure has a health amplification effect: haze episodes (with PM_{10} as the main component and indicator), although accounting for less than 2% of the total study duration, led to 14.2% of cases related to PM_{10} (Aik, et al., 2020). Especially children's immune systems are not yet fully developed, making them more sensitive (Dostal, et al., 2011; Nucci, et al., 2017). Conjunctivitis symptoms are also associated with the exposure index of biomass smoke (Del Risco, et al., 2010). For various subtypes, allergic conjunctivitis is more directly related to immune and inflammatory responses, being sensitive to PM (Kim, et al., 2011; Liu, et al., 2024; Mimura, Matsubara, 2014). Notably, in studies conducted in three different regions of China (Hong, et al., 2016; Lu, et al., 2021; Zhou, et al., 2023), only in Shanghai the pathogenic effects were not found, suggesting PM has regional specificity. When it comes to keratoconjunctivitis, black carbon is considered an important risk (Asonye, Bello, 2004). PM has been found to be negatively correlated with acute microsporidial keratoconjunctivitis (Das, Basu, 2021). $PM_{2.5}$ is associated with the exacerbation of vernal keratoconjunctivitis (VKC) (Harada, 2019; Levanon, et al., 2023), while PM_{10} is positively correlated with both atopic keratoconjunctivitis (AKC) and VKC (Levanon, et al., 2023; Miyazaki, et al., 2019; Miyazaki, et al., 2020). As for rhinoconjunctivitis, previous studies have suggested that there is no significant correlation with PM (Anderson, et al., 2010; Gehring, et al., 2015), but a study has shown that allergic rhinoconjunctivitis patients with high levels of IgE are sensitive to short-term exposure (Li, et al., 2022). Indoor dust exposure is another risk factor (Fieten, et al., 2023). Occupational exposure to organic dust may cause significant irritation to the nose and eyes, leading to rhinoconjunctivitis as well (Hoffmeyer, et al., 2014). Environmental tobacco smoke is closely related: exposure to tobacco smoke in home can increase the prevalence in children by about 80% (Zuraimi, et al., 2008), with maternal smoking being the strongest predictor, which increases the possibility by nearly 3 times (Singh, et al., 2018). While no significant association was observed in a study of Swedish farmers (Kronqvist, et al., 1999), this may be due to the fact that the working environment of farmers is filled with extremely high concentrations of strong allergens that can mask the effects of tobacco smoke. Additionally, the working and living environments of farmers generally have great ventilation, which dilutes the tobacco smoke.

The overall trend of population-based studies consistently acknowledges the impact of NO_2 on conjunctivitis (Bourcier, et al., 2003; Chang, et al., 2012; Gui, et al., 2023; Guo, et al., 2021; Lu, et al., 2019; Song, et al., 2019; Yan, et al., 2023). Specifically, research in Ontario, Canada, has observed different lag patterns between genders, with the peak occurring on day 7 for females and day 5 for males (Szyszkowicz, et al., 2016). As for allergic conjunctivitis, there is a statistically significant association with NO_2 (Hong, et al., 2016; Phantu, Bootdee, 2022; Zhong, et al., 2019), and the elderly and females are susceptible populations (Liu, et al., 2024). Lu et al. determined the critical concentration threshold of 27 $\mu g/m^3$ for the impact of NO_2, which is significantly lower than the current standards in China and WHO (Lu, et al., 2021). The prevalence of VKC and AKC is significantly related to the levels of nitrogen oxides (NO_x) as well (Levanon, et al., 2023; Miyazaki, et al., 2020). Surprisingly, NO_2 was not significantly associated with rhinoconjunctivitis (Gehring, et al., 2015; Tagliaferro, et al., 2024). Exposure to CO is significantly associated with an increase in conjunctivitis outpatient visits (Gui, et al., 2023; Ruan, et al., 2024). Numerous studies have confirmed that O_3 is a risk factor for conjunctivitis (Chang, et al., 2012; Cheng, et al., 2023; Gui, et al., 2023; Lai, 2019; Lu, et al., 2019; Ruan, et al., 2024; Yan, et al., 2023), without an apparent safe threshold (Gui, et al., 2024), and researchers have tried to make use of machine learning to predict the disease burden based on it (Chen, et al., 2020; Lim, et al., 2023). Interestingly, when the concentration is extremely high (237 $\mu g/m^3$), it may protect against conjunctivitis through other mechanisms (such as UV shielding). O_3 significantly increases the risk of allergic conjunctivitis (Hong, et al., 2016; Liu, et al., 2024; Lu, et al., 2021; Qiu, et al., 2024; Zhong, et al., 2019), VKC (Levanon, et al., 2023) and rhinoconjunctivitis (Riediker, et al., 2001), but without acute microsporidial keratoconjunctivitis (Das, Basu, 2021). For SO_2, short-term exposure is significantly associated with an increased risk of conjunctivitis (Chen, et al., 2021; Lu, et al., 2019; Ruan, et al., 2024; Yan, et al., 2023).

Climatic factors have a significant impact on various subtypes of conjunctivitis, and season is the most pronounced. Nonspecific conjunctivitis is more prevalent in cold seasons (autumn and winter), possibly related to the seasonal distribution of air pollutants (Li, et al., 2016). Allergic conjunctivitis and VKC are more prevailing in spring (Qiu, et al., 2021), which accounts for 29.6% new cases of allergic conjunctivitis (Zhong, et al., 2019) and increases the likelihood of VKC exacerbation by 13 times (Gupta, et al., 2025). As for rhinoconjunctivitis, it is observed that children born in spring and summer are less likely to develop the disease, which is correlated with immune tolerance induced by high-dose pollen exposure (Hesselmar, et al., 2001).

Considering weather conditions, humidity increases the number of acute microsporidial keratoconjunctivitis (Das, Basu, 2021) and acute hemorrhagic conjunctivitis (Zhang, et al., 2021), and indoor dampness significantly increases the risk of rhinoconjunctivitis (Dotterud, et al., 2000). Regarding the association between precipitation and conjunctivitis, a positive correlation is generally present, with a significant lag effect (Das, Basu, 2021; Lim, et al., 2023; Zhang, et al., 2021). Temperature has a "U-shaped" relationship with the disease. Conjunctivitis is significantly positively correlated within the range of 13–32 ℃, especially in summer (24-28 ℃) and autumn (13-23 ℃) (Khalaila, et al., 2021; Zhang, et al., 2021). Meanwhile, when the mean operative temperature of rooms is ≤ 15 ℃ in winter, the prevalence significantly decreased (Fujita, et al., 2024), implying that low temperature is positively related to conjunctivitis as well. And extreme temperature (≥ 28.7 ℃ or ≤ -10.5 ℃) is associated with an increase in outpatient visits (Gui, et al., 2023). Temperature also synergistically increases the impact of air pollutants: high temperature enhances the effects of $PM_{2.5}$, PM_{10}, CO, and NO_2, while low temperature only increases CO and NO_2 impacts (Wang, et al., 2022). As for specific subtypes, allergic conjunctivitis (Hong, et al., 2016; Lu, et al., 2021; Zhong, et al., 2019) and VKC (Levanon, et al., 2023) are also related to temperature similarly. A study has found that the impact of conventional wind speed (3.1 m/s) is not significant, but instantaneous strong winds increase the relative risk by 17% (Bourcier, et al., 2003). Interestingly, research in Urumqi demonstrated that extremely low wind speed (1% of the conventional speed) has a weak protective effect (Gui, et al., 2023). High wind speed may increase ocular surface discomfort and conjunctivitis by directly exerting mechanical effects or affecting tear film stability; the protective effect of low wind speed may lie in reducing the spread of irritants in the air while having a mild diluting effect to prevent the accumulation of pollutants. Besides, dust carried by the wind can directly irritate the eyes, trigger allergic reactions, and increase the risk of worsening VKC symptoms by approximately 4.35 times (Gupta, et al., 2025). Wind can also aid in the dissemination of microsporidian spores and increase the likelihood of ocular infections, particularly when it is humid and rainy, showing a positive correlation with the prevalence of acute microsporidial keratoconjunctivitis (Das, Basu, 2021). Asian dust storms are complex natural phenomena originating from central Asian deserts and transported over long distances by monsoons. Previous studies had only a vague understanding of its relationship with conjunctivitis (Yang, 2006). It is revealed that during the Asian dust storm period, the relative risk of conjunctivitis visits for school-age children (≥ 6 years old) increased by 9.48%, and for pre-school children (< 6 years old), 1.48% (Chien, et al., 2014).

Light, particularly UV, serves as a critical exposure determinant influencing various forms of conjunctivitis. The severity of conjunctivitis is significantly associated with sun exposure, and UV is the main cause of actinic conjunctivitis (Engel, et al., 2009). For allergic conjunctivitis, exposure to sunlight increases the risk by 3.56 times (Gupta, et al., 2025). Keratoconjunctivitis is also affected: solar radiation has been considered as a risk factor for VKC (Gupta, et al., 2025; Levanon, et al., 2023), and a study found 85.8% cases were caused by welding, which is one of the most severe occupations exposed to UV (Yen, et al., 2004).

Population-based studies have shown a significant correlation between pollen and conjunctivitis (Cakmak, et al., 2002; Motreff, et al., 2014), including Ambrosia, Artemisia, Plantaginaceae, Poaceae, Cupressaceae, Quercus, Fraxinus, etc. Especially for allergic conjunctivitis, symptoms highly overlap with the peak pollen season (Calderon-Ezquerro, et al., 2018; Qiu, et al., 2021). Pollen sensitization has a lag effect, and as the concentration increases, it becomes stronger and lasts longer (Sheng, et al., 2022). Grass (Ridolo, et al., 2007), birch (Caillaud, et al., 2014), cedar and cypress pollen (Yoshida, et al., 2013) are special risk factors (Kronqvist, et al., 1999; Riediker, et al., 2001; Zeghnoun, et al., 2005) for rhinoconjunctivitis, and exposure to high levels of pollen during pregnancy may increase the risk of children being allergic to the same allergen (Kihlström, et al., 2003). Despite that, no relationship has been found between greenness and rhinoconjunctivitis (Dadvand, et al., 2015). There is generally a difference in conjunctivitis between urban and rural areas. The risk of VKC (Gupta, et al., 2025) in urban areas is significantly lower than in rural areas. Urbanization reduces dust, pollen, and other irritants exposomes and brings about more abundant medical resources. However, rural areas are not a risk factor for rhinoconjunctivitis (Viinanen, et al., 2007). This may be related to the timing, dose, and mode of contact between the allergen in rural areas and human body, as well as the pathology of rhinoconjunctivitis, all of which influence the immunomodulatory mechanisms. The ICMR EYE SEE study group carried a cross-sectional-cum-cohort study to investigate the relationship between various geographical regions (northern plains, hilly regions of north east, high altitude areas of north and coastal areas of south) and VKC, finding that the prevalence in high-altitude areas was abnormally high compared to plains (adjusted OR = 4.91, 95% CI = 1.29-18.90), while coastal regions were protective factors (adjusted OR = 0.18, 95% CI = 0.06-0.51) (Gupta, et al., 2025). This may be related to the extreme dryness and coldness in high-altitude areas, while coastal regions are relatively cool and humid with fewer allergens. Geographical factors may interact with meteorological conditions through unique exposure patterns, affecting the manifestation of symptoms.

The evidence for the impacts of exposure to organic contaminants is as follows. Short-term exposure to highly active volatile organic compounds (VOCs) like toluene, propylene, and 1-octene-3-ol is significantly related to the outpatients of nonspecific conjunctivitis (Araki, et al., 2012; Chang, et al., 2013). Methyltetrahydrophthalic anhydride (Yokota, et al., 1999) and pyrethroids (Xiong, et al., 2010) have also been proven to be significant pathogenic factors of conjunctivitis. Chlorinated paraffins (especially short-chain) (Huang, et al., 2024) can increase the risk of allergic conjunctivitis, and extremely low doses of trichlorfon and paraquat dichloride can exacerbate the disease by non-specifically enhancing IgE-mediated allergic reactions (Miyata, et al., 1993). The impact of phthalates on allergic rhinoconjunctivitis is also investigated. Most interestingly, urinary phthalate metabolites are not significantly correlated with the disease, while phthalates in dust are significantly positively associated with allergic rhinoconjunctivitis (Ait Bamai, et al., 2016; Ait Bamai, et al., 2014; Bekö, et al., 2015; Callesen, et al., 2014; Ketema, et al., 2022). Actually, local exposome (like dust) may be more likely to directly trigger an allergic eye reaction than systemic exposure (like diet). Exposure to latex can also slightly increase the incidence of rhinoconjunctivitis (Archambault, et al., 2001). As for keratoconjunctivitis, it is reported that volatiles from coal tar pitch can cause phototoxic keratoconjunctivitis under the synergistic effect of UV (Emmett, et al., 1977). Supplementary Figure S4 briefly illustrates the association between the exposomes and conjunctivitis.

Inconsistencies in findings are not uncommon in research on conjunctivitis. Although numerous studies have confirmed the PM-conjunctivitis link as discussed, a study in Israel observed no significant correlation (Khalaila, et al., 2021). Their investigation sites were located in the desert, where natural PM predominated and avoided the confounding effects of anthropogenic air pollution, suggesting it is necessary to place emphasis on the sources and components of particles when analyzing their effects. There are also different results in terms of seasonality: one study indicates that the conjunctiva is more sensitive to NO_2 in summer (Ruan, et al., 2024), while another one suggests the impact of NO_2 is more pronounced in the cold season (Bao, et al., 2021). This may be related to the different target subjects and their behavioral patterns in the two studies: the former one focused on children (0-18 years old), who engage in more outdoor activities like swimming (Esschert;, et al., 2019); the latter involved subjects of all age groups. Both studies show that females exhibit higher sensitivity, while research in Tai'an has found that men are more susceptible (Chen, et al., 2021), which may suggest that differences in incidence rates between genders are not necessarily caused by biological differences, but rather the results of a combination of local occupation-life patterns and exposure time-dose distribution. In some cities, females may exhibit higher risks due to the use of cosmetics (adsorb NO_2, exacerbating irritation and disrupting the normal defense functions of the eyes) and contact lenses (physical irritation and ocular surface damage). In contrast, males in Tai'an may engage in more outdoor work, presenting an opposite gender trend. It is of concern for SO_2 that two studies based on patients from the Eye Center of the Second Affiliated Hospital of the Zhejiang University School of Medicine have found differing results: a case-crossover study of 9,737 outpatients (2014-2016) found the strongest association in children aged 2–5 years (Fu, et al., 2017); another study with a longer time span (2014–2019) and a larger sample size (539,649 individuals), proposed that the elderly are more sensitive (Chen, et al., 2023). This may be because the first one mainly focuses on acute effects, while the latter focuses on sustained damage and lag effects.

The conclusions of various population-based studies on the impact of other factors such as weather and pollen on conjunctivitis are also somewhat inconsistent. A time-series study in China, considered Urumqi as a protective factor (Gui, et al., 2023), while another research in France, concluded that humidity has no significant correlation with conjunctivitis (Bourcier, et al., 2003). The discrepancy may result from the humidity pattern in Urumqi, where the extreme dryness leads to unstable tear films, triggering and exacerbating conjunctivitis, which may also increase the concentration of allergens and pollutants in the air, further irritating the ocular surface. For allergic conjunctivitis, humidity generally plays a protective role (Zhong, et al., 2019) since it may reduce the suspension and spread of allergens such as pollen and pollutants (Lu, et al., 2021). While high humidity combined with high temperature is positively correlated with the risk of allergic conjunctivitis (Zhao, et al., 2023). This may be that high-temperature plus high-humidity conditions promote the release of pollen and the growth of mold, and enhance the synergistic effects of air pollutants and allergens. A study in the northeast China found a significant positive correlation between wind speed and allergic conjunctivitis incidence (Lu, et al., 2021), but no significant association was observed in Shanghai (Hong, et al., 2016), which may be due to the impact of wind is not as pronounced as it is in arid regions under the humid climate of Shanghai. Of note, a special circumstance warrants attention in pollen research. Burr et al. not only fail to support the viewpoint that pollen leads to allergic rhinoconjunctivitis, but even reveal a slight negative correlation: rural children with higher exposure have fewer symptoms (Burr, et al., 2003). The researchers believe that continuous natural pollen exposure, especially in early life, may reduce the risk through immune regulatory mechanisms.

Research on the mechanisms linking air pollutants to conjunctivitis is relatively scarce. Exposure to $PM_{2.5}$ can cause eyelid edema and tearing, and prolong the tear breakup time, leading to conjunctivitis, in murine model (Tang, et al., 2019). It can enhance the Th2 immune response by promoting the maturation of dendritic cells, thereby exacerbating allergic conjunctivitis, validated through *in vivo* study (Hwang, et al., 2021). Besides, exposure to diesel exhaust particles increases inflammatory factors expression in human conjunctiva (Fujishima, et al., 2013). O_3 induces oxidative stress responses and upregulates IL-6 and TNF-α in an experimental animal model of allergic conjunctivitis, but does not directly cause cell death or mitochondrial dysfunction (Lee, et al., 2017). Weather mechanisms are also under-researched, primarily focusing on keratoconjunctivitis. Dryness stress recruits monocytes from the blood to the conjunctiva via the C-C motif chemokine ligand 2 (CCL2)-C-C motif chemokine receptor 2 (CCR2) signaling axis and promotes their differentiation into $MHCII^+$ macrophages with antigen-presenting capabilities *in vivo*. These cells highly express pro-inflammatory genes (such as markers of M1-type macrophages and genes related to inflammasome), thereby driving ocular surface inflammatory responses, leading to goblet cell loss and ultimately keratoconjunctivitis (Alam, et al., 2021). How pollen causes allergic conjunctivitis are also being unveiled. Using ragweed pollen as a model, researchers found that intact pollen suspension could induce typical eosinophilic infiltration and epithelial hyperplasia, while pollen extract or pollen shell alone was not sufficient. Mechanistically, the pollen shell, rather than the extract, could directly stimulate the conjunctival epithelium to release IL-33, which in turn promotes the expansion of $CD4^+ST2^+$ T cells and the production of IL-5 through the ST2 receptor, driving eosinophil recruitment (Fukase, et al., 2021).

Conclusively, conjunctivitis is primarily influenced by air pollutants, temperature, humidity, pollen, and organic pollutants. This is largely because its pathogenesis is closely linked to allergic reactions, making conjunctivitis the most pollen-sensitive among major ocular diseases. Pollen assessments were primarily based on high-quality data from local or national environmental monitoring stations (e.g., the National

Aerobiological Network Survey and MeteoSwiss). Conversely, outcome definitions varied considerably. Most studies relied on questionnaires to collect information and assess outcomes (e.g., the International Study of Asthma and Allergies in Childhood, ISAAC, questionnaire) (Yoshida, et al., 2013), while only a minority of studies incorporated clinical examinations and ancillary tests (e.g., serum IgE monitoring, skin prick tests) (Kihlström, et al., 2003). Consequently, beyond exposure misclassification, the primary sources of bias stem from disease assessment, including recall bias and misdiagnosis bias (Yoshida, et al., 2013). Notably, less than 50% of pollen-related clinical studies accounted for confounding variables. Furthermore, these adjustments were often incomplete, warranting caution when interpreting the results. Air pollutants such as PM, NO_2, and SO_2 are considered detrimental, a conclusion supported by several large-scale prospective studies (Chen, et al., 2022; Gehring, et al., 2015). These findings remain robust even after adjusting for other air pollutants and exposomes like humidity and temperature (Chen, et al., 2021; Szyszkowicz, et al., 2016). However, there is currently a lack of preclinical research to elucidate the underlying mechanisms, and causal inferences remain limited. The effects of humidity remain highly controversial and difficult to categorize as strictly protective or deleterious, requiring case-by-case evaluation. The existing research evidence regarding the effects of ionizing radiation, greenness, and heavy metals on DED is insufficient, and cautious judgment is therefore required. Researches on the impacts of light intensity, blue light, altitude, and latitude on DED are still lacking.

Conjunctivitis prevention and control should focus on the refined intendance of the "exposure-host" interaction. Beyond general measures including air pollution management, responses to extreme climates, humidity or temperature control and so on, the following aspects warrant particular consideration: pollen is the priority for prevention, and individuals should monitor local pollen indices, reduce outdoor activities during peak seasons, or use anti-allergy eye drops in advance, and wash the faces and rinse the conjunctival sac promptly and change the clothes after returning home (Calderon-Ezquerro, et al., 2018); to minimize exposure to floor dust, regular cleaning and dust removal are recommended, and the use of carpets should be reduced, especially in households where people frequently sit on the floor (Ait Bamai, et al., 2016); special attention should be given to susceptible populations, including children, the elderly, and allergy-prone individuals, strengthening protective measures and correcting harmful habits such as eye rubbing.

3.1.3 Pterygium

The impacts of air pollutants on pterygium are not as strong as other eye diseases, with more significant associations primarily found in dust exposure (Khoo, et al., 1998; Nakaishi, et al., 1997). The relationship between indoor smoke and pterygium is weak: in Tandon's study, among the three regions surveyed, only the indoor smoke in coastal Prakasam had a significant correlation (Tandon, et al., 2022). Effects of other chemical gases, including NO_2, SO_2, and O_3, are also extremely weak (Fu, et al., 2021; Lee, et al., 2017; Zeng, et al., 2025). In reports regarding meteorology, humidity does not seem to be a major independent risk factor. The 2017 national cross-sectional study in South Korea, using precise environmental monitoring data and multivariate statistical models, found no significant association between humidity and the overall prevalence or postoperative recurrence rate of pterygium after adjusting for confounding factors such as age, gender, and sun exposure time (Lee, et al., 2017). This finding highly coincides with Darrell's epidemiologic study on American veterans as early as 1963 (Darrell, Bachrach, 1963). Important findings have been obtained in the epidemiological studies on light exposure, indicating that sunlight is a significant risk factor (Al-Bdour, Al-Latayfeh, 2004; Chun, et al., 2018; Fekadu, et al., 2020; Khoo, et al., 1998; Rim, et al., 2013; Tang, et al., 1999; Threlfall, English, 1999; Vojniković, et al., 2007). The association between occupational sun exposure and pterygium exhibits remarkable significance: in the salt industry, the prevalence of pterygium among brine workers (21.0%) is significantly higher than that among dry salt workers (9.1%) and non-salt workers (9.4%) (Mathur, et al., 2005), due to direct exposure and the intense reflected sunlight from brine/salt crystals. Pterygium is also closely related to UV (Darrell, Bachrach, 1963; Stevenson, et al., 2021),with the evidence from Australia (McCarty, et al., 2000), India (Asokan, et al., 2012), and China (Lin, et al., 2019; Yan, et al., 2006), particularly occupational exposure (Mackenzie, et al., 1992; Stoynovska, et al., 2018). It is primarily correlated with long-term cumulative UV exposure rather than short-term intense exposure (Garźon-Chavez, et al., 2018; Hatsusaka, et al., 2021; Suresh, et al., 2022), and both UV-A and UV-B are significantly associated with the occurrence (Taylor, et al., 1989; Taylor, et al., 1992). Besides, the role of visible light should not be overlooked. A doubling of blue light exposure increases the pterygium risk by approximately 85% (Taylor, et al., 1992).

A large number of epidemiological studies targeting different populations have consistently shown a significant negative correlation between urbanization level and the risk of pterygium: the ratios of prevalence between rural and urban areas in Australia, South India, United States, and South Korea are 5.28 (McCarty, et al., 2000), 4.11 (Asokan, et al., 2012), 1.52 (Darrell, Bachrach, 1963), and 1.2 (Rim, et al., 2013), respectively. This may be because rural areas involve more outdoor labor and longer sun exposure time, while urban areas have more high-rise buildings and shadows, and are mainly characterized by indoor work. Meanwhile, urban residents are more likely to use sunglasses and hats, while rural areas have weaker protective awareness, with lower education levels, poorer health consciousness, and fewer medical resources. From a geographical perspective, the ICMR-EYE SEE study group compared the prevalence of pterygium in plain, hilly, and coastal areas and found it was highest in coastal regions (Tandon, et al., 2022). This may be attributed to higher levels of UV exposure, exacerbated by the strong reflection of UV from sea surfaces. And residents in coastal areas are mostly engaged in fishing and agriculture, working outdoors for extended periods and lacking effective eye protection. Besides, it is reported that the lower the latitude, the higher the risk (Darrell, Bachrach, 1963; Mackenzie, et al., 1992), and this trend is consistent with the geographical distribution of UV intensity. Similarly, altitude itself may not be an independent risk factor, but the accompanying strong UV and high-altitude climate are the main pathogenic reasons (Lu, et al., 2009; Lu, et al., 2007).

Based on KNHANES 2008–2011, it is found that blood lead and mercury levels were significantly positively correlated in a dose-dependent manner, while blood cadmium was not significantly associated with overall pterygium risk (Han, et al., 2022). Arsenic exposure is also closely related to pterygium. A cross-sectional study found that the prevalence in the exposed group was significantly higher than that in the control group, and the prevalence increased with the cumulative amount of arsenic, indicating that long-term intake of arsenic through drinking water may be associated with the occurrence of pterygium (Lin, et al., 2008).

The primary controversy regarding exposome for pterygium centers on the complex impact of PM, for which no consensus has yet been reached. Ramirez et al. surveyed factory workers and denied the correlation (Ramirez, et al., 2018). In the Korean population, there is also no significant association between PM_{10} and overall pterygium or postoperative recurrence, although primary pterygium is weakly related (Lee, et al., 2017). However, two recent studies in China confirmed the influence of $PM_{2.5}$ and PM_{10}, with a lag effect (Fu, et al., 2021; Zeng, et al., 2025). Ramirez's study focuses on occupational exposome, and the outcome indicators in the Chinese research, different from the first two studies, are not clinical examinations but outpatient data, which may not be so accurate but are more sensitive, suggesting PM primarily leads to mild and early lesions and is unlikely to exacerbate or worsen the disease.

As reflected in the aforementioned epidemiological research, light is the most critical factor influencing pterygium, and its core mechanisms have been extensively investigated, with particular emphasis on the role of UV. It does not cause significant damage to corneal endothelial cells, but a decrease in density is observed (Doughty, Oblak, 2005; Li, et al., 2018). Research has not established a direct correlation between UV intensity and p53 expression, a key regulator of the cell cycle and DNA repair, despite UV disease-promoting effects via DNA damage (Pelit, et al., 2009). UV stimulation can upregulate the expression of *cysteine rich motoneuron protein1 (CRIM1)*, which then activates extracellular signal–regulated kinases (ERK) phosphorylation, thereby inhibiting *B-cell lymphoma 2 (BCL-2)* expression, promoting cell apoptosis, and suppressing proliferation to prevent the onset of pterygium, observed by *in vitro* experiments. Therefore, *CRIM1* is the core regulator of the corneal response to UV, and mutant H412P *CRIM1* can lead to increased susceptibility (Maurizi, et al., 2019). Through mitogen-activated protein kinases (MAPK) and epidermal growth factor receptor (EGFR) signaling pathways, UV-B promotes IL-6, IL-8, and VEGF in *in vitro* experiments (Di Girolamo, et al., 2002; Di Girolamo, et al., 2006), moreover inducing the upregulation of *Toll-like receptor 3 (TLR3)* expression in pterygium superficial epithelial cells and activating NF-κB (Lai, et al., 2021), thus promoting cell proliferation. UV-B can also induce the expression of *MMP-1* in pterygium epithelial cells and limbal epithelial cells through the ERK1/2 MAPK-dependent signaling pathway, enhancing the degradation of the extracellular matrix (ECM) and promoting the tissue remodeling and invasive growth of pterygium (Di Girolamo, et al., 2003). Besides, it inhibits the nuclear factor erythroid 2-related factor 2 (Nrf2)/ARE pathway through Src kinase-mediated signaling pathway in *in vitro* experiments, thereby downregulating the expression of *proteasome subunits the beta 5 (PSMB5)*, which may weaken the cell's ability to clear oxidatively damaged proteins, promote inflammation and fibrosis, and facilitate the progression of pterygium (Aletras, et al., 2018). The mechanisms associated are illustrated in Supplementary Figure S5.

Pterygium is primarily affected by various air pollutants, sunlight, and urbanization. Research has mainly focused on clinical cohorts, with preclinical studies conducted exclusively in the context of UV exposure. UV is detrimental to the occurrence and development of diseases, and clinical studies only adjusted for demographic characteristics and failed to incorporate other expomes into their models (Chun, et al., 2018; Hatsusaka, et al., 2021); therefore, the interpretation of their results warrants caution. Although numerous, these clinical studies lack prospective cohort designs, lacking sufficient exploration of causal associations and needing for further improvement in overall research quality. Exposome assessments were relatively comprehensive, utilizing multiple approaches including government-issued meteorological data (Lin, et al., 2019), questionnaires (Doughty, Oblak, 2005; Taylor, et al., 1989), and occupational exposure estimations (Chun, et al., 2018). Outcome definitions were generally clear, as they were primarily assessed and graded by clinicians based on ophthalmic examinations (Taylor, et al., 1989). Urbanization exerts a protective effect against the disease, and the present studies have accounted for the confounding effects of factors such as UV and humidity (Darrell, Bachrach, 1963). The biases primarily consist of information bias derived from questionnaire surveys (Asokan, et al., 2012; McCarty, et al., 2000) and selection bias associated with the sampled population (Darrell, Bachrach, 1963; Rim, et al., 2013). There are relatively few studies on exposomes such as blue light, latitude, and heavy metals, and prospective studies are lacking; therefore, the analysis of conclusions must be conducted with caution. Research on exposomes including CO, temperature, light intensity, ionizing radiation, and pollen remains entirely absent.

Addressing the impact of exposure on pterygium centers on blocking cumulative UV. This can be achieved by wearing UV-protective eyewear and wide-brimmed hats (Fekadu, et al., 2020; Lin, et al., 2019; Rim, et al., 2013), along with enforcing protective measures for high-risk occupations (such as fishermen and salt workers) (Mathur, et al., 2005). Concurrently, efforts to control heavy metal pollution should be continuously advanced, especially near industrial zones, alongside strengthening monitoring of high-risk populations (Han, et al., 2022; Lin, et al., 2008). Given the relative scarcity of medical resources in rural areas, it is necessary to promote the allocation of resources to primary care levels, enhance grassroots eye disease screening capabilities, and facilitate the early detection and guidance of pterygium (Asokan, et al., 2012).

3.2 Cataract

There is abundant evidence discussing the exposure of cataract. Air pollutants take a critical role: smoke, including cigarette smoke and indoor kitchen smoke (especially generated from the combustion of biomass fuels), has been proven to be closely related to cataract in numerous studies (Lai, et al., 2024; Noda, et al., 2010; Owusu, et al., 2025; Patel, et al., 2022; Pokhrel, et al., 2005; Sreenivas, et al., 1999; Vashist, et al., 2020); it is known that CO and SO_2 are risk factors (Sagie, et al., 2024; Shin, et al., 2020), but no evidence for hydrogen sulfide (H_2S) (Bates, et al., 2017), and O_3 is widely considered to have a protective effect (Choi, et al., 2018; Grant, et al., 2021; Sagie, et al., 2024; Shin, et al., 2020). Noting meteorological factors, concerns have been reported that high temperature may cause the disease (Echevarria-Lucas, et al., 2024; Lv, et al., 2022; Sagie, et al., 2024; Wallace, et al., 1971), with nuclear cataract being the commonest (Kinoshita, et al., 2023; Kodera, et al., 2020; Sasaki, et al., 2002). However, researchers have also found a negative correlation between extremely high temperature and cataract (Xie, et al., 2020). The difference in results may be attributed to the fact that it reduces outdoor activity and affects patients' willingness to seek medical consultation. Besides, precipitation is believed to be negatively correlated (Echevarria-Lucas, et al., 2024). Light is the most direct factor influencing cataract formation. Sunlight has become an independent risk factor (Brilliant, et al., 1983; Delcourt, et al., 2000; Latebo, et al., 2024; Leske, et al., 1991; listed, 1991; Neale, et al., 2003; Rosmini, et al., 1994; See, et al., 2007; Sreenivas, et al., 1999; Vashist, et al., 2020; Zigman, et al., 1979), especially during adolescence (Pastor-Valero, et al., 2007), Specifically, waterclefts subtype cases appeared to have significantly higher mean annual sunlight exposure than controls (Durant, et al., 2006). Extensive research has established a positive correlation between UV and cataract (Anduze, 1993; Burton, et al., 1997; Cullen, et al., 1994; Delavar, et al., 2018; Delcourt, et al., 2014; Garźon-Chavez, et al., 2018; Suresh, et al., 2022; Varssano, et al., 2017; Wang, et al., 2012; Zhu, et al., 2015), especially senile cataract (Garrigan, et al., 2021) and nuclear cataract (Kinoshita, et al., 2023; Miyashita, et al., 2019; Sasaki, et al., 2002). Occupational UV is one of the major sources (Stoynovska, et al., 2018), but arc weld workers, as one of the careers exposed to occupational artificial UV most, found no increased risk (Megbele, et al., 2012; Slagor, et al., 2016). Actually, this may be related to increased awareness of occupational exposure and enhanced protective measures, effectively reducing the exposure dose for welders. And long-term high UV exposure magnifies the association between poor socio-economic status and cataract-related blindness burden (Deng, et al., 2021). Among UV components, UV-B is found to have a greater association (Jose, 1986; Meyer, et al., 2005; Michael, et al., 1996; Okuno, et al., 2012; Taylor, 1980; Taylor, 1989), particularly for women (Hayashi, et al., 1998). The formation of cataract is nonlinearly correlated with the duration of exposure to 300 nm UV (Ayala, et al., 2000), and the sensitivity decreases with increasing exposure time (Galichanin, et al., 2014). Furthermore, different exposure intervals can cause varying degrees of damage to the lens (Ayala, et al., 2000; Michael, et al., 1999). The maximum tolerable dose has been evaluated extensively in experiments (e.g., 2.9 kJ/m^2 for mice, 3.01-5.2 kJ/m^2 for rats, and 69 kJ/m^2 for guinea-pigs, varing among different species and different ages) (Congdon, et al., 2000; Dong, et al., 2005; Meyer, et al., 2008; Michael, 2000; Mody, et al., 2006; Mody, et al., 2012), and it also increases with the extension of the interval time (Dong, et al., 2007). And UV-B will aggravate the regional differences since different regions of the lens have different susceptibility (Abraham, et al., 2010): cortical (Taylor, et al., 1988; West, et al., 2005) and posterior subcapsular (Bochow, et al., 1989) regions chiefly. Infrared (IR) is also identified as a risk factor (Lydahl, 1984), and 1,090 nm IR close to the threshold dose has been proven to induce cataract with a time delay (Yu, et al., 2015). Though clinical research found no evidence of visible light causing cataract (Taylor, et al., 1992), it is verified in experiments that violet light (407 nm) induces the strongest cataract, blue light (463 nm) has great individual differences, and red light (635 nm) causes slight or no cataract (Haag, et al., 2021; Zeller, et al., 2022). Moreover, researchers have confirmed that fluorescent light has little effect (Wolf, Penn, 2001).

Ionizing radiation mainly includes cosmic rays, X-rays, and γ-rays, which are characterized by short wavelengths, high frequencies, and high energy. The primary concern is for workers in nuclear facilities: chronic occupational exposure significantly increases the incidence of all types of cataracts (Azizova, et al., 2016; Azizova, et al., 2018), and the higher the dose, the shorter the incubation period (Adams, et al., 1983; Villeneuve, et al., 2025). Another focus is on pilots and astronauts, who have a higher probability of exposure to cosmic rays. Pilots have a much higher probability of developing cataract than ordinary people (Rafnsson, et al., 2005), and astronauts have an even higher prevalence than pilots (Jones, et al., 2007), with a potential for delayed onset (Cox, et al., 1992). The main areas where astronauts develop cataracts are the posterior capsule and the cortex, while nuclear cataract is relatively rare (Chylack, et al., 2009; Rastegar, et al., 2002), with exact reasons remaining unclear. Some medical staffs are also frequently exposed to ionizing radiation, being high-risk group (Milacic, 2009): it is shocking that for radiologists, even doses below the limits set by the International Commission on Radiological Protection can still promote the development of cataract (Chodick, et al., 2008; De Stefano, et al., 2016; Lian, et al., 2015; Little, et al., 2020; Little, et al., 2018); a study has also mentioned that exposure for orthopedic surgeons also needs attention, with the prevalence reaching 20% (Hijikata, et al., 2025).

The epidemiological characteristics vary significantly across different regions. Vashist et al. compared the differences in cataract prevalence among plain, hilly, and coastal areas, found coastal area is the highest (42.4%), followed by the plain area (31.9%) (Vashist, et al., 2020). This may be related to differences in vegetation cover, climatic conditions, or lifestyle across different terrains. For instance, hilly area has more vegetation cover that can attenuate sunlight; and residents in coastal areas may be more involved in fishing activities, directly receiving more sun exposure, and the water surface also reflects sunlight, further increasing their exposure. It should be noted, however, that the latitudes of the three regions in this study are inconsistent, leading to differences in solar intensity and effective sunlight durations, which may affect the rigor of the results. It is also found that the location of cortical cataract varies with latitude. The lower the latitude, the higher the prevalence in the lower nasal quadrant (Sasaki, et al., 2003). As altitude increases, UV also intensifies, so as mentioned earlier, the prevalence should rise theoretically. Reciprocally, it has been identified that the prevalence is negatively correlated (Brilliant, et al., 1983; Garrigan, et al., 2021). Despite the increased damage to the lens caused by enhanced UV, high-altitude areas may have more cloud cover, and surrounding mountains may block sunlight, shortening the actual duration of sunshine and reducing the amount of UV. Apart from that, urbanization is negatively correlated with the risk of cataract based on large-scale studies in India and China (Garrigan, et al., 2021; Wang, et al., 2012). The consequence may include less outdoor work, higher education levels, and abundant medical resources in cities, which can reduce UV exposure, improve awareness of protection, and provide timely treatment.

In relevant studies on heavy metals, by measuring the lead content in the tibia, patella, and blood, it is found that cumulative lead may promote cataract (Mosad, et al., 2010; Schaumberg, et al., 2004) while short exposure (reflected from blood level) may not be sufficient (Wang, et al., 2016). Analysis showed that every 2-fold increase in urinary cadmium was associated with a 23% higher risk of cataract surgery (Wang, et al., 2016), and a plausible hypothesis is that it mediates oxidative stress (Mosad, et al., 2010). A cross-sectional study conducted on Amazon population found that high levels of mercury exposure can also lead to the development of cataract (OR = 4.45, 95% CI = 1.43–13.83) (Lemire, et al., 2010). Selenium and arsenic are two metalloid elements that are widely present in nature and share many similarities in chemical properties and mechanisms of toxicity (Sun, et al., 2014). Research has revealed a negative correlation between selenium and age-related cataract (Lemire, et al., 2010). Particularly, it is closely related to the level of mercury exposure, for selenium can counteract the cataractogenic effects of mercury through its antioxidant properties. And for arsenic, a multi-elements model in a case-control study has confirmed that it can increase the risk of cataract by around 7 times (Li, et al., 2023). Discussions on the relationship between organic pollutants and cataract have focused on per- and poly-fluoroalkyl substance (PFAS), a class of persistent synthetic chemicals used in diverse industrial and consumer products, including some food-contact materials and grease-resistant packaging. It is demonstrated that exposure to PFAS was positively associated with cataract significantly (perfluorohexane sulfonic acid OR = 1.579, 95% CI = 1.003-2.514; perfluorononanoic acid OR = 1.629, 95% CI = 1.065-2.506) (Liu, et al., 2025).

Researchers also hold divergent viewpoints regarding the impact of exposomes on cataract. Some studies indicate that $PM_{2.5}$ and PM_{10} are associated with the disease, with exposure increasing the risk by 9.1-16.5% and 6.9-7.1% (Abdolalizadeh, Falavarjani, 2023; Hegelund, et al., 2024; Lawrence, et al., 2020; Li, et al., 2023; Shin, et al., 2020; Wu, et al., 2022), and the likelihood of surgery by 14-22% and around 21% (Chua, et al., 2021; Sagie, et al., 2024), respectively, while several studies suggest that PM is not correlated with cataract (Choi, et al., 2018; Gayraud, et al., 2024; Grant, et al., 2021; Shin, et al., 2020; Wang, et al., 2025). This discrepancy may be attributable to variations in exposure concentration and duration across studies (the range for those supporting the association is 9.93–185 μg/m^3 and 19.14–280 μg/m^3 over 1–18 years for $PM_{2.5}$ and PM_{10}, respectively, while studies disagreeing mentioned 9.91 μg/m^3 and 16.22 μg/m^3 separately for 12.4 years). Most research holds the view that NO_2 is positively associated with the incidence (Gayraud, et al., 2024; Hegelund, et al., 2024; Li, et al., 2025; Shin, et al., 2020). Nevertheless, a report reached a completely opposite conclusion (Grant, et al., 2021), and a recent prospective cohort study involving 114,930 people pointed out that no significant correlation was found between cataract and NO_x (Wang, et al., 2025). Regarding weather conditions, the association between humidity and cataract is also controversial. Research from China demonstrates that high humidity has a protective effect (Lv, et al., 2022), while another study conducted in Israel concludes that it promotes the disease (Sagie, et al., 2024). This may be due to different methods and strategies applied: the former's outcome was self-report, which may have a large bias, while the latter used surgery records reflecting more serious cases; there were huge differences in race and confounding factors (such as socioeconomics, etc.) in the two countries. Although we have presented substantial evidence in the preceding content supporting the role of sunlight in cataract development, disagreement persists among some studies (Collman, et al., 1988; Dolezal, et al., 1989; Perkins, 1985; Salducci, Gioia, 2020; Wong, et al., 1993). The differences in results may be due to a lack of variability in geographic sun exposure or methods for quantifying exposure being too crude, and lifestyle factors like vitamin C intake may also have an impact. For ionizing radiation, similar to radiologists and orthopedic surgeons, studies from multiple countries, including Thailand (Matsubara, et al., 2017), France (Jacob, et al., 2013), Italy (Andreassi, et al., 2016), Spain (Vano, et al., 2010), and Malaysia (Ciraj-Bjelac, et al., 2010) have shown that interventional cardiologists face an extremely high risk (3.2-10.6 times). Of note, a later study in Poland did not observe any statistical correlation between occupational ionizing radiation exposure and lens opacification in interventional cardiologists, with even lower doses than former studies (Domienik-Andrzejewska, et al., 2019). Further investigation is necessary to confirm the relationship. Besides, cross-sectional (Kruse, et al., 2005) and case-control (Sabbioni, et al., 2005) studies demonstrated that trinitrotoluene (TNT), a common organic contaminant in military and industrial blasting, is positively related to cataract. Nevertheless, a subsequent study disagrees with this view (Naderi, et al., 2013). A possible explanation is that the workers surveyed in the latter study used comprehensive protective equipment such as chemical masks, gloves, and goggles, which reduced direct exposure.

Researchers are also committed to elucidating the underlying mechanisms. For air pollutants, *in vivo* experiments showed that long-term exposure to PM pollution increases risk by disrupting the redox balance of the lens (Vitar, et al., 2020). Another intriguing discovery is ferroptosis: in the lenses of cataract patients in $PM_{2.5}$-polluted areas, upregulation of STEAP family member 3 (STEAP3) and downregulation of glutathione peroxidase 4 (GPX4), CDGSH iron sulphur domain 3 (CISD3), and aldo-keto reductase family 1 member C1/2 (AKR1C1/2) were detected, which are ferroptosis biomarkers (Sheng, et al., 2024). The essence of ferroptosis is the extreme manifestation of redox imbalance, and this study further deepens the understanding of the impact of redox balance on cataract. Smoke can induce early pathological changes in lens epithelial cells (LECs) by damaging the Na^+/K^+ pump, confirmed by *in vitro* experiments (Rao, et al., 1995). Although no strong correlation between tobacco smoke and cataract was found in *in vivo* experiments (Khan, et al., 2021), researchers revealed that p-benzoquinone (p-BQ) in tobacco smoke causes structural and functional damage to αA-crystallin, which is an efficient molecular chaperone that plays a key role in maintaining the integrity and transparency of the lens (Chowdhury, et al., 2018). Great efforts have also been made in weather impact. Localized temperature increase in the area where the iris contacts the lens can damage the anterior capsule epithelial cells of the lens *in vivo*, causing fiber rupture and vacuolization, which ultimately leads to lens opacification (Langley, et al., 1960). Facing high temperatures, HSP-70 is expressed to mitigate damage and delay the onset of cataract, while when the temperature is too high (≥ 50 °C), the protective effect begins to fail *in vitro* (Dzialoszynski, et al., 2016). HSP and α-crystallin have synergistic functions, especially in maintaining the stability and transparency of lens proteins in response to heat stress. αB-crystallin is a small heat shock protein (sHSP) with chaperone activity, and the generation of advanced glycation end product (AGE) via glycation is one of the key modifications. During αB-crystallin-mediated client protein chaperoning, short-term (1 hour) exposure to high temperature with methylglyoxal can promote AGE-mediated intermolecular cross-linking of proteins, resulting in early cataract formation (Nandi, et al., 2020).

To date, there have been many hypotheses about how light influences cataract, but the exact mechanism remains unclear. The opacification observed in the lens *in vivo* after high-dose exposure to UV-B may be a result of osmotic swelling (Söderberg, 1990), and UV-B can induce crystalline protein to form amyloid fibers (Cetinel, et al., 2017). Apoptosis may be another major reason: it appeared to play a crucial role in the process of UV-B disrupting redox balance in the lens to induce cataract formation with *in vivo* experiments (Wang, et al., 2010). It is reported that UV-B up-regulates the expression of *TP53* (Ayala, et al., 2007), inducing apoptosis in LEC (Galichanin, et al., 2010; Li, Spector, 1996; Meyer, et al., 2014), and down-regulates Yes-associated protein (YAP)/forkhead box M1 (FOXM1)/Nrf2 axis, promoting ROS accumulation (Hong, et al., 2024). In addition, it enhances the interaction between nuclear factor of activated T cells 5 (NFAT5) and NF-κB p65, upregulates the α-SMA protein, and induces the production of ROS (Chung, et al., 2017). With ROS, UV-B activates the NF-κB pathway, down-regulates sodium vitamin C transporter 2 (SVCT2), reduces vitamin C intake, and intensifies oxidative stress (Guo, et al., 2023). It triggers mitochondrial oxidative stress in LECs directly as well, leading to apoptosis and promoting cataract eventually (Ji, et al., 2015). Thioltransferase (TTase) and thioredoxin (Trx) system is a vital mechanism for the lens to resist oxidative stress, while aging weakens the ability (Zhang, et al., 2012). In terms of genetics, UV alters the chromatin pattern and induces morphological changes (Söderberg, 1988). GSTO2*Asn142Asp polymorphism significantly increases the sensitivity to UV (Stamenkovic, et al., 2014). Moreover, UV-B-mediated DNA damage may accumulate in LECs, leading to gene mutations and ultimately causing cortical cataract (Mesa, Bassnett, 2013; Stevens, et al., 2005). Development mechanisms of cortical cataract also include overexpression of *MMP-1* induced by UV-B in LECs, leading to ECM degradation and disruption of growth signaling pathways, which in turn destroys lens fiber structure, with *in vitro* evidence (Sachdev, et al., 2004). There are also studies regarding ephrin type-A receptor 2 (Epha2) (Dave, et al., 2019), prostaglandin E2 (PGE2) (Andley, et al., 1996), growth differentiation factor 15 (GDF15) (Osada, et al., 2011), excision repair cross-complementation group 6 (ERCC6) (Wang, et al., 2016), glutathione S-transferase mu 1 (GSTM1) (Saadat, Farvardin-Jahromi, 2006) and other molecules, which have also been confirmed to participate in the pathological process. Some studies suggest that preclinical research conducted on model animals cannot actually reflect the impact of UV-B on human, as there are significant differences in the response of human lenses and those of experimental animals (Vrensen, 1994), including differences in dose and duration between experimental UV-B exposure and real-life situations, as well as the fact that nocturnal animals like mice may not be able to cope with strong light exposure and there are considerable differences in defense mechanisms like antioxidant systems among different species. When it comes to UV-A, the initial hypothesis was founded on evidence from animal studies demonstrating that it was not cataractogenic even after long-term exposure (Jose, Pitts, 1985), conversely later studies revealed that it could penetrate the lens nucleus, causing oxidative stress, protein degradation, and structural damage *in vivo* (Giblin, et al., 2002), and the photolytic products generated by UV-A stimulation could induce covalent modification, aggregation of lens proteins, and oxidative damage *in vitro* (Kohli, et al., 1996), suggesting it is also one of the important mechanisms of cataract formation. Research on the mechanisms of how IR causes cataract has primarily focused on thermal conduction damage. It has been found *in vivo* that IR of various wavelength regions generally does not directly cause lens injury: IR-A is primarily absorbed by the iris and then conducts heat to the lens (Langley, et al., 1960; Okuno, et al., 2021), while the energy of IR-B/C is absorbed by the cornea and also transfers heat to the lens (Okuno, 1994). Hence, the pathogenesis is more of a thermal injury mechanism rather than a photochemical one (Yu, et al., 2015), the same as Goldmann theory states.

For ionizing radiation, histological studies have found that the characteristics of cataract lesions caused by long-term low-dose radiation are different from those caused by short-term high-dose exposure, including feathery fibers appearing in the anterior lens, equatorial germinal epithelium forming plaques with vacuolized fibers (Hayes, Fisher, 1979; Rini, et al., 1983). Genetic background in gene diversity groups determines radiation sensitivity (Kleiman, et al., 2024; McCarron, et al., 2022). In *in vivo* experiments, insufficient single dose of *ataxia telangiectasia mutated* (*ATM)* enhances the sensitivity to X-rays (Hall, et al., 2006), and the loss of double heterozygosity of *ATM* and *Rad9* further enhances the susceptibility (Kleiman, et al., 2007). Ionizing radiation is also associated with chromosomal aberrations (Zhou, et al., 2016), and it can induce DNA damage and oxidative stress, promoting the aging of LECs (Ahmadi, et al., 2022). Furthermore, DNA damage can temporarily activate *p21*, which interferes with the disassembly of the nuclear envelope in differentiating LECs and promotes cataract, but not through apoptosis (Rini, et al., 1983; Udroiu, et al., 2020). In terms of microwaves, it could be due to the pressure waves generated by the microwave through the thermoacoustic effect (Stewart-DeHaan, et al., 1985). *In vivo* research has also speculated that it generates high temperature locally, which ultimately damages the lens through the thermal effects mentioned earlier (Kramár, et al., 1987). Similarly, the morphological changes in the lens caused by high-frequency, high-intensity ultrasound indicate that these injuries are the result of thermal phenomena (Lizzi, et al., 1978).

The mechanisms by which various exposomes influence cataract are also detailed in Supplementary Figure S6.

Overall, cataracts are influenced by a variety of exposomes, including various air pollutants, humidity, temperature, UV, ionizing radiation, and urbanization. Among these, UV is considered harmful, as demonstrated by a substantial body of both clinical and preclinical research. Although there are two large-scale prospective studies (Delavar, et al., 2018; Slagor, et al., 2016), the clinical research has not adequately adjusted for other exposomes, with considerations limited solely to latitude and altitude (Wang, et al., 2012; Zhu, et al., 2015), warranting caution when interpreting the conclusions. Exposome assessment methods included satellite data (Deng, et al., 2021), questionnaires (Perkins, 1985), and geographic or occupational proxies (Garrigan, et al., 2021), requiring further improvement in accuracy. Outcome definitions were accurate, incorporating standardized grading systems and assessments by ophthalmology specialists (Kinoshita, et al., 2023). Ionizing radiation is the second most significant risk factor, and numerous preclinical studies have elucidated the specific mechanisms. In the clinical literature, only three prospective studies adjusted for the effects of UV (Chodick, et al., 2008; Little, et al., 2020; Little, et al., 2018), while the remaining studies failed to adjust for the associations between other exposomes and cataracts. Regarding bias control, since the study populations primarily consisted of pilots or workers with clearly documented working hours, information bias was effectively minimized (Rafnsson, et al., 2005); however, the healthy worker effect has been extensively discussed (Jacob, et al., 2013). What is special is that, despite the lack of preclinical studies and high-quality prospective clinical studies, the existing four retrospective studies suggest that O_3 has a protective effect which is different in other diseases, and this conclusion remains valid after adjustment for multiple pollutants. All exposome assessment data were derived from national environmental monitoring departments. Factors such as humidity and altitude have also been suggested to be associated with cataract in existing studies, yet the body of evidence is insufficient and further validation is required. Research on the association between cataract and exposomes including light intensity and greenness remains a gap in the current literature.

To address the impact of exposomes on cataract, systematic preventive and control measures should be implemented. These measures should center on UV protection, while integrating occupational exposome management, air pollution mitigation, and the promotion of healthy lifestyles. The focus of UV protection should be on lifelong physical barrier protection, including wearing UV-blocking eyewear and wide-brimmed hats, as well as avoiding prolonged outdoor activities during peak UV intensity hours (Garźon-Chavez, et al., 2018). Occupational exposome primarily encompasses factors such as ionizing radiation and chemical substances. The overall strategy should involve strict adherence to operational protocols, the use of protective equipment, dose monitoring and control, the establishment of occupational health records, and regular ophthalmic examinations (Naderi, et al., 2013; Slagor, et al., 2016). Air pollution mitigation strategies should emphasize the adoption of clean energy sources and the improvement of kitchen ventilation (Patel, et al., 2022). And healthy lifestyle includes maintaining a balanced nutritional diet (e.g., adequate intake of vitamins and trace elements like selenium), ensuring safe drinking water (e.g., contents of harmful substances like heavy metals are below safety threshold), and smoking cessation (Guo, et al., 2023; Lai, et al., 2024; Lemire, et al., 2010; See, et al., 2007).

3.3 Refractive errors

Compelling evidence has confirmed that specific exposomes are important inducers of refractive errors, including myopia (primary focus currently), hyperopia, and astigmatism. In the context of air pollution, an increase in $PM_{2.5}$ damages both near and distance vision (Yan, et al., 2024): it is discovered to increase the prevalence of myopia in children, adolescents, and the elderly (Dadvand, et al., 2017; Kai, et al., 2025; Ruan, et al., 2019), having also been substantiated by animal experimental evidence (Wei, et al., 2019); Lin et al. linked ambient $PM_{2.5}$ with presbyopia for the first time and observed a positive association (Lin, et al., 2019). The prevalence of refractive error is significantly associated with long-term smoke exposure as well (Owusu, et al., 2025), including smoke from the combustion of biomass fuels and kitchen cooking. Prenatal exposure to environmental tobacco smoke is associated with early onset of myopia (Huo, et al., 2021), and early exposure in preschool children can increase the prevalence of astigmatism by more than 30% (Li, et al., 2019). Two studies based on WHO the Study on global AGEing and adult health project explored and confirmed the relationship between O_3 and refractive errors: after the concentration exceeded 55 $\mu g/m^3$, for every increase of one standard deviation (10 $\mu g/m^3$), the risk of myopia increased by 26% (Ruan, et al., 2019), and presbyopia 37% (Lin, et al., 2019). Exposure to NO_x significantly increases the risk of myopia, especially in children (Dadvand, et al., 2017; Wei, et al., 2019). Climate, especially seasonal changes, has an important impact on the progression of refractive errors. Ulaganathan et al. conducted a 12-month study measuring the changes in axial length across different seasons. They found that emmetropic individuals have slower axial elongation (-0.01 ± 0.05 mm) than myopic individuals (0.04 ± 0.05 mm) in summer, which may be related to greater and stronger sunlight inhibiting axial elongation through the dopamine pathway (Reidy, et al., 2024), while no significant difference in winter (Ulaganathan, et al., 2019).

Notable differences in daily light intensity exposure have been reported between students with myopia and emmetropia (Bhandari, et al., 2022; Dhakal, et al., 2024;

Landis, et al., 2018; Read, et al., 2014). Further research has found that high-intensity light can slow down the growth of the eye axis in children (Ashby, et al., 2009; Karouta, Ashby, 2014; Read, et al., 2015) and reduce the diurnal variation amplitude of it (Ulaganathan, et al., 2019). Experiments suggest intermittent intense light is more effective than continuous intense light in inhibiting chicken myopia, though this finding may not be directly applicable to humans (Lan, et al., 2014). While for adults, exposure to strong light intensity has no significant effect on refractive status (Ostrin, 2017). It is possibly because the growth of the adult eye axis has already slowed down or stopped. But the evidence of this study is not sufficient, considering the limited sample size (only 55 people). Besides, insufficient light exposure duration is an important risk factor for myopia (Zhang, et al., 2014), especially in children (6-12 years old) (Ma, et al., 2024), pinpointing the early primary school years as the critical period for intervention. Different wavelengths have significant effects on refractive errors. Torii et al. conducted two retrospective cohort studies, one for children and another for adults, and the results of both showed that violet light can slow down the progression of myopia (Torii, et al., 2017; Torii, et al., 2017). Violet light is abundant outdoors, but measurements have found a lack of exposure indoors (Kondo, et al., 2025). Considering that people, especially in urban areas, have significantly reduced outdoor activities in modern society, this may be one of the reasons for the high prevalence of myopia nowadays. As for UV, higher UV-B exposure is significantly associated with a lower risk of myopia during the key periods of ages 14-19 and 20-39, and this protective effect is enhanced with increasing severity of myopia (Williams, et al., 2017). Sunlight exposure is a protective factor, showing a negative correlation with both the occurrence and progression of myopia (Lee, et al., 2023; McKnight, et al., 2014; Wang, et al., 2015; Yang, et al., 2021). Fluorescent lighting is believed to promote hyperopia and astigmatism firmly, and has no significant correlation with myopia (Czepita, et al., 2004; Czepita, et al., 2005; Czepita, et al., 2004; Czepita, et al., 2012). In addition, low frequency ($\leq$ 1Hz) and red/blue scintillation light may promote myopia by increasing accommodation fluctuation (Zhang, et al., 2021). Experiments have also demonstrated that flashing light can induce myopic shifts, although the degree is not as significant as that caused by form deprivation (Yu, et al., 2011). Interestingly, different types of night-time lighting can have varying effects on myopia (Guggenheim, et al., 2003): table lamps at night generally act as protective factors (Sun, et al., 2024), while outdoor artificial light can contribute to the progression of myopia in youth (Liu, et al., 2024). Supplementary Figure S7 summarizes the studies related to light and refractive errors.

Greenness is extensively recognized as a protective factor against myopia (Dadvand, et al., 2017; Peng, et al., 2021; Yang, et al., 2022): the larger the areas and the higher the densities, the lower the risk (Yang, et al., 2024). Specifically, the degree of greenness within a 500-meter buffer zone around schools is associated with a lower risk in individual adolescents and a lower prevalence in schools (Zhang, et al., 2023). Preschool astigmatism is negatively associated with greenness as well (Huang, et al., 2021). Research has also found that refractive errors in middle-aged and older adults are also affected (Yan, et al., 2024). Urbanization is widely recognized as a risk factor for the occurrence of myopia (Ip, et al., 2008; Li, et al., 2023; Shapira, et al., 2019). The main reasons are primarily due to artificial night lighting and air pollution, cramped urban housing types (like apartments), reduced greenness, and heavier academic burdens. However, some studies suggest that the progression of myopia is slower in urban areas: a study constructed a multi-dimensional urban score using satellite remote sensing data and found that for each 1-unit increase, the risk of myopia progression in students decreased by approximately 16% in the short term (within 1 year) and by 27% in the long term (within 2 years) (Li, et al., 2023). It is possibly due to more abundant medical resources and more widespread corrective measures. Spatial frequency is a concept that describes the rate of change of spatial details in an image, that is, the frequency of change per unit of visual angle (Li, et al., 2025). Indoor low spatial frequency is associated with myopia in children (Li, et al., 2025). But current assessments of spatial frequency mainly rely on photographs, which may not fully reflect the real-life environment. Research has shown that children living in areas with high population density and in smaller homes tend to have longer axial lengths and higher degrees of myopia (Choi, et al., 2017). This may be because visual stimuli in small spaces are concentrated at near distances, leading to peripheral hyperopic defocus and a lack of distant viewing behaviors. A prospective cohort study in Shenzhen, China, a representative of dense cities in East Asia, demonstrated that the higher the building area density of a school, the lower the risk of myopia (Zeng, et al., 2025), which seems to contradict the previous study. In fact, in urban areas, where land area and building height are limited for schools, a higher building area density means more indoor activity space. Zhang et al. proposed using the proportion of shadow area as a proxy indicator for the residential environment and found that it is negatively correlated with myopia (Zhang, et al., 2024). This is because a larger shadow area means taller buildings and greater separation distances between them, indicating a more spacious living environment with better ventilation and lighting.

Geography can also affect refraction: a study found that the prevalence of myopia among Tibetan students aged 12–18 was significantly lower (39.7% versus 47.6%, $p = 0.008$) than that in Chongqing (with an altitude difference of approximately 3,545 m) (Xiang, et al., 2024). Intense UV exposure at high altitude may be the key factor. But non-cycloplegic refraction used in this study may overestimate myopia, and the cross-sectional design cannot assess the disease progression. A prospective birth cohort study has systematically explored the association between prenatal arsenic exposure and childhood myopia. It found that umbilical cord blood arsenic levels were significantly positively correlated with axial elongation and the risk of myopia (OR = 1.72), with the association being more pronounced in boys. Moreover, children of mothers with vitamin D levels below 20 ng/ml are more vulnerable (Tong, et al., 2025). It is suspected that arsenic can induce oxidative stress, leading to axial elongation and the occurrence of myopia, while vitamin D, due to its antioxidant properties, can exert a protective effect, and it also regulates dopamine metabolism.

As research advances, perspectives on refractive errors have become increasingly diverse, and more profound controversies have emerged in succession. Unlike $PM_{2.5}$, which is universally recognized to cause harm to refractive errors, although it is suggested that PM_{10} can also impair both distant and near vision (Yan, et al., 2024), no significant correlation was found in the multivariate model in a recent study (Kai, et al., 2025). Refractive errors exhibit seasonal variations, and birth season has also been found to be closely associated with myopia: babies born in winter are more likely to develop myopia in China (Huo, et al., 2021); nevertheless, a study in Israel indicates that the risk of moderate to severe myopia is higher for those born in summer (Mandel, et al., 2008). In comparison, the sample size of the latter study (276,911 people) is much larger than that of the former (291 people). The subjects of the two studies also differ significantly; the Chinese study investigated infants aged 1-18 months, while the Israeli study surveyed adolescents aged 16-22 years. Therefore, the study in China mainly focuses on the impact of seasons of birth on early refractive status, while the study in Israel examines the influence on long-term myopia risk.

There are also many interesting controversies regarding the impact of nighttime lighting on refractive status. Czepita's team initially believed that turning on the light during sleep before the age of two would increase the prevalence of myopia (Czepita, et al., 2004), while in the same year, they stated in their second paper that there was no such effect (Czepita, et al., 2004). A year later, their research once again pointed out that it could still exacerbate anisometropia (Czepita, et al., 2005). However, their subsequent study ultimately confirmed that there was no significant correlation with myopia (Czepita, et al., 2012). Their research conclusions have flipped several times, with the direction and significance of the associations appearing unstable. This suggests that night-time lighting may have been confounded by other conditions, like genetic factors. In animal experiments, Backhouse et al. found that strong light at night led to a significantly greater elongation of the eye axis compared to other time periods, resulting in rapid progression of myopia (Backhouse, et al., 2013). They explained that this was because strong light in the evening (16:00–18:00) disrupted the circadian rhythm, weakening the "nocturnal growth arrest" mechanism, leading to excessive elongation of the eye axis, which has also been confirmed by other research (Nickla, Totonelly, 2016). In contrast, Sarfare et al. found that strong night (16:30–19:30) light exposure significantly inhibited form-deprivation-induced axial elongation (Sarfare, et al., 2020). It should be noted, however, that the latter experiment had one additional hour of exposure per day, lasted four days longer, with light intensity 3 times that of the former. These differences in experimental conditions may affect the results; for example, the light intensity of Backhouse's study may be too weak to inhibit myopia, but sufficient to disrupt the circadian rhythm.

A cross-sectional study in Japan has shown that organophosphate pesticides inhibit cholinesterase activity, leading to abnormal neuromuscular transmission, which may subsequently lead to late-onset myopia (Ishikawa, et al., 1998). However, another study in the United States found no significant association between exposure to organophosphates or pyrethroids and myopia (Migneron-Foisy, et al., 2017). Compared to the Japanese study (106 subjects), this study has a much larger sample size (5,147 people for organophosphate, 2,911 people for pyrethroid), with more robust statistical results. Additionally, it employs a detection method that measures the levels of organophosphate or pyrethroid metabolites in urine, which is highly specific, rather than measuring cholinesterase activity.

The research on the mechanism of refractive errors has predominantly focused on the impacts of light. High-intensity light can directly activate the retinal signaling pathway, enhancing the signals that slow down axial growth, with extensive *in vivo* experimental evidence (Backhouse, et al., 2013; Biswas, et al., 2024; Sarfare, et al., 2020; Smith, et al., 2012), and the dopamine signaling pathway is one of the core pathways. Strong light alters DA-related genes (Landis, et al., 2021), activates dopamine D1 receptor signal of bipolar cells in the retinal ON pathway to inhibit the occurrence of form deprivation myopia (Chen, et al., 2017; Zhou, et al., 2016); activates dopamine D2 receptor, regulating the growth rate of eyeball, inhibits the development of myopia but cannot change the set point of emmetropization (Ashby, Schaeffel, 2010; Zhang, Qu, 2019), supported by *in vivo* experiments. In the natural visual environment, the protective effects of strong light (below damage threshold) and myopic defocus (focus light in front of the retina with dual-power lenses) against myopia were additive (Zheng, et al., 2018). Periodic strong light can make the vitreous chamber shallower (Cohen, et al., 2011), thereby inhibiting myopia, while continuous strong light, although deepening the vitreous chamber, makes the cornea flat, still promoting hyperopia (Cohen, et al., 2008). Although the population-based studies mentioned earlier found that prolongation of light exposure can inhibit myopia, excessive light duration may induce myopic refractive shift (Zhou, et al., 2010) by causing phototoxic retinal degeneration (Mutti, et al., 1998) in animal model.

How different wavelengths of light affect refractive errors has been partially revealed. Violet light upregulates the expression of the myopia-protective gene *early growth response 1 (EGR1)* (Torii, et al., 2017), inhibits the thinning of the choroid and elongation of the eye axis (Jeong, et al., 2023), and suppresses the development of myopia with the cone phototransduction pathway dependent on *G protein subunit alpha transducin 2 (Gnat2)* (Strickland, et al., 2020). Blue light can prevent changes in eye axis length and refraction caused by different temporal frequencies *in vivo* (Rucker, et al., 2015). It can stimulate dopamine release (Wang, et al., 2018). After exposure, the density of S-cone cells significantly increased, especially in the ventral retina. Meanwhile, blue light significantly reduced the expression of retinoic acid and retinoic acid receptor beta (RAR-β) in the retina and promoted scleral thickening and collagen-I expression, leading to hyperopic shifts (Zou, et al., 2024). However, it can also induce RPE dysfunction and regulate scleral remodeling and axial development through the β-catenin/type I collagen (COL1) pathway to mediate refractive error as well (Dai, et al., 2021). Actually, the effects of blue light depend on its dose and intensity; it may lead to the occurrence of myopia and even other ocular diseases only when it reaches the damage threshold. In contrast to blue light, green light leads to a significant increase in the density of M-cone cells, especially in the dorsal retina, and activates the retinoic acid signaling pathway *in vivo*, being a risk factor (Zou, et al., 2024). So it can be inferred that the inhibitory effect of greenness on myopia may not originate from the reflection of green light. Actually, the reason is likely that green plants can remove air pollutants (such as PM) through adsorption by leaves. Greenness may also reduce mental stress, promoting dopamine secretion, and encourage outdoor activities, exposing the eyes to stronger light and alleviating fatigue, so as to slow down the elongation of the eye axis. Research has focused on orange light *in vivo* as well, which is also proven to cause myopia in similar mechanisms (Riddell, et al., 2025). It seems that long-wavelength light is more likely to cause myopia, while short-wavelength light is protective, but red light is somewhat unique. It primarily activates long-wavelength-sensitive cone cells and may inhibit axial elongation through the longitudinal chromatic aberration signaling pathway (Gawne, et al., 2017). Hyperopia induced by red light is significantly affected by spectral purity but not intensity (Gawne, et al., 2023). But red flashes can activate the cellular communication network factor 2 (CCN2) pathway, which in turn activates the p38 and phosphatidylinositol 3-kinase (PI3K) signaling pathways, leading to myopia (Wang, et al., 2013). Compared with the previously mentioned monochromatic light, limited bandwidth light shows significantly different results. Short-wavelength light with limited bandwidth (including blue light) promotes myopia slowly, since bandwidth is too narrow, the chromatic aberration signal is weakened, and the axial control signal “STOP” is attenuated (Khanal, et al., 2023). UV can slow the progression of myopia, and vitamin D may be involved in in chick experimental myopia models (Mori, et al., 2016). While further studies have shown that high-intensity UV-A can inhibit the transforming growth factor beta (TGF-β) signaling pathway in human scleral fibroblasts, reduce the level of Smad3, and consequently decrease collagen synthesis, which leads to scleral thinning and promotes excessive elongation of the eye axis *in vitro* (Hsiao, et al., 2023).

The mechanism hypothesis of spatial frequency and refraction is that outdoor high-frequency information can enhance retinal contrast sensitivity, and the lack of it may interfere with normal ocular development by affecting the retinal dopamine signaling pathway, so in the indoor environment may lead to excessive axial elongation of the eye, similar to the mechanism of form deprivation myopia (Flitcroft, et al., 2020). Besides, it has been confirmed that high altitude increases choroidal thickness, significantly raises retinal dopamine levels, and regulates the expression of D1R/D2R, thus interfering with axial elongation and inhibiting myopia (Han, et al., 2025). The above mechanisms are summarized in Supplementary Figure S8.

In summary, refractive errors are influenced by factors such as air pollutants, light, and urbanization. The literature is predominantly clinical, with preclinical research primarily focusing on light-related aspects. Light intensity is a significant protective factor, and this conclusion remains valid even after eliminating the effects of weather (Read, et al., 2014). Exposome assessments, which combined wearable recorders with subjective reports, were relatively accurate (Landis, et al., 2018). The main sources of bias were instrument measurement bias and sample selection bias (Read, et al., 2014). These findings are also supported by numerous preclinical studies; however, these studies mainly observed phenomena such as axial length changes in animal models and lacked mechanistic explanations (Karouta, Ashby, 2014; Landis, et al., 2021). Outdoor sunlight is beneficial for refractive errors, but its assessment relied heavily on questionnaires (Kumar, et al., 2021; Lee, et al., 2023), leading to substantial information and recall bias. The protective association between greenness and refractive errors is the strongest among major ocular diseases, and this remains robust after adjusting for mean annual temperature and relative humidity (Yan, et al., 2024). Unfortunately, adjustment for other exposomes, such as air pollutants, is lacking. Studies utilizing satellite remote sensing data (Dadvand, et al., 2017; Zhang, et al., 2023) and objective refraction combined with unified diagnostic criteria (Zhang, et al., 2023) demonstrated high consistency and quality assurance in both exposome assessment and outcome definition, but this also introduced common exposure misclassification and measurement biases. Research on exposomes such as CO, SO_2, latitude, and organic pollutants is still in its infancy and requires more robust, high-quality evidence to draw definitive conclusions regarding their benefits or harms. Furthermore, there is a lack of relevant studies investigating the effects of humidity, ionizing radiation, and heavy metals.

The core of refractive error prevention and control is optimizing the visual environment, among which light is the most critical factor. Sufficient evidence and specific underlying mechanisms have been provided in the previous text—maintaining adequate light intensity is essential for the prevention of both myopia and hyperopia. Accordingly, schools can prevent myopia by improving classroom lighting (Hua, et al., 2015; Zhou, et al., 2017), and moderate light intensity (above 1,000 lux) is enough to achieve the protective effect (Wu, et al., 2018). In fact, sunlight is the most readily accessible protective measure. Increasing sun exposure through enhancing outdoor activities (≥ 60 min daily (Sun, et al., 2024)) is confirmed to prevent the development of myopia (Hagen, et al., 2018; Kumar, et al., 2021; Naqvi, et al., 2021). Additionally, urban planning and community construction also play a critical role in refraction protection: the density of building spaces should be rationally arranged to avoid overly crowded living environments (Choi, et al., 2017; Li, et al., 2025), while increasing greenness (Dadvand, et al., 2017; Huang, et al., 2021; Yan, et al., 2024). Interventions targeting special populations and critical life stages also need to be prioritized. Prenatal exposure exerts significant impacts, and pregnant women should avoid tobacco smoke exposure, as well as contact with arsenic-contaminated water sources (Huo, et al., 2021; Tong, et al., 2025); children and adolescents should avoid premature and excessive close-range eye use, and undergo regular refractive screening (Ma, et al., 2024). Besides, exposure to air pollution and chemical substances should also be avoided. Notably, mechanisms such as UV and the dopamine pathway have emerged as potential intervention targets, and novel myopia control methods based on photo-biomodulation may be developed in the future.

3.4 Glaucoma

A large body of evidence has focused on the effects of air pollutants on glaucoma. Studies consider long-term exposure to PM as a significant risk factor (Huang, et al., 2024; Li, et al., 2022; Li, et al., 2025; Sun, et al., 2024; Zhang, et al., 2025), including $PM_{2.5}$ (Abdolalizadeh, Falavarjani, 2023; Chiang, et al., 2021; Chua, et al., 2019; Foster, et al., 2024; Grisafe, et al., 2021; Luo, et al., 2022; Ma, et al., 2024; Sun, et al., 2021; Wang, et al., 2019; Wang, et al., 2025; Yang, et al., 2021) and PM_{10} (Min, Min, 2020; Wang, et al., 2022). Of note, distinct vulnerabilities exist among specific populations: patients with diabetes mellitus exhibit heightened susceptibility induced by $PM_{2.5}$ (OR = 1.7, 95% CI = 1.084-2.764) (Chiang, et al., 2021), while children face a significant risk of developing glaucoma following both short-term and long-term exposure to PM_{10} (Min, Min, 2020). Apart from this, long-term ambient black carbon exposure may increase intraocular pressure in elderly people (Nwanaji-Enwerem, et al., 2019), and it also has a synergistic effect with $PM_{2.5}$ (Gayraud, et al., 2023). Concerns about the impact of NO_2 have been addressed in plenty of studies (Grisafe, et al., 2021; Li, et al., 2022; Wang, et al., 2022), which not only lead to acute angle-closure glaucoma (Zhang, et al., 2025) but also promote the occurrence of primary open-angle glaucoma (Huang, et al., 2024). Moreover, Huang et al. investigated NO_x, and the results show that long-term exposure can increase the risk of primary open-angle glaucoma by about 3% (Huang, et al., 2024). Besides, studies support the positive association between CO, SO_2 and glaucoma (Li, et al., 2022; Wang, et al., 2022; Zhang, et al., 2025). A retrospective cohort study investigated the relationship between the occurrence of primary angle-closure glaucoma and seasons. As it elucidates, the disease has no obvious seasonal pattern and is not affected by seasonal light time (Ivanisević, et al., 2002). Numerous studies have also considered the impacts of meteorological factors. Cold stress has been identified as a primary cause linking temperature to glaucoma. A case-crossover study of 7,746 people suggests that low ambient temperature or sudden temperature drop significantly increases the disease risk (Zhu, et al., 2023). Regarding precipitation, the excess risk values for daily outpatient visits for primary glaucoma were -4.2% per 10-unit increase (Wang, et al., 2022), suggesting a protective effect.

Generally, the radiation we exposed to in daily life is chronic low-dose (most commonly occupational exposure), which has not been found to have a significant association with glaucoma, unlike other eye diseases, with the evidence of two prospective cohort studies, one in American radiologists with 921,076 person-years (excess relative risk/Gy = -0.57, 95% CI = -1.46-0.60, $p = 0.304$) (Little, et al., 2018) and another in Russian workers in nuclear facilities with 544,236 person-years (excess relative risk/Gy = 0.01, 95% CI = -0.12-0.19, $p > 0.50$) (Bragin, et al., 2019). Most recently, a study with a follow-up period of up to 32 years provided strong empirical support for this viewpoint, even for the cumulative radiation dose > 50 mSv (Villeneuve, et al., 2025). The possible reason is that low-dose ionizing radiation does not significantly affect structures such as the trabecular meshwork and ciliary body, and therefore does not show a significant risk association. Researchers have also explored the relationship between heavy metals including lead, arsenic, and glaucoma. After 10.6 years' follow-up, Wang et al. concluded that lead may be an important risk factor for primary open-angle glaucoma in the United States population (Wang, et al., 2018). Arsenic has also been identified ($\beta = 1.090$, 95% CI = 0.313–1.835), and it is possible to use machine learning to predict future incidence based on it (Wang, et al., 2025).

The impact of some exposed factors on glaucoma also remains controversial, with air pollutants and light being the primary subjects of contention. O_3 can induce oxidative stress, which is one of the pathogenic mechanisms, theoretically leading to glaucoma. A study in Hefei verified this hypothesis (Zhang, et al., 2025), while another study in Shenyang found a negative correlation (Wang, et al., 2022). In terms of study design, the

Hefei study used hospitalization data for acute angle-closure glaucoma, while the Shenyang study investigated outpatient visits for primary glaucoma. Hospitalization may be more accurate in diagnosis, but could potentially miss mild cases, and primary glaucoma encompasses various disease subtypes, both contributing to the differences in the results. Although O_3 concentrations in the two studies were similar, the study in Hefei had a longer observation period, suggesting that O_3 cumulative exposure is necessary. It is also worth noting that in the study in Shenyang, although precipitation was also a protective factor, the results lost statistical significance when O_3 and precipitation were included in the model at the same time, suggesting that there is multicollinearity between O_3 and meteorological factors. Therefore, the results need to be interpreted with caution, and further research is needed. There have been controversies regarding the impact of UV on glaucoma. Wang et al. evaluated the trends and variations in global glaucoma burden using DALYs and found it was positive with UV (Wang, et al., 2019). The authors believe that high UV may increase the risk by promoting exfoliation syndrome (the leading cause of secondary open-angle glaucoma) or increasing oxidative stress. However, the use of national-level data in this study may mask internal differences: in some large-area countries, significant discrepancies may exist in data like average daily levels of UV across different regions. Huang et al. compared the prevalence of UV-related cancer of the head and neck with that of primary open-angle glaucoma, and found no significant correlation (Huang, et al., 2022). Notably, when using cancer as a proxy for UV, individuals may have already been exposed to extremely high doses of UV. It is possible that exposure to lower doses could also trigger glaucoma, which cannot be inferred from this study. This study only focused on one subtype, and more research is needed to supplement the findings.

In terms of mechanisms, $PM_{2.5}$ upregulates inducible nitric oxide (NO) synthase, increases the formation of 3-nitrotyrosine, and elevates ROS levels, leading to a gradual increase in intraocular pressure and aqueous humor outflow resistance *in vivo* (Li, et al., 2021). It also promotes the upregulation of the NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome, caspase-1, IL-1β, and gasdermin D (GSDMD) protein levels, reduces the viability of trabecular meshwork cells, and leads to glaucoma *in vivo* (Li, et al., 2021). In addition, serum uric acid may have a mediation effect (Li, et al., 2024). Apart from that, *in vitro* experiments revealed that hypoxia can drive the disorder of TGF-β1-Ras protein activator like 1 (RASAL1) signaling axis through epigenetic mechanisms (McDonnell, et al., 2014), promoting trabecular meshwork fibrosis (McDonnell, et al., 2016). The currently known main mechanisms are shown in Supplementary Figure S9, which is still insufficient, with more attention needed.

Glaucoma is primarily influenced by various exposomes, including air pollutants, temperature, UV, and ionizing radiation, though preclinical evidence remains generally scarce. Among air pollutants, PM poses the most significant threat to the disease, and this finding remains robust even after adjusting for other pollutants like NO_2 and SO_2 (Li, et al., 2025; Wang, et al., 2022). Outcome definitions, referenced by ICD codes, are well-established. NO_2 has the second strongest clinical evidence after PM, and its association has been validated using both single-pollutant and multi-pollutant models (Wang, et al., 2022). Exposome assessments were based on government-issued air quality monitoring data (Li, et al., 2022; Wang, et al., 2022) and land use regression models (Sun, et al., 2024; Wang, et al., 2025), with excellent accuracy. The risk of bias was formally evaluated, encompassing selection bias (e.g., databases capturing only a subset of patients (Li, et al., 2025)), information bias (e.g., cases derived solely from inpatient records (Sun, et al., 2024)), and exposure misclassification (Wang, et al., 2025). Currently, research on temperature, ionizing radiation, sunlight, and heavy metals is limited, and the level of evidence is insufficient to draw reliable conclusions. Furthermore, studies on humidity, urbanization, altitude, latitude, and organic pollutants remain a blank.

Focusing on the two core objectives of reducing cold stress injury and lowering air pollutant exposure, a systematic preventive and control strategy for glaucoma should be implemented across multiple dimensions, including personal protection, environmental governance, and chronic disease management. The emphasis lies in protecting optic nerve and trabecular meshwork function, preventing acute attacks, and delaying disease progression. Since low temperature exacerbates disease progression, attention should be paid to abrupt temperature drops, and enhanced warmth for the head and eyes. Low-tension glaucoma patients exhibit a dysfunction in vascular regulation in response to cold water stimulation, with a significant reduction in mean blood flow (Drance, et al., 1988). In consequence, it is recommended that patients reduce outdoor activities, enhance indoor warmth, and monitor intraocular pressure when there is a cold wave or a diurnal temperature difference ≥ 4 ℃. Air pollution exposure primarily necessitates environmental governance, encompassing initiatives such as promoting industrial emission reductions and controlling traffic exhaust emissions. Individuals can minimize outdoor time during periods of severe air pollution and utilize air purifiers.

3.5 Retinal diseases

Retina serves as the material basis for visual function, capturing light and processing the stimuli generated. Various retinal diseases, mainly including age-related macular degeneration (AMD)—the leading cause of irreversible blindness in the elderly, and diabetic retinopathy (DR), can severely affect vision and display a significant influence on global health and socioeconomics (Yu, et al., 2025).

3.5.1 Age-related macular degeneration

AMD is vulnerable to exposure, and relevant research has been summarized in Supplementary Figure S10. Long-term mixed exposure to various air pollutants increases the risk of AMD (Li, et al., 2025). Numerous population-based studies have revealed a significant association between $PM_{2.5}$ and AMD from different perspectives and have provided preliminary causal evidence (Abdolalizadeh, Falavarjani, 2023; Chua, et al., 2022; Grant, et al., 2021; He, et al., 2023; Liang, et al., 2022; Zhang, et al., 2025). And CO has also been found to be detrimental (Chang, et al., 2019; Ju, et al., 2022). As for climate, Rouvas et al. found that the recurrence frequency of wet AMD has a distinct seasonal distribution: the recurrence rate significantly increased in summer (from June to September) (Rouvas, et al., 2023). The authors speculated that this might be due to increased temperature and enhanced UV exposure. But this result should be interpreted cautiously, considering the limited sample size (129 eyes) and lack of generalizability (only patients with one type of treatment were included). Meteorological factors may indirectly affect the occurrence and progression of AMD, but the evidence is still in its infancy, and there are significant regional and population differences: in a national cross-sectional study in China, atmospheric pressure is a protective factor, while humidity and temperature can increase the risk of onset by 2.793 and 3.276 times, respectively (He, et al., 2023); Hunt et al. investigated the impact of precipitation and snow, only finding a positive correlation between winter snowfall and AMD, with risk increasing by only 0.5% (Hunt, et al., 2022); dust storms is revealed to be positively associated with outpatient visits for dry AMD among people under 50 years old (Chen, et al., 2022). As for greenness, our large-scale prospective cohort study based on the Chinese population assessed its protective effect and found that the higher the level of greening in the residential area, the lower the risk of developing AMD (Qu, et al., 2025). Specifically, when the normalized difference vegetation index (NDVI) value within the 1,000-meter buffer zone around the residence exceeded 0.4, the harmful effects of UV were significantly weakened and no longer statistically significant, and this threshold remained consistent across different regions in China.

Chemicals associated with AMD have also attracted widespread attention. Research revealed that the higher the concentration of nitrate nitrogen in rural drinking water, the higher the disease incidence (Klein, et al., 2013). Despite the known neurotoxicity of arsenic, its contribution to the risk of AMD is not statistically significant (Wei, et al., 2025). Considering heavy metals, mercury exposure has also been shown to be possibly associated (Dantzig, 2005; Wei, et al., 2025), whereas no evidence has been provided to suggest a significant link between lead and AMD (Damar Güngör, et al., 2018; Wei, et al., 2025). In organic chemistry, two studies based on data from the National Health and Nutrition Examination Survey (NHANES) 2005–2008 consistently found that serum PFAS, particularly PFOS, are significantly associated with the risk in middle-aged and elderly populations: Kang et al. systematically evaluated various PFAS and found an inverted U-shaped relationship between overall PFAS exposure burden and AMD (Kang, et al., 2024); Chen et al. further revealed that serum total cholesterol and high-density lipoprotein play a partial mediating role, suggesting that PFAS may promote the disease by disrupting lipid metabolism, as potential mechanisms (Chen, et al., 2025).

In fact, regarding the impact of exposomes on AMD, there are far more controversies than conclusive findings. Take air pollutants as an example. PM_{10} may lead to an increased risk and changes in retinal structure (Chua, et al., 2022), especially in middle-aged and elderly individuals (Ju, et al., 2022). While recent studies have indicated that there is no statistically significant association between PM_{10} and AMD in the general population (Wang, et al., 2025; Zhang, et al., 2025). Previous studies may have overestimated the effects due to confounding biases and collinearity of pollutants. There is currently a lack of independent causal evidence for the impact of PM_{10}, and its effects may only be present in specific susceptible populations (such as myopia patients). Ju et al. and Chang et al. have found that exposure to NO_2 nearly doubles the risk of AMD in the elderly, mainly associated with the early stage (Chang, et al., 2019; Ju, et al., 2022). However, considerable studies have questioned it: a case-control study found that NO_2 was only significantly associated with active exudative AMD, but not with any AMD (Hunt, et al., 2022); a cross-sectional study found no significant correlation between NO_2 and self-reported AMD, though there is a substantial association with retinal structural changes (such as thickening of the photoreceptor outer layer) (Chua, et al., 2022); more recently, Wang and Zhang's studies both even concluded that NO_x, including NO_2, is not associated (Wang, et al., 2025; Zhang, et al., 2025). It can be noted that in Ju's study, the exposure level of NO_2 was approximately twice that in Wang's, indicating that there may be significant differences in NO_x levels across different regions, and racial differences may also account for the varying results. Additionally, the overall impact direction of O_3 on AMD is inconsistent. Two studies in China (Jia, et al., 2024; Qu, et al., 2024) and the United States IRIS registry study (Hunt, et al., 2022) all support a positive correlation. Nevertheless, a study in South Korea considered O_3 to be a protective factor (Ju, et al., 2022). It is worth noting that the exposure concentrations in the two Chinese studies were significantly higher than those in South Korea, which may imply that the comprehensive effect of high-concentration O_3 is mainly harmful, while low-concentration is protective. It may be because O_3 can damage RPE cells through oxidative stress or inflammation, but it can also absorb UV to exert a protective effect (Qu, et al., 2024).

The relationship between sunlight exposure and AMD has long been a topic of interest, but the findings of studies vary significantly. A large number of studies support that sunlight is a risk factor (Cruickshanks, et al., 1993; Nano, et al., 2013), and strong exposure in children may lead to early onset (Vojniković, et al., 2009; Vojniković, et al., 2010), but remaining controversy regarding the stage of AMD affected (Cruickshanks, et al., 2001; Hirakawa, et al., 2008; Klein, et al., 2014; Schick, et al., 2016; Tomany, et al., 2004). Hunt et al. provided a specific analysis: global horizontal irradiance is significantly positively correlated with active exudative AMD, while direct normal irradiance is significantly negatively correlated (Hunt, et al., 2022). The authors speculated that global horizontal irradiance is primarily composed of short-wave scattered light which is more likely to reach the retina and poses a greater potential hazard to photoreceptor cells, and in contrast, after penetrating the thick atmosphere, direct normal irradiance contains more long-wave components, which may cause less damage and might even have a protective effect (actually, direct normal irradiance can more effectively penetrate the skin and stimulate the synthesis of vitamin D, and it also changes people's behavior, including wearing hats and sunglasses). Some studies do not support the pathogenicity of solar exposure (Darzins, et al., 1997; Delcourt, et al., 2001; Khan, et al., 2006). UV is considered the most significant component in sunlight that contributes to AMD (Plestina-Borjan, Klinger-Lasić, 2007; Qu, et al., 2024; Vojniković, et al., 2007), and a study yielded that there is a U-shaped relationship between UV and early AMD, but not with late AMD (Delcourt, et al., 2014). There is controversy over the impact of UV-A and UV-B on AMD (Amari, et al., 2023; Nadarević, et al., 2014). Interestingly, Taylor's study of 838 Chesapeake Bay watermen did not find a correlation between UV-B and AMD (Taylor, 1989). The authors acknowledged that this was surprising and speculated that it might be because the lens absorbs most of the UV-B, resulting in too low a dose reaching the retina, which was supported by West that for individuals with intact lenses, even long-term high-intensity exposure does not increase the risk (West, et al., 1989). They did not rule out UV-A, as it has stronger penetrating power and is more likely to reach the retina. Taylor et al. also investigated the impact of visible light and concluded that blue light exposure is significantly associated with late AMD (Taylor, et al., 1990; Taylor, et al., 1992). Whereas evidence does not support a link between it and neovascular AMD (Fletcher, et al., 2008).

Individuals living in high-latitude areas have a higher risk of developing active exudative AMD (Hunt, et al., 2022). This is somewhat surprising, implying that sunlight or UV may have a protective effect, which seems to contradict the previous statements. The potential mechanisms may involve atmospheric scattering effects and vitamin D synthesis. High-latitude areas, with shorter daylight hours, lower solar elevation angles, and a thicker O_3 layer absorbing UV more strongly, have weaker UV intensity, which may lead to reduced endogenous vitamin D synthesis in the human body, promoting the disease. The evidence does not support latitude associated with any AMD or non-exudative AMD. This may suggest that latitude plays a role in disease progression rather than initial occurrence, highlighting the importance of distinguishing disease subtypes and activity status in research.

Different views are also held on the effects of the heavy metal cadmium. It is reported that cadmium accumulates significantly in the retina of AMD patients, particularly in males (Wills, et al., 2009). Studies have also measured cadmium levels in urine (Erie, et al., 2007; Gao, et al., 2024; Wei, et al., 2025) and blood (Damar Güngör, et al., 2018; Erie, et al., 2007), only finding urinary cadmium is significantly associated with early AMD. It is speculated that short-term exposure does not significantly increase the risk, given that urinary cadmium reflects long-term accumulation and blood cadmium only indicates short-term exposure. While the research results of Kim do not support this view, discovering that blood cadmium is positively correlated in an approximately linear manner (Kim, et al., 2016). It is worth noting that the sample size of Kim (3,865 individuals) is much larger than that of Erie (106 individuals) or Güngör (55 individuals), and further research is still needed to confirm the impact.

Research on the mechanisms of air pollutants has primarily focused on environmental tobacco smoke. Its exposure induces oxidative stress in RPE cells *in vivo* (Smit-McBride, et al., 2018), leading to mitochondrial dysfunction, lipid peroxidation (Yu, et al., 2012), and glutathione depletion (Bertram, et al., 2009), as confirmed by *in vitro* experiments. It also upregulates the expression of *VEGF* and *HO-1*, resulting in cell damage, senescence, and apoptosis (Bertram, et al., 2009; Yu, et al., 2012). Additionally, it alters miRNA expression and activates inflammatory pathways like IL-17A, promoting the recruitment and activation of eosinophils, Th2 lymphocytes, and macrophages (Smit-McBride, et al., 2018). The expression and secretion of ECM components are also increased, leading to the formation of deposits (Yu, et al., 2012). Tobacco smoke can synergize with *high-temperature requirement factor A1 (HtrA1)* overexpression as well, increasing choroidal neovascularization and exacerbating the pathological changes of AMD *in vivo* (Nakayama, et al., 2014). It contains a variety of harmful components: 2-ethylpyridine and benzo(e)pyrene can destroy mitochondria through oxidative stress, activate the caspase cascade, and induce apoptosis in RPE cells (Mansoor, et al., 2014; Sharma, et al., 2008); indeno-1,2,3-cd pyrene can synergize with blue light to cause mitochondrial damage, ROS accumulation and apoptosis (Zinflou, Rochette, 2019); hydroquinone downregulates monocyte chemoattractant protein-1 (MCP-1), leading to insufficient macrophage recruitment and impaired drusen clearance, thereby worsening dry AMD, and it also increases *VEGF* expression and neovascularization, accelerating the progression of wet AMD (Pons, Marin-Castaño, 2011). Similarly, e-cigarettes promote the pathological process of wet AMD by activating the choroidal inflammatory response and disrupting the VEGF/pigment epithelial derived factor (PEDF) balance as well. With *in vivo* and *in vitro* evidence, $PM_{2.5}$ causes damage to the blood-retinal barrier, RPE leakage, and retinal edema, and its long-term effects can promote AMD (Gu, et al., 2023), especially indoor $PM_{2.5}$, since it may contain perfluorooctanoic acid, which can gradually cause retinal inflammation through the cornea (Tien, et al., 2020).

Mechanisms by which light affects AMD have been extensively studied as well. Light exposure induces ROS and activates the Rho/Rho-associated coiled-coil forming kinase (ROCK) pathway, leading to the disruption of intercellular junctions and pathological changes in the RPE and choroid *in vivo* (Narimatsu, et al., 2013). Light induces oxidation of docosahexaenoate in RPE cells, generating 4-hydroxy-7-oxohept-5-enoic acid esters and 2-(ω-carboxyethyl)pyrrole, which can lead to mitochondrial membrane depolarization, loss of lysosomal membrane integrity, cellular senescence, and death without lipofuscin *in vitro* (Cheng, et al., 2019). Long-term high-intensity exposure activates the peroxisome proliferator-activated receptor g coactivator 1 alpha (PGC-1α)/estrogen-related receptor alpha (ERR-α) pathway, upregulates *VEGF* expression, promotes choroidal neovascularization, leads to progressive retinal degeneration, and ultimately results in a condition similar to human wet AMD, observed in *in vitro* studies

(Albert, et al., 2010; Ueta, et al., 2012); while short-term intense exposure can induce a chronic, progressive degenerative lesion in the central retina, similar to dry AMD, through mechanisms such as early macrophage recruitment and Müller cell gliosis *in vivo* (Rutar, et al., 2010). As for UV, it is involved in the pathological process through mechanisms such as disrupting energy balance, causing oxidative stress, and damaging the ECM, revealed by *in vivo* experiments (Kraljević Pavelić, et al., 2015), while moderate UV exposure may improve AMD-related pathological features by activating antioxidant and complement regulatory mechanisms, revealed by *in vitro* experiments (Hallam, et al., 2017). Violet light has been reported to have potential protective effects against dry AMD by alleviating light-induced retinal functional degeneration (*in vivo*) (Chen, et al., 2024). Blue light is another research focus within the visible spectrum. Narrow-band blue light in the range of 415-455 nm exerts the greatest toxicity to RPE cells loaded with N-retinylidene-N-retinylethanolamine, or A2E (*in vitro*) (Arnault, et al., 2013; Marie, et al., 2019). Blue light disrupts the mitochondrial fusion/fission balance in RPE cells *in vitro*, inducing mitochondrial fragmentation and thereby triggering apoptosis, exacerbated by A2E (Alaimo, et al., 2019). Furthermore, it can cause the oxidation of A2E and its precursors and isomers in the retina (Wielgus, et al., 2010), and promote the photo-degradation of bis-retinoids, releasing harmful products such as methylglyoxal (Ueda, et al., 2016), in *in vivo* experiments. Blue light reversibly inhibits the specific phagocytic function of RPE cells (Olchawa, et al., 2022). Meanwhile, cellular metabolism is reduced, with upregulation of stress proteins such as HO-1 and HSP-27, and overexpression and secretion of MMP (Feng, et al., 2014; Kernt, et al., 2012). The increase of intracellular ROS (Abdouh, et al., 2022) and the decrease of mitochondrial membrane potential activate caspase, leading to apoptosis (Abdouh, et al., 2024; Roehlecke, et al., 2009). Blue light also reduces angiogenin and increases fibroblast growth factor (FGF) secretion, leading to choroidal neovascularization *in vitro* (Vila, et al., 2015; Vila, et al., 2017). Research has found that in protoporphyria mice, Bruch's membrane is thickened, and the choriocapillaris is narrowed, similar to AMD (Gottsch, et al., 1993). Apart from that, blue light emitting diode (LED) was revealed to induce degeneration of the RPE, atrophy of photoreceptors, and accumulation of macrophages and drusen-like material, recapitulating the key pathological features of non-exudative AMD (Kim, et al., 2016; Nakamura, et al., 2018). Exposure to white LED causes oxidative stress in RPE cells, disruption of tight junctions, and autophagy dysfunction, which are highly consistent with the pathological changes observed in AMD patients (Jaadane, et al., 2017), and it is also believed that the blue light component is primarily responsible. High-color-temperature LED light induces ROS accumulation, activates the MAPK and NF-κB signaling pathways, and thereby participates in the occurrence and development of the disease (Shen, et al., 2016).

The specific mechanisms have been comprehensively summarized in Supplementary Figure S11.

AMD is influenced by a wide range of exposomes, including air pollutants, temperature, humidity, light, greenness, urbanization, altitude, latitude, heavy metals, and organic pollutants. PM has been identified as a risk factor for AMD, supported by two large-scale prospective studies and multiple preclinical studies, providing preliminary evidence for a causal relationship. The effects of PM remain robust after adjusting for multiple pollutants, such as O_3, NO_2, and SO_2 (Grant, et al., 2021). PM exposure data were primarily sourced from national public databases (Grant, et al., 2021) and estimated via satellite remote sensing combined with hybrid models (Liang, et al., 2022), with the data quality being generally high, while being prone to exposure misclassification bias. Blue light is also considered harmful, with preclinical studies providing extensive mechanistic explanations. However, clinical studies have conducted limited confounding analyses, excluding factors such as air pollutants and temperature (Taylor, et al., 1992); therefore, these associations require further clinical validation. Outcome definitions were based on standardized grading of fundus photographs, ensuring high accuracy (Taylor, et al., 1990). Research on SO_2, humidity, greenness, urbanization, altitude, latitude, and organic pollutants is predominantly clinical, relatively scarce, and warrants cautious interpretation. The association between pollen and AMD remains unexplored, likely due to the relatively weak link between AMD pathogenesis and allergic mechanisms.

The preventive and therapeutic measures for AMD require precise interventions tailored to different etiologies. In terms of light injury, UV protection is similar to cataract and pterygium, yet the focus of AMD prevention and protection extends to blue light, with a stronger emphasis on the protection of RPE cells (Alaimo, et al., 2019; Taylor, et al., 1990). AMD also necessitates reduced exposure to air pollutants, particularly tobacco smoke (Nakayama, et al., 2014; Smit-McBride, et al., 2018). Studies have clarified that seasonal variation may be an independent risk factor for wet AMD recurrence, so clinicians should enhance patient follow-up during warmer seasons (Rouvas, et al., 2023). Future measures should also focus on urban planning, with an emphasis on increasing green spaces, particularly in the 1,000-meter buffer zone surrounding residential areas (Qu, et al., 2025).

3.5.2 Diabetic retinopathy

As one of the most direct influencing factors, there is abundant evidence demonstrating the detrimental effects of air pollution on DR. NO_x has been widely demonstrated to be significantly correlated (Wang, et al., 2025; Zhang, et al., 2025; Zuo, et al., 2024), while no significant associations have been observed for SO_2 and O_3 (Zuo, et al., 2024). Besides, what sunlight brings is mostly damaging effects. A study based on data from the KNHANES 2008–2011 investigated the relationship between daily sunlight exposure duration and the risk of DR. The results showed that among diabetic patients aged 40 and older, those with ≥ 5 hours of daily sunlight exposure had a 2.66-fold higher risk than those with < 5 hours (Lee, et al., 2020). Apart from that, residential greenness, as an intervenable urban exposome, is increasingly recognized for its potential role in the prevention and control of DR. Our large-scale national cross-sectional study was the first to systematically assess the relationship between exposure to residential greenness and the prevalence among diabetes patients. We included 484,380 adult patients with diabetes from 129 cities across 27 provinces in China. The results indicated that for every 0.1 increase in NDVI, the risk decreased by 10% (Jia, et al., 2023).

Evidence of heavy metals and organic chemicals is also presented. DR is more closely associated with heavy metals than other eye diseases: three studies based on populations in the United States and China have consistently indicated that heavy metals may play an important role in DR. These studies screened a total of 14 heavy metals and found that cobalt, antimony, mercury, strontium, and cadmium were significantly correlated (Gui, et al., 2024; Li, et al., 2023; Meng, et al., 2024). Heavy metals may contribute to the disease through inducing oxidative stress, disrupting the balance of trace elements, and promoting cellular senescence. Despite differences in study design and populations, the results suggest that heavy metal exposure may be a potential modifiable exposome, and further research is required to clarify its causal associations. For organic chemicals, based on NHANES 2011–2018, Wang et al. systematically evaluated the relationship between 22 VOCs in the blood and DR for the first time (Wang, et al., 2024). They found that VOCs were positively associated with DR, especially 1,2-dibromoethane, carbon tetrachloride, and 2,5-dimethylfuran, and combined VOCs were related to the disease in a nonlinear dose–response manner. Moreover, the effects of mixed exposures were not simply additive, and VOCs might act through multiple pathways, such as oxidative stress, endoplasmic reticulum stress, and retinal microvascular endothelial damage.

An increasing number of epidemiological studies have focused on the impact of exposure on DR, and also find out some intriguing issues. Interestingly, three studies conducted in China have all confirmed a positive correlation between $PM_{2.5}$/PM_{10} and DR (Pan, et al., 2020; Shan, et al., 2021; Zuo, et al., 2024). In contrast, Wang's study in the United Kingdom denied the impact of $PM_{2.5}$ (Wang, et al., 2025), and another study in the United Kingdom and a study in Europe both concluded that neither $PM_{2.5}$ nor PM_{10} had a significant association with DR (Wang, et al., 2024; Zhang, et al., 2025). Comparative analysis reveals that $PM_{2.5}$ and PM_{10} concentrations in Europe are significantly lower than in China and may fail to reach the threshold. Differences in the composition and sources of PM across regions may lead to varying degrees of ocular irritation as well. There are also disparities in diabetes control between China and Europe, which may indirectly affect the development and progression of DR.

The relevant mechanistic research remains incomplete. *In vivo* studies have found that after light deprivation, retinopathy in diabetic mice is significantly alleviated, with improved visual function, reduced capillary degeneration, decreased expression of inflammatory genes, inhibited apoptosis, and reduced gliosis (Thebeau, et al., 2020). This means that light-induced signaling transduction is a key driving factor in the occurrence and development of DR, and that reducing light exposure can delay disease onset through anti-inflammatory, affecting perivascular *altered aquaporin-4 (AQP4)* expression, and other mechanisms (Vasović, et al., 2024). Meanwhile, *in vivo* and *in vitro* experiments demonstrated that low-intensity far-red light can significantly inhibit diabetes-induced retinal ganglion cell death, increasing superoxide production and *intercellular adhesion molecule 1 (ICAM-1)* expression, and restore visual function (Tang, et al., 2013), which may potentially serve as a therapeutic approach.

DR is closely associated with various air pollutants, sunlight, heavy metals, and organic pollutants, with the current literature primarily consisting of clinical studies. PM is the most critical risk factor, and its association with DR was mainly evaluated using two-pollutant models to adjust for the effects of other co-exposures, including NO_2, SO_2, and CO (Pan, et al., 2020; Zuo, et al., 2024). Exposure data were primarily sourced from government public databases (Zuo, et al., 2024), satellite remote sensing (Shan, et al., 2021), and land-use regression models (Wang, et al., 2025), ensuring high monitoring data quality. Outcome definitions were highly accurate, as clinicians diagnosed DR based on examinations such as fundus photography in accordance with ICD standards (Wang, et al., 2025). The main risks of bias in this area include exposure misclassification. Heavy metals have also been identified as risk factors. While studies effectively adjusted for potential interference from other heavy metals (Li, et al., 2023), they lacked adjustments for non-metallic exposomes. Heavy metal levels were assessed via urinary testing, which offers good comparability (Li, et al., 2023); however, given that heavy metals accumulate in the body, the representativeness of this biomarker remains debatable. Consequently, the primary risks of bias in heavy metal research include measurement bias (relying on a single urine sample, which may not fully represent the true long-term body burden of metals) (Li, et al., 2023), residual confounding (failing to cover all potentially relevant metal elements and other exposomes), and causal inference bias (the lack of prospective studies prevents a sufficient demonstration of causality). Furthermore, research on O_3, SO_2, sunlight, and organic pollutants is limited and subject to significant design constraints, making it difficult to accurately reflect causal relationships. Finally, the associations between DR and a wide range of other exposomes, such as humidity, temperature, light intensity, blue light, and ionizing radiation, have yet to be fully explored.

To address the issue of DR, the core strategy is to superimpose exposure protection on the basis of optimal glycemic control. Prevention and control measures can be taken from multiple dimensions, including personal protection and environmental governance, focusing on three core aspects: controlling light exposure, reducing environmental toxins (particles, heavy metals, organic pollutants), and utilizing protective factors. The fundamental goal is to alleviate oxidative stress and inflammatory damage to the retina, and delay the progression of microvascular lesions (Thebeau, et al., 2020). As elucidated before, studies have revealed a potential association between sunlight and DR, so simple measures such as reducing sun exposure and wearing protective eyewear may become efficient strategies for early prevention (Lee, et al., 2020). The governance of hazardous substances requires strengthening source control: promoting industrial emission reduction, controlling heavy metal pollution in soil and water bodies, and incorporating VOC emission limits into quality standards for building materials and other products (Gui, et al., 2024; Li, et al., 2023; Meng, et al., 2024; Wang, et al., 2024; Zuo, et al., 2024). Protective factors mainly include increasing greenness (Jia, et al., 2023). Therefore, urban planning should increase the area of parks and community green spaces, especially in areas with a high density of diabetic patients. Meanwhile, surrounding greenness level should be taken into consideration when choosing housing. Diabetic patients are also encouraged to spend more time doing activities in green spaces, but sun protection should be properly conducted at the same time.

3.6 Other eye diseases

Many other eye diseases are also closely related to exposome, which are only briefly outlined here. Specifically, various exposomes play key roles in eye neoplasms. Sunlight is a significant cause of ocular melanoma (Vajdic, et al., 2002; Vajdic, et al., 2003). Surprisingly, the association between melanoma and natural UV is not significant (Arockiaraj, et al., 2024; Guénel, et al., 2001; Pane, Hirst, 2000), while artificial UV, especially occupational exposure (Holly, et al., 1996), like the arc light to which welders are frequently exposed, significantly increases the risk (Guénel, et al., 2001). Besides, from high to low latitude, external eye melanoma increased by 2.48 times, while from low to high latitude, internal ocular melanoma increased by 4.91 times (Yu, et al., 2006). And the relative risk of intraocular malignant melanoma for individuals born in the southern United States was 2.7 compared with those born in the North (Tucker, et al., 1985). As for retinoblastoma, $PM_{2.5}$ concentration is positively correlated with unilateral retinoblastoma (Heck, et al., 2013), and bilateral tumor is significantly associated with CO during early pregnancy. Interestingly, unlike melanoma, researchers have found that sunlight is actually a protective factor (Orjuela-Grimm, et al., 2021). But exposure to UV-B has no obvious relationship with the incidence (Jemal, et al., 2000). Organic contaminants are also associated with the occurrence of retinoblastoma, especially during the early life stage (Heck, et al., 2015; Thompson, et al., 2022). In addition, ocular squamous cell carcinoma (Gichuhi, et al., 2016; Newton, et al., 1996; Newton, et al., 2002; Sun, et al., 1997), corneal mesenchymal tumor (Kusewitt, et al., 1997; Sabourin, et al., 1993), eyelid basal cell carcinoma (Lindgren, et al., 1998) and other ocular tumors are related to various exposomes, among which UV is the core.

Exposure is also of great significance for inflammatory and infectious eye diseases. Numerous population-based studies have progressively elucidated the positive correlation between uveitis and a variety of air pollutants, including $PM_{2.5}$ (Tan, et al., 2022), NO_x, and others (Bai, et al., 2021). Seasonal and meteorological factors are significant influencing factors. The incidence of uveitis attacks is significantly higher in winter than in autumn (Gómez-Mariscal, et al., 2020). Rainy and windy weather may be associated with uveitis flare-ups, but no significant associations are found between the disease and atmospheric pressure, temperature, humidity, or UV (Gómez-Mariscal, et al., 2020). While high temperature and low humidity increase hospitalization risk (Cao, et al., 2022), implying they exacerbate pre-existing uveitis rather than acting as initial triggers. For iridocyclitis and episcleritis, exposure to silica dust significantly increases the risk (Makdoumi, et al., 2024). And for blepharitis, exposure to common air pollutants in large cities, such as $PM_{2.5}$, PM_{10}, SO_2, and CO, significantly contributes to increasing the probability of illness among residents (Malerbi, et al., 2012; Zhao, et al., 2023). Slightly differently, its correlation with NO_2 is relatively weak (Malerbi, et al., 2012; Zhao, et al., 2023). Nevertheless, NO_2 significantly increases the number of cases of dacryoadenitis (Mu, et al., 2022; Song, et al., 2019), which may be due to the direct exposure of the lacrimal glands. Besides, short-wave blue light may cause solar retinitis through non-thermal photochemical damage (Ham, et al., 1978). Infectious eye diseases are also closely related to exposomes (Ludema, et al., 2014): temperature and sunlight are protective factors for trachoma (Hägi, et al., 2010), while drought (Schwab, et al., 1995) and high latitude (Schémann, et al., 2007) have been found to increase the prevalence; the higher the soil moisture and the closer to rivers, the higher the prevalence of onchocerciasis, while seasonal precipitation can reduce it (Botto, et al., 2005; Shrestha, et al., 2023; Shrestha, et al., 2022). Microplastics are gradually emerging as a significant exposome. Although one animal study found no association with ocular diseases (Kim, et al., 2021), a two-center clinical study detected microplastics in human vitreous, and revealed a significant correlation with ocular health parameters such as intraocular pressure in retinopathy (Zhong, et al., 2024). Moreover, Zhang et al. detected microplastics in aqueous humor for the first time, with pyrolysis-gas chromatography/mass spectrometry, and polyethylene and polyvinyl chloride are the most common (Zhang, et al., 2025). Other eye diseases, such as upper eyelid ptosis (Satariano, et al., 2015), trichiasis (Schémann, et al., 2007), meibomian gland dysfunction (Hao, et al., 2022), Graves' ophthalmopathy (Dantzig, 2005; Jia, et al., 2024; Palyga, et al., 2017), pseudoexfoliation syndrome (Huang, et al., 2022; Kandeeban, et al., 2023; Pasquale, et al., 2014; Stein, et al., 2011; Sureshkumar, et al., 2023; Taylor, 1980), chronic ocular graft-versus-host-disease (Gehlsen, et al., 2022), and nonarteritic anterior ischemic optic neuropathy (Liu, et al., 2023) are also influenced by exposomes, not being elaborated here anymore.

The mechanisms by which exposomes affect eye diseases are also being continuously explored at present. PM can induce pyroptosis mediated by NLRP3 inflammasome through activation of NF-κB and MAPK signaling pathways, thereby causing structural and functional disorders of meibomian glands, found by *in vivo* experiments (Tu, et al., 2024). Specifically, $PM_{2.5}$ induces lipid accumulation and promotes the disease through metabolic disturbance and inflammation mediated by signal transducer and activator of transcription (STAT)/ROS *in vitro* (Duong, et al., 2024). Returning to normoxia after hyperoxia treatment in premature infants leads to relative retinal hypoxia, which significantly upregulates VEGF and hypoxia inducible factor 1 subunit alpha (HIF-1α), triggering pathological neovascularization. While dark rearing during hyperoxia treatment increases retinal oxygen demand, which can mitigate hyperoxia-induced vasoconstriction and obliteration, and suppress the abnormal upregulation, thereby exerting a protective effect against retinopathy of prematurity (ROP) (Kozulin, et al., 2011). Besides, UV-A exacerbates ferroptosis by releasing iron ions, leading to corneal endothelial cell death and subsequently causing Fuchs endothelial corneal dystrophy. The impact of UV-A also exhibits gender differences (Saha, et al., 2024). It activates the estrogen metabolism pathway, inducing DNA damage, which results in a higher incidence and more severe condition in females (Liu, et al., 2020). Microplastics are retinotoxic and induce retinal degeneration. These effects have been extensively explored in recent preclinical studies, which have also begun to elucidate the underlying mechanisms. Both in vivo and in vitro models (including cell cultures and organoids) have confirmed that microplastics damage the retina, with smaller particles, particularly nanoplastics, posing greater hazards (Gao, et al., 2025; Li, et al., 2024; Piao, et al., 2026). This damage arises because microplastics disrupt mitochondrial dynamics, trigger a sharp rise in ROS, and precipitate an oxidative stress burst (Li, et al., 2024). Moreover, studies have shown that antioxidant enzymes are suppressed, whereas restoring Sirtuin 1 expression exerts a protective effect (Piao, et al., 2026). Ferroptosis is also activated during this process, further exacerbating retinal injury (Liu, et al., 2026). As part of the pathogenic mechanism, microglial activation of the SPP1 signaling pathway promotes neutrophil infiltration and neutrophil extracellular traps formation (Zhou, et al., 2026), while complement-mediated phagocytosis and pro-inflammatory responses are concurrently engaged (He, et al., 2024). The mechanisms behind the association of eye malformation (Narotsky, et al., 2011; Warren, et al., 2006) (such as anophthalmia, microphthalmia (Barbagallo, et al., 2022; Narotsky, et al., 2025), and retinal dysplasia (Schweitzer, et al., 1987)), eclipse blindness (Ham, et al., 1978) and other diseases with multiple exposomes have also been elucidated. Part of the key mechanisms are summarized in Supplementary Figure S12, S13, and S14.

Supplementary Tables S2, S3, S4, and S5 provide detailed information on the studies on the impact of exposomes on eye diseases collected so far, encompassing both population-based studies and preclinical experiments. Figure 2 further summarizes the research landscape on eye diseases and exposome. In this chart, the size of each circle represents the number of studies, while the color indicates the quality of evidence, based on a scoring system we developed. As shown, air pollutants have received considerable attention. Research on cataracts and UV exposure stands out for both its volume and quality, providing comprehensive evidence of the harmful effects of UV on cataracts. The impacts of O_3 and sunlight vary markedly across different eye conditions: O_3 may be protective against cataracts but potentially harmful in diseases like conjunctivitis; sunlight appears beneficial for refractive errors yet may accelerate the progression of conditions such as AMD. Urbanization is generally associated with favorable outcomes for most eye diseases, likely due to a reduction in risk factors.

4. Exposome-mediated mechanistic pathways common to ocular diseases

Although various exposomes may influence the onset and progression of diverse eye diseases through complex mechanisms (as aforementioned), commonalities exist in underlying mechanisms. The associations between these exposomes and ocular diseases often involve shared core pathophysiological processes, primarily including oxidative stress, cell responses, inflammation and immune reactions, ECM remodeling, vascular alterations, etc. In-depth analysis of these cross-disease common mechanisms can enhance the understanding of the link between exposomes and the eye, offering new insights and directions for developing comprehensive prevention measures and broad-spectrum therapeutic strategies for ocular diseases.

Oxidative stress represents the most central common pathway triggered by exposomes, as the earliest and most direct molecular response typically, with an essential form of chemical imbalance. Air pollutants (e.g. PM (Li, et al., 2021; Liu, et al., 2024; Vitar, et al., 2020), cigarette smoke (Mansoor, et al., 2014; Smit-McBride, et al., 2018; Zinflou, Rochette, 2019)), light (Albarracin, et al., 2011; Benedetto, Contin, 2019; Picard, et al., 2011; Tang, et al., 2021) (e.g. blue light (Kim, et al., 2016; Marek, et al., 2018; Olchawa, et al., 2022; Wang, et al., 2023), UV (Chung, et al., 2017; Giblin, et al., 2002; Mody, et al., 2006)), ionizing radiation (Ahmadi, et al., 2022), and heavy metals (e.g. lead (Modgil, et al., 2015)) can induce oxidative stress in eye diseases through various pathways. Interestingly, intermittent UV may enhance the antioxidant response to exert a protective effect (Hallam, et al., 2017). The mechanisms involved in oxidative stress mainly include ROS initiation, mitochondrial dysfunction, lipid peroxidation, etc. One of the most common sources of ROS is O_2. For instance, the excited state formed by the absorption of blue light by Indeno-1,2,3-cd pyrene can react with O_2 to generate ROS (Zinflou, Rochette, 2019). Moreover, UV-B can induce the conversion of intracellular O^-, OH^-, NO^-, etc. into ROS (Hong, et al., 2024). Mitochondria, as the core organelles responsible for energy supply via aerobic respiration, are also the primary sites of oxidative stress: blue light can impair mitochondrial dynamics and lead to excessive accumulation of ROS, initiating oxidative stress (Wang, et al., 2023); UV-B can induce mitochondrial membrane potential loss and oxidative stress in LECs (Ji, et al., 2015). Lipid peroxidation is a major consequence of oxidative stress. It has been detected in studies regarding influence of $PM_{2.5}$, cigarette smoke, and UV-A on eyes, often leading to lipid metabolic disorders, and is closely associated with ferroptosis (Bertram, et al., 2009; Giblin, et al., 2002; Liu, et al., 2024). Additionally, it is worth mentioning the antioxidant system of cells, which is mainly composed of reduced glutathione (GSH)-oxidized glutathione (GSSG) circulation, superoxide dismutase (SOD), etc (Vitar, et al., 2020). Indeed, exposomes can trigger early antioxidant responses, yet persistent oxidative stress often exceeds its compensatory capacity (Bertram, et al., 2009; Vitar, et al., 2020; Wang, et al., 2010). Blue light can activate stress defense pathway and up-regulate HO-1 and SOD (Roehlecke, et al., 2009); UV-B promotes GSTM1, peroxiredoxin 2 (PRDX2), SOD, and catalase, inducing the activation of antioxidant defense systems (Kraljević Pavelić, et al., 2015). In the terminal stage, various exposomes destroy the antioxidant system and even make it collapse. After $PM_{2.5}$ exposure, GSH/GSSG ratio and GPX4 decreased significantly (Liu, et al., 2024). Oxidative stress is ubiquitous in a variety of ocular diseases induced by exposomes: in DED, oxidative stress induces imbalance of the Nrf2/NF-κB pathway, defective mucus secretion (Han, et al., 2017; Yu, et al., 2023); in cataract, it can lead to osmotic pressure imbalance in LECs (Galichanin, et al., 2010); in refractive errors, it enables the remodeling of multiple structural components of the eyeball (Mutti, et al., 1998); in AMD, it leads to autophagic dysfunction, macrophage infiltration, deposition of drusen-like substances (Jaadane, et al., 2017; Nakamura, et al., 2018); in uveal melanoma, it accelerates cell proliferation and enhances the metastatic potential (Di Cesare, et al., 2009). Actually, as the initial effect of exposure, the downstream reaction of oxidative stress is closely related to cell death and inflammation generally.

Cell responses primarily encompass cell death, as well as aberrations in proliferation and differentiation. Cell turnover and fate change are deeply implicated in the pathological mechanisms of various ocular diseases. Cell death encompasses various forms, including apoptosis, pyroptosis, and ferroptosis. Among these, apoptosis is the most predominant, and can be induced by exposomes such as PM (Song, et al., 2020), environmental tobacco smoke (Bertram, et al., 2009; Mansoor, et al., 2014), light (Mutti, et al., 1998; Sudharsan, et al., 2017; Torbidoni, et al., 2006; Yang, et al., 2008), and formaldehyde (Vitoux, et al., 2018). A significant portion of apoptosis is attributed to DNA damage induced by exposure-related factors (Galichanin, et al., 2010; Lai, et al., 2007). Impaired DNA may alter the regulation of apoptosis-related proteins, for instance, DNA damage activates p53 and then upregulates caspase-3 (Ayala, et al., 2007). Actually, caspase is one of the core components of the apoptotic mechanisms (Arnault, et al., 2013; Wang, et al., 2016). 2-ethylpyridine and Benzo(e)Pyrene in cigarette smoke or blue light can induce apoptosis by activating caspase-3/7 via the caspase-8, caspase-9, or caspase-12 pathways (Feng, et al., 2014; Mansoor, et al., 2014; Sharma, et al., 2008). Various conditions including light (especially UV) can also promote apoptosis through multiple mechanisms, such as increasing the content of pro-apoptotic proteins like c-fos (Krishnan, et al., 2008; Li, Spector, 1996), inhibiting the production of anti-apoptotic proteins like BCL-2 (Maurizi, et al., 2019), activating Fas/FasL system (Podskochy, Fagerholm, 2002), and elevating the level of sphingosine 1-phosphate in photoreceptor cells (Terao, et al., 2019). Representative diseases mainly include DED (goblet cells apoptosis leads to decreased mucin secretion (Vitoux, et al., 2018)), photokeratitis (corneal cells apoptosis induces tissue inflammation (Podskochy, Fagerholm, 2002)), cataract (LECs apoptosis disrupts cell arrangement and induces local changes in refractive index (Michael, 2000)), myopia (photoreceptor cells apoptosis and retinal thinning (Mutti, et al., 1998)), AMD (photoreceptor apoptosis, RPE dysfunction and Bruch's membrane disruption (Albert, et al., 2010)), etc. In the context of pyroptosis, it can be induced by factors such as PM and altitude, and its occurrence is mediated by mechanisms of NLRP3 and GSDMD (Li, et al., 2021; Xin, et al., 2022): exposomes activate NLRP3, leading to the activation of caspase-1, which cleaves GSDMD, resulting in the formation of membrane pores and pyroptosis, mainly involving meibomian gland dysfunction, glaucoma, and high-altitude retinopathy (Li, et al., 2021; Tu, et al., 2024; Xin, et al., 2022). For ferroptosis, the primary relevant exposomes are PM and light. The specific mechanism is that abnormal iron metabolism leads to intracellular accumulation, which generates a large amount of ROS through

Fenton reaction. Meanwhile, the antioxidant mechanisms such as the GSH-GSSG cycle fail to respond, resulting in lipid peroxidation and the destruction of cell membranes and other structures (Liu, et al., 2024; Stockwell, 2022; Tang, et al., 2021). Under the action of $PM_{2.5}$ or UV, intracellular levels of Fe^{2+}, ROS, and malondialdehyde increase, whereas the GSH/GSSG ratio and the expression of *GPX4* decrease (Liu, et al., 2024; Saha, et al., 2024; Sheng, et al., 2024). It has been proven that the related diseases are Fuchs endothelial corneal dystrophy (Saha, et al., 2024), experimental autoimmune uveitis (Liu, et al., 2024), and age-related cataract (Sheng, et al., 2024). Exposomes can also drive cells to develop toward another extreme—abnormal proliferation, with mechanisms including FGF secretion, increased *Ras* expression, and activation of the MAPK and PI3K signaling pathways (McDonnell, et al., 2016; Sabourin, et al., 1993; Wang, et al., 2013). This is primarily associated with ocular tumors such as uveal melanoma and corneal mesenchymal tumor (Di Cesare, et al., 2009; Sabourin, et al., 1993). Studies have shown that cell proliferation can also induce trabecular meshwork fibrosis and subsequently lead to glaucoma (McDonnell, et al., 2016), and scleral cell proliferation can cause axial elongation of the eye, resulting in myopia (Wang, et al., 2013).

Inflammation is critical to the amplification of exposure-induced damage, and serves as a response at the tissue level of an organism. It can be induced by air pollutants (e.g., particle (Duong, et al., 2024; Fujishima, et al., 2013; He, et al., 2024; Li, et al., 2021), tobacco smoke (Smit-McBride, et al., 2018; Wang, et al., 2021), and O_3 (Lee, et al., 2017)), meteorological factors (e.g., desiccation (Alam, et al., 2021)), light (Albarracin, et al., 2011; Parmar, et al., 2016; Thebeau, et al., 2020; Vasović, et al., 2024) (e.g., blue light (Kim, et al., 2016) and UV-B (Di Girolamo, et al., 2002)), organic pollutants (e.g., formaldehyde (Vitoux, et al., 2018)), heavy metals (e.g., lead (Modgil, et al., 2015)), and other factors. Inflammatory factors (including pro-inflammatory factors, anti-inflammatory factors, and chemokines) are the direct effect induced by exposomes (Di Girolamo, et al., 2002; Fujishima, et al., 2013; Gu, et al., 2023; Lee, et al., 2017; Tien, et al., 2020; Vitoux, et al., 2016; Vitoux, et al., 2018). For example, UV-B can promote the release of TNF-α and IL-6 by activating NF-κB and MAPK pathways (Di Girolamo, et al., 2006; Lai, et al., 2021). NLRP3 inflammasome is the key component of the inflammatory mechanisms, capable of activating caspase-1, thereby leading to the release of IL-1β and triggering pro-inflammatory reactions (Li, et al., 2021; Smit-McBride, et al., 2018). Additionally, infiltration of inflammatory cells (neutrophils, macrophages, etc.) is involved in inflammation (Meyer, et al., 2013). Of particular interest, UV-B may affect both eyes by triggering a systemic inflammatory reaction (Meyer, et al., 2013; Söderberg, 1990). Inflammation has a complex relationship with the pathological process of diseases. DED is prone to chronic inflammation, which in turn leads to corneal damage (Han, et al., 2017); inflammation induces lipid accumulation and promotes meibomian gland dysfunction (Duong, et al., 2024); ocular surface inflammation leads to hyperemia and edema, which further induces allergic conjunctivitis and keratoconjunctivitis sicca (Alam, et al., 2021; Fujishima, et al., 2013; Lee, et al., 2017); inflammation-induced abnormal proliferation of epidermal cells participates in the formation and progression of pterygium (Lai, et al., 2021); inflammatory infiltration can lead to lens light scattering and then cataract (Meyer, et al., 2013); inflammatory responses can induce damage to the trabecular meshwork tissue, leading to glaucoma (Li, et al., 2021); inflammatory factors induce the destruction of the barrier function of RPE and promote the progression of AMD (Gu, et al., 2023; Smit-McBride, et al., 2018; Tien, et al., 2020).

In addition, several other mechanisms are universally involved in the process by which exposomes affect the eyes. For instance, immune responses, which are predominantly observed in allergic diseases such as allergic conjunctivitis, are typically associated with exposure to PM, pollen and other agents, with the underlying mechanisms including Th2-type immune responses and the production of IgE (Hwang, et al., 2021; Miyata, et al., 1993). As well as the ECM, whose destruction, deposition and remodeling all exert significant impacts. Disruption of the ECM can impair the adhesion and nutrient exchange between RPE cells and photoreceptors, directly leading to photoreceptor dysfunction and death (Kraljević Pavelić, et al., 2015). MMP can degrade the ECM, promote the metastasis of cancer cells (Lai, et al., 2007), and also destroy the fiber structure of the lens to induce cataract (Sachdev, et al., 2004). The deposition of ECM contributes to drusen formation, ultimately leading to diseases such as AMD (Gottsch, et al., 1993; Yu, et al., 2012), while ECM remodeling can cause scleral thinning and axial eye elongation, ultimately resulting in myopia (Hsiao, et al., 2023; Wang, et al., 2013). Besides, other mechanisms, such as neovascularization (Kozulin, et al., 2011; Pons, Marin-Castaño, 2011; Sabourin, et al., 1993; Vila, et al., 2015) and the regulation of DA signaling (Chen, et al., 2017; Cohen, et al., 2011; Landis, et al., 2021; Liu, et al., 2015), are also of great importance. Figure 3 summarizes these major shared mechanisms.

It is noteworthy that these mechanisms do not exist in isolation, and there is complex crosstalk among them, with mutual causality and reciprocal influences. Oxidative stress often leads to cell death and the release of inflammatory factors. For instance, in AMD, ROS induce mitochondrial network disintegration and subsequently trigger cell apoptosis (Zinflou, Rochette, 2019), and in glaucoma ROS can initiate NLRP3-mediated inflammatory responses (Li, et al., 2021). Inflammatory responses can exacerbate oxidative stress, mainly through inflammatory factors and the respiratory burst of inflammatory cells (Meyer, et al., 2013; Smit-McBride, et al., 2018). Inflammation can also induce cell death: in DED the inflammatory microenvironment induces apoptosis of goblet cells (Vitoux, et al., 2018), and in DR when inflammation is alleviated, apoptosis is also observed to decrease accordingly (Thebeau, et al., 2020). Many immune cells are involved in inflammatory responses. For example, desiccation stress recruits monocytes, promotes their differentiation into MHCII-positive macrophages, and upregulates the expression of inflammatory genes (Alam, et al., 2021). Moreover, inflammatory factors disrupt RPE barrier, thickening Bruch membrane, and also indirectly promote the formation of retinal neovascularization (Gu, et al., 2023). Although diverse exposomes influence various ocular diseases through their respective complex pathways, they ultimately converge on shared pathophysiological mechanisms, notably oxidative stress, cell response, and inflammation. Unfortunately, current research has primarily focused on elucidating the pathogenic mechanisms of exposomes, whereas the protective effects of certain exposomes against eye diseases have not been thoroughly elaborated. Elucidating the cross-disease common mechanisms is conducive to breaking through the research limitations of a single disease and provides novel theoretical basis for the development of broad-spectrum preventive measures and therapeutic strategies.

5. From Association to Causality: Strengthening Inference

In ocular exposome research, causal inference serves as a statistical framework designed to identify and quantify the causal effect of exposomes (e.g., $PM_{2.5}$) on study outcome (e.g., glaucoma) (Bae, et al., 2017; Glass, et al., 2013; Rothman, Greenland, 2005). Unlike conventional exposure-outcome association analysis, which aims to quantify statistical dependence, causal inference aims to determine the true effect of an exposome. This concept can be illustrated by a counterfactual scenario: what would have happened to ocular health if the exposure level had been different for the same individual? Thus, causal inference is crucial in ocular exposome research, as establishing causality enables the identification of effective interventions and their effects, thereby guiding decision-making and policy formulation (Figure 4, Supplementary Table S6, S7).

Although randomized controlled trial (RCT) represents the gold standard for causal inference, they are rarely feasible in ocular exposome research when the exposure of interest is known or suspected to be harmful, assigning such exposomes as interventions would be unethical. Consequently, causal evidence is primarily derived from observational studies. Against this background, establishing causality requires a comprehensive evaluation across both study design and methodological dimensions. The study design dimension concerns the structural features of the research that permit causal inference, and we operationalize this through the Bradford Hill criteria, with particular emphasis on temporality, exposure–response gradients, biological plausibility, and consistency across studies. The methodological dimension focuses on the analytical tools for estimating causal effects using observational data; we employ directed acyclic graphs (DAGs) to identify confounders and apply methods such as propensity score matching (PSM), inverse probability weighting (IPW), and instrumental variable approaches to quantitatively evaluate causal effects. From a study design perspective, the Bradford Hill criteria offer a useful framework (Shimonovich, et al., 2021), emphasizing temporal sequence, exposure-response curves, biological plausibility and consistency of findings across studies. Among these, temporal sequence relationship is the most essential, requiring that exposome clearly precedes the onset of the ocular outcome; exposure-response curves provide supportive evidence when increasing exposure levels are associated with a monotonic increase in disease risk; biological plausibility demands that the observed association be coherent with existing toxicological or pathophysiological knowledge; consistency across studies refers to the replication of similar findings in different populations, settings, or study designs, reducing the likelihood that the observed relationship is spurious or due to local biases. From a methodological perspective, causal identification primarily relies on DAGs (Evandt, et al., 2017; Glymour, et al., 2019) to encode qualitative causal assumptions and provide criteria for identifying causal effects from observed data; while the quantitative estimation of causal effects is typically conducted within the potential outcome framework (the Rubin Causal Model), which defines causal effects as comparisons of potential outcomes under different exposure conditions. Methods such as PSM, IPW, and instrumental variable approach serve to control for confounding factors, thereby strengthening causal claims from observational studies. These requirements demonstrate that robust causal evidence in ocular exposome research derives primarily from three sources: prospective cohort studies, preclinical study validation, and natural experiments.

Applying the full Bradford Hill framework to the evidence synthesized in this review reveals meaningful gradations that the methods discussion alone cannot capture. Based on the Bradford Hill criteria for causal inference, we systematically evaluated the associations between various exposome and ocular diseases, and summarized the criteria numbers that were not met for each exposure–disease pair in Supplementary Table S8. Overall, specificity and experimental evidence were the most frequently missing items, indicating that current studies are generally weak in excluding confounding factors and providing experimental validation. Second, biological gradient and biological plausibility were also not confirmed in many associations, reflecting that dose–response relationships and mechanistic explanations remain insufficient. In contrast, temporality was satisfied for the vast majority of exposure–disease pairs, with only a few exceptions (e.g., heavy metals and organic contaminants in relation to DR) lacking temporal evidence. For AMD, almost all air pollutants (PM, NO_2, O_3, CO, SO_2)

lacked specificity or preclinical evidence, whereas humidity, temperature, and UV performed relatively well across multiple criteria. For DED, most exposomes failed to meet specificity, experimental evidence, and biological plausibility, but temporality and strength of association were relatively reliable. UV and cataract, UV and pterygium, and outdoor light and myopia satisfy not only temporality, dose-response, and biological plausibility, but also strength of association, coherence with experimental models, and replication across independent populations and geographic gradients: the cumulative evidence for these relationships exceeds what is available for many accepted clinical risk factors and warrants causal rather than associative language. For $PM_{2.5}$ and multiple ocular outcomes, the sufficient-component-cause model, which posits that disease arises only when a complete set of component causes is assembled, remains a useful conceptual framework for understanding why the same exposome may harm some individuals and populations but not others. The regional inconsistencies documented throughout this review—where $PM_{2.5}$ shows harmful effects in Chinese populations but not in European ones—are notable, but we acknowledge that attributing this discordance primarily to genuine biological heterogeneity would be an over-interpretation of the current evidence. Chinese and European studies differ along multiple dimensions beyond population genetics, including $PM_{2.5}$ composition and sources, absolute exposure levels and exposure ranges, co-exposure mixtures, outcome ascertainment methods, healthcare access patterns, and study design features, and any or all of these factors could contribute to the observed heterogeneity. For heavy metals, PFAS, and microplastics, current evidence remains associative, based on single-study designs without sufficient mechanistic convergence to meet the full criteria. Acknowledging these distinctions explicitly matters for what follows - prevention recommendations anchored in causal evidence carry different weight for clinicians and policymakers than those built on association alone.

Prospective cohort studies offer a primary advantage in establishing a reliable temporal sequence between the exposure and the study outcome. By design, these studies exclude individuals who already present with the outcome at baseline (Cui, et al., 2026; Qu, et al., 2025; Yan, et al., 2024), thereby ensuring that the exposome clearly precedes the outcome. This temporal relationship is critical for minimizing reverse causation bias, a situation in which the presumed outcome influences the likelihood of exposure, and for strengthening the validity of exposure–response curves (Zhang, et al., 2021). To fully leverage these strengths for causal inference in ocular exposome research, however, robust methodological approaches are essential. Two analytical strategies are commonly employed, depending on the researcher's knowledge of the confounding structure. First, when the underlying confounding structure is well understood, DAGs, provide a principled framework for confounding control. DAGs can identify a minimally sufficient adjustment set of confounders, mediators, and colliders. Adjusting for this set, and crucially, avoiding adjustment for mediators or colliders, enables unbiased estimation of the total or direct causal effect of interest (Feeney, et al., 2025). Second, when many measured confounders are suspected, methods grounded in the potential outcome framework, such as PSM and IPW, are often more suitable, as they were designed to create balanced pseudo-populations with respect to measured confounders.

Preclinical study validation serves primarily to assess the biological plausibility of observed associations, thereby providing complementary evidence that reinforces findings from prospective cohort studies. When mechanistic results align with those obtained from cohort studies, they satisfy the Bradford Hill criterion of consistency across diverse types of evidence (Zhang, et al., 2025). This convergence across different study designs strengthens the overall causal argument, as it reduces the likelihood that the observed relationship is spurious or driven solely by methodological artifacts. It is worth noting that such experiments are typically conducted in mice or other laboratory animals. Although cross-species extrapolation introduces certain limitations, the ability to deliberately expose animals to environmental pollutants under controlled conditions makes these experiments conceptually similar to RCTs in terms of establishing causal relationships, endowing this evidence with appreciable causal weight (Qi, et al., 2022). In this context, conventional causal inference methods (e.g., adjustment for confounding) are no longer required as the randomization allocation eliminates confounding by design. Instead, the emphasis shifts to fulfilling Bradford Hill criteria.

Temporality and replicability are easy to be proved, while biological plausibility remains the most critical challenge-specifically, the relevance of the exposure route. For example, ocular instillation studies poorly model real-world airborne exposure (Qi, et al., 2024), which occurs primarily via respiratory inhalation. Consequently, experiments employing inhalation-based exposure protocols provide more reliable and biologically relevant evidence.

Natural experiments, also known as quasi-experimental research, emulate the logic of the RCT by leveraging pollution-related policies interventions to create a quasi-randomized comparison (Behi, Nolan, 1996; de Vocht, et al., 2021; Ohlsson, Kendler, 2020). This approach is invaluable in environmental epidemiology where true RCTs are infeasible. Two approaches are primally used: regression discontinuity design (RDD) and difference-in-differences (DID) (Sasabuchi, 2022; Wang, et al., 2024). To illustrate, using the $PM_{2.5}$ - glaucoma relationship as an example. RDD assumes that intervention assignment is determined by a specific threshold. For instance, when the $PM_{2.5}$ concentration reaches to 30 μg/cm^3 in an area, a policy intervention is triggered to reduce the $PM_{2.5}$ concentration. Researchers could obtain the causal relationship between $PM_{2.5}$ and glaucoma by comparing the incidence of glaucoma in this region with that in another comparable, non-intervention region where the $PM_{2.5}$ concentration may be 29 μg/cm^3. This process achieves approximate randomization since grouping solely based on $PM_{2.5}$ concentration. In contrast, DID estimates the causal effects by comparing changes in disease incidence over time between intervention group and control group. For instance, one may calculate the change in the incidence of glaucoma before and after the policy intervention for $PM_{2.5}$ concentration at the same time points for both the intervention and control groups, and then test whether the two changes differ significantly. By subtracting the pre-post change in the control group from that in the intervention group, DID eliminates time-invariant confounders and common time trends, yielding the effect of $PM_{2.5}$ intervention and further provide the causal evidence between $PM_{2.5}$ and the incidence of glaucoma. Despite these unique methodological advantages, well-conducted natural experiment studies remain notably absent in the field of ocular exposome research. Besides, DID relies on the parallel trends assumption, which requires that in the absence of the intervention, the average outcomes for the treated and control groups would have followed parallel paths over time. DID additionally assumes no simultaneous confounding events and correct model specification, and violations of the parallel trends assumption can lead to biased causal estimates. For RDD, valid inference depends on the assumption that units just above and just below the threshold are comparable in all respects except treatment assignment, which approximates local randomization in the neighborhood of the threshold. Assumption requires that the assignment variable is not manipulable by study subjects, that the functional form of the relationship between the assignment variable and the outcome is correctly specified, and that the bandwidth around the threshold is chosen appropriately.

In interpreting the evidence synthesized in this review, reverse causation warrants particular attention, given the heavy reliance of the existing literature on cross-sectional and retrospective study designs. Individuals with ocular symptoms or early-stage disease may systematically alter behaviors that also influence their exposure profiles, thereby generating spurious or distorted exposome–disease associations. For DED, patients with pre-existing ocular surface discomfort may reduce outdoor time, leading to a potentially misleading inverse association between outdoor activity and disease, or may increase healthcare-seeking behavior, inflating the apparent association with clinical diagnoses. For myopia, children who develop early myopia may preferentially engage in prolonged near-work activities and avoid outdoor exposure, creating a circumstance in which the behavioral pattern is a consequence, rather than a cause, of the refractive condition. For cataract and AMD, individuals with early visual impairment may limit outdoor activity to reduce glare sensitivity or fall risk, thereby altering their measured exposure to sunlight and air pollutants in ways that bias cross-sectional estimates. For conjunctivitis, patients with acute symptoms may seek care at clinics with specific geographic or temporal exposure profiles, generating a non-causal association between certain environmental triggers and disease incidence when assessed cross-sectionally. Consequently, findings derived predominantly from cross-sectional or retrospective designs should be regarded as hypothesis-generating, and their translation into causal claims or clinical recommendations should await prospective validation.

In summary, obtaining causal evidence linking exposomes to ocular diseases requires integrating rigorous causal inference methods with the Bradford Hill criteria, which could be achieved through prospective cohort studies, preclinical study validation, and natural experiments. Despite the growing recognition of these methodological and designed priorities, current research in ocular exposome remains notably deficient in addressing all three areas: 1) the widespread absence of standardized imaging phenotypes hampers cross-study comparability and reproducibility, as heterogeneous definitions of ocular outcomes are often employed across studies. This lack of harmonization not only limits the generalizability of individual studies but also impedes the accumulation of robust evidence needed for causal inference. 2) the vast majority of existing investigations rely on single time-point measurements for both exposure and outcome, thereby failing to capture dynamic changes over time, especially for those participants who change residences or lifestyle behaviors during the study period, as their long-term exposure profiles may be mischaracterized. Thus, studies remain vulnerable to non-differential misclassification bias, attenuating true effect estimates to detect causal relationships. 3) most analytical frameworks still focus on single exposure analyses, although real-world exposomes invariably involve complex mixtures of environmental agents. The application of interpretable mixture analysis methods, such as weighted quantile sum (WQS) regression and Bayesian kernel machine regression (BKMR), remains scarce, meaning that the independent and interactive effects of multiple co-occurring exposomes on ocular diseases are largely unexplored (Guo, et al., 2026; Wen, et al., 2024), leaving a critical gap in our understanding of real-world scenarios. Addressing these gaps will be essential for moving the field beyond simple association toward robust causal inference, and provide the credible evidence needed to inform public health recommendations and clinical interventions for exposome-related ocular diseases.

6. Actionable Prevention, Clinical Practice, and Policy

The extensive evidence reviewed across above eye diseases—from ocular surface diseases to retinal diseases—reveals that exposomes are not marginal contributors but central determinants of ocular health. Translating these findings into practice requires a multi-layered framework that empowers patients, equips clinicians, and guides policymakers. We have classified all recommendations into three grades based on the quality of evidence from a multidimensional evaluation of clinical and preclinical studies: established recommendations (supported by high-quality, consistent evidence from multiple studies), precautionary advice (suggested by existing research but has not yet reached a level of certainty), and speculative proposals (speculated based on current evidence but remains to be clarified).

6.1 Actionable Prevention Framework

6.1.1 Established recommendations

From the patient-level, for UV and light protection, given the consistent evidence linking UV exposure to cataract (Anduze, 1993; Burton, et al., 1997; Cullen, et al., 1994; Delavar, et al., 2018; Delcourt, et al., 2014; Garźon-Chavez, et al., 2018; Jose, 1986; Meyer, et al., 2005; Michael, et al., 1996; Okuno, et al., 2012; Suresh, et al., 2022; Taylor, 1980; Taylor, 1989; Varssano, et al., 2017; Wang, et al., 2012; Zhu, et al., 2015), pterygium (Darrell, Bachrach, 1963; Stevenson, et al., 2021; Taylor, et al., 1989; Taylor, et al., 1992), and ocular surface squamous neoplasia (Gichuhi, et al., 2016; Newton, et al., 1996; Sun, et al., 1997), patients should adopt a tiered protection strategy. Broad-spectrum sunglasses (blocking 99–100% of UV-A and UV-B) with wraparound designs are superior to standard frames, as reflected UV from snow, water, and sand poses substantial risks—particularly relevant for pseudoexfoliation syndrome (Pasquale, et al., 2014).

From clinic-level, for risk stratification, ophthalmologists should routinely collect exposome histories, including occupation (welders, farmers, street sweepers, radiologists (Chodick, et al., 2008; De Stefano, et al., 2016; Lian, et al., 2015; Little, et al., 2020; Little, et al., 2018)), residential location (urban vs. rural, proximity to major roads or agricultural fields), fuel use, smoking status (including prenatal exposure for pediatric patients (Huo, et al., 2021; Tong, et al., 2025)), and outdoor activity patterns. This information enables stratified prevention: for example, patients with high cumulative UV exposure and early lens changes may benefit from more frequent monitoring for cortical cataract (Taylor, et al., 1988; West, et al., 2005), while those with high $PM_{2.5}$ exposure and DED warrant earlier intervention for meibomian gland dysfunction (Duong, et al., 2024; Tu, et al., 2024). For counseling, exposome counseling should be integrated into routine visits, using the "reduce–barrier–repair" framework. For a patient with progressing myopia, counsel on increasing outdoor light exposure (≥ 60 minutes daily (Sun, et al., 2024)) while reducing near-work in poorly lit, low-spatial-frequency indoor environments (Li, et al., 2025).

6.1.2 Precautionary advice

From the patient-level, blue light filtering is less urgent for general prevention, while for patients with DED (Kaido, et al., 2016; Marek, et al., 2018) or AMD (Arnault, et al., 2013; Kim, et al., 2016; Marie, et al., 2019; Nakamura, et al., 2018) may be prudent, especially from LED sources at night. Clinicians might consider that wearing hats alone is insufficient for pseudoexfoliation syndrome, but effective for ocular surface squamous neoplasia (Gichuhi, et al., 2016)—advice must be lesion-specific. For indoor air strategies, indoor smoke from biomass fuel combustion is a modifiable risk factor for cataract (Lai, et al., 2024; Noda, et al., 2010; Owusu, et al., 2025; Patel, et al., 2022; Pokhrel, et al., 2005; Sreenivas, et al., 1999; Vashist, et al., 2020) and refractive errors (Owusu, et al., 2025). Switching to cleaner cooking technologies (improved stoves, ventilation hoods, or electric alternatives) should be prioritized in low-resource settings where solid fuel use remains common. Patients with meibomian gland dysfunction should be counseled that PM exposure induces lipid accumulation and pyroptosis (Duong, et al., 2024; Tu, et al., 2024)—ventilation alone is insufficient without particle filtration. For exposure avoidance during extremes, weather-related risks follow a U-shaped pattern. Preliminary evidence suggests that patients avoid outdoor activities during cold waves (temperature drops ≥ 4 ℃ increase acute angle-closure glaucoma risk (Zhu, et al., 2023)), extreme heat (> 32 ℃ may protect dry eye (Chaturvedi, et al., 2023) but high temperature with low humidity exacerbates conjunctivitis (Zhao, et al., 2023)), and high-wind dusty conditions (Das, Basu, 2021; Gupta, et al., 2025). For those with AMD, preliminary evidence also suggests that reducing midday sun exposure during summer months may lower recurrence risk of wet AMD (Rouvas, et al., 2023). Pregnant women in areas with high air pollution should be advised that early pregnancy NO exposure is associated with bilateral retinoblastoma (Ghosh, et al., 2013), and prenatal arsenic exposure increases childhood myopia risk (Tong, et al., 2025)—though definitive causality requires further study, precautionary counseling is warranted.

From clinic-level, for a diabetic patient with early retinopathy, reducing sunlight exposure (≥ 5 hours daily increases risk 2.66-fold (Lee, et al., 2020)) and heavy metal screening if geographically indicated (Gui, et al., 2024; Li, et al., 2023; Meng, et al., 2024) may be prudent. For a patient with recurrent conjunctivitis, preliminary evidence suggests doctors identifying seasonal triggers (spring pollen (Calderon-Ezquerro, et al., 2018; Qiu, et al., 2021), winter cold (Li, et al., 2016), summer O_3 (Ruan, et al., 2024)) and providing targeted behavioral advice rather than merely using nonspecific antihistamines.

6.1.3 Speculative proposals

From the patient-level, it is speculated that for individuals living in low-latitude coastal regions or high-altitude areas, daily protection is not merely during summer, with relevant evidence remaining under investigation. From clinic-level, future studies are needed to determine whether children born in winter (higher myopia risk (Huo, et al., 2021)) or living in areas with low greenness (Yang, et al., 2024; Zhang, et al., 2023) may benefit from earlier cycloplegic refraction. Adults in high-altitude regions (increased pterygium (Lu, et al., 2009; Lu, et al., 2007), but potentially protective for myopia (Han, et al., 2025; Xiang, et al., 2024)) require differential counseling. It remains to be established whether populations residing in high-latitude areas with snow cover warrant pseudoexfoliation syndrome screening, as reflected UV exposure is substantial despite lower ambient UV (Stein, et al., 2011).

6.2 Policy Recommendations

6.2.1 Established recommendations

Air quality standards should incorporate ocular endpoints. Current thresholds for $PM_{2.5}$, NO_2, and O_3 are set based on respiratory and cardiovascular outcomes, yet ocular effects occur at lower concentrations. For example, NO_2 shows significant association with conjunctivitis at 27 μg/m^3 (Lu, et al., 2021)—well below WHO guidelines. O_3 has a U-shaped relationship with AMD (Jia, et al., 2024; Ju, et al., 2022; Qu, et al., 2024) and DED (Kim, et al., 2020; Kim, et al., 2019; Rocha, et al., 2023): low concentrations may be protective, while high levels are harmful. Policies should avoid simplistic linear targets and instead establish exposure windows that account for cumulative effects.

Besides, urban greenness is a modifiable protective factor for myopia (Dadvand, et al., 2017; Peng, et al., 2021; Yang, et al., 2022; Yang, et al., 2024; Zhang, et al., 2023), AMD (Qu, et al., 2025), and DR (Jia, et al., 2023). Planning regulations should mandate minimum NDVI values (> 0.4 within 500–1,000 m of schools and residential areas (Qu, et al., 2025)) based on evidence that this threshold eliminates UV harm. Greenness likely operates through multiple pathways: air pollutant removal, promotion of outdoor activity, and psychological stress reduction. Cost-benefit analyses should include avoided myopia progression (reduced lifetime refractive care costs) and delayed AMD progression (reduced anti-VEGF treatment burden).

As for school lighting & building design, school lighting environments require regulatory attention. Policies should ensure illumination > 1,000 lux during outdoor activity periods (Wu, et al., 2018). Building codes for schools should consider spatial frequency and window design: low spatial frequency indoor environments are associated with myopia (Li, et al., 2025), while higher building area density (more indoor space) paradoxically reduces risk (Zeng, et al., 2025)—suggesting that overcrowding, not density per se, is harmful. Prioritizing low-resource settings. Scalability in low-resource settings requires prioritization. The highest-impact interventions are: promoting clean cooking (reduces cataract (Lai, et al., 2024; Noda, et al., 2010; Owusu, et al., 2025; Patel, et al., 2022; Pokhrel, et al., 2005; Sreenivas, et al., 1999; Vashist, et al., 2020) and refractive errors (Owusu, et al., 2025)), distributing low-cost wrap-around sunglasses in high-altitude/coastal regions (reduces pterygium (Asokan, et al., 2012; Lin, et al., 2019; McCarty, et al., 2000; Yan, et al., 2006), cataract

(Anduze, 1993; Burton, et al., 1997; Cullen, et al., 1994; Delavar, et al., 2018; Delcourt, et al., 2014; Garźon-Chavez, et al., 2018; Suresh, et al., 2022; Varssano, et al., 2017; Wang, et al., 2012; Zhu, et al., 2015), climatic droplet keratopathy (Taylor, 1989; Taylor, et al., 1989; Taylor, et al., 1992)), and designing school outdoor areas with >1,000 lux illumination (Wu, et al., 2018) (reduces myopia). These require minimal technology but substantial behavioral change—community health workers can deliver environmental eye health education alongside existing programs.

6.2.2 Precautionary advice

Climate adaptation strategies must address ocular risks. Preliminary evidence suggests that cold wave warnings should include advice for glaucoma patients (indoor warming, intraocular pressure monitoring) (Zhu, et al., 2023). Heatwave planning should consider that high temperature with high humidity increases allergic conjunctivitis risk (Zhao, et al., 2023), while dry heat exacerbates DED (Madden, et al., 2013; Zhong, et al., 2018). Dust storm forecasting should trigger public health messages about eye protection, as Asian dust storms increase conjunctivitis visits by 9–10% in children (Chien, et al., 2014). Seasonal precipitation patterns affect onchocerciasis transmission—vector control should be timed accordingly (Botto, et al., 2005; Shrestha, et al., 2023; Shrestha, et al., 2022). Besides, occupational protection regulations require updating. Welders remain at risk for keratoconjunctivitis (Yen, et al., 2004) and uveal melanoma (Guénel, et al., 2001) despite awareness; enforced use of proper goggles (not merely face shields) may be prudent. Radiologists and nuclear workers, even at low doses, show cataract risk (Chodick, et al., 2008; De Stefano, et al., 2016; Lian, et al., 2015; Little, et al., 2020; Little, et al., 2018)—lens monitoring should continue.

6.2.3 Speculative proposals

Fluorescent lighting promotes hyperopia and astigmatism (Czepita, et al., 2004; Czepita, et al., 2005; Czepita, et al., 2004; Czepita, et al., 2012); LED lighting with high color temperature induces oxidative stress in RPE (Shen, et al., 2016). It remains to be established whether policies should guide full-spectrum lighting with violet component (shown to slow myopia progression (Torii, et al., 2017; Torii, et al., 2017)). Besides, it remains to be established whether agricultural workers exposed to pesticides (acephate, bromacil associated with retinoblastoma (Thompson, et al., 2022)) need protective eyewear and ventilation. Street sweepers and coal miners have double DED risk (Echieh, et al., 2021; Sun, et al., 2007)—dust control measures and regular ocular surface assessments should be evaluated and established.

7. Future Perspectives & Conclusions

As research into ocular exposome expands, it becomes clear that exposomes play an underestimated yet profound role in ocular health and disease. Although existing studies have characterized the effects of air pollution, weather, light exposure, heavy metals, and radiation on ocular health, numerous emerging exposomes remain underrecognized and insufficiently investigated. The interactive effects of co-occurring multiple exposomes are highly complex and warrant further exploration. Future research should leverage advanced detection technologies and novel methodological approaches to identify and validate exposomic biomarkers at an early stage (Liang, Walker, 2023), conduct well-designed implementation trials, clarify the pathogenic mechanisms of emerging hazards, and generate robust real-world evidence. These efforts will ultimately inform the development of targeted and precision prevention strategies for ocular health.

7.1 Future Perspectives

Urbanization has accelerated ocular exposure to a growing array of emerging risk factors, thereby exerting a profound impact on global eye health. Artificial light at night (ALAN) has been associated with an increased risk of AMD (Kim, et al., 2024). However, the association between ALAN and myopia remains controversial. Future research should be advanced systematically across multiple domains. First, standardized preclinical models are required to unify key parameters including illuminance, exposure timing, duration, and spectral composition, thereby clarifying threshold ranges that distinguish beneficial photobiological effects from harmful circadian disruption (Li, et al., 2026; Nickla, Totonelly, 2016). Second, high-quality prospective cohort studies are warranted, utilizing personal light dosimeters for precise exposome assessment to distinguish between light sources while rigorously controlling for confounders including genetics, outdoor activity, and sleep patterns. Third, research should explore non-linear relationships and gene-environment interactions to identify susceptible populations and critical exposure windows. Finally, by integrating preclinical mechanistic experiments with randomized controlled intervention trials, the field can generate robust evidence to underpin the development of precision public health guidelines.

Artificial intelligence (AI) is poised to revolutionize ocular exposomics by serving as a powerful engine for both high-dimensional data integration and precision prevention. In research settings, deep learning and machine learning algorithms excel at synthesizing multimodal datasets—ranging from high-resolution satellite-derived environmental metrics and wearable sensor data to longitudinal electronic health records and ocular imaging (Graham, et al., 2025). These tools enable the deciphering of complex, non-linear interactions between chemical mixtures and ocular phenotypes, facilitating the identification of novel digital and molecular biomarkers. Regarding clinical prevention, AI-driven predictive modeling allows for real-time, individualized risk stratification and early warning systems, shifting the paradigm from reactive treatment to proactive mitigation of exposome hazards. It is important that add in world model as the AI moves from digital to physical world and the exposome we live in. Furthermore, AI-enhanced automated screening platforms extend the reach of ocular health monitoring to underserved urban areas, bridging the gap between macro-scale environmental surveillance and micro-scale personalized eye care. Ultimately, the synergy between AI and exposome provides a robust framework for establishing evidence-based public health interventions tailored to diverse environmental contexts.

To evolve from association-based observations to robust causal inference, ocular exposomics must integrate rigorous statistical frameworks with multi-dimensional study designs (Bae, et al., 2017). Since RCTs are often ethically unfeasible for exposome hazards, the field should prioritize prospective cohort studies, preclinical study validation, and natural experiments. Prospective cohorts are vital for establishing temporal sequences and minimizing reverse causation. Future research should leverage DAGs for confounding control or utilize PSM and IPW to mimic randomized conditions (Feeney, et al., 2025). Mechanistic studies, particularly those using inhalation-based protocols, remain critical to satisfy the Bradford Hill criterion of biological plausibility. Furthermore, natural experiments using Regression Discontinuity or Difference-in-Differences designs offer underutilized opportunities to evaluate policy interventions as quasi-randomized trials (Wang, et al., 2024). Moving forward, the field must overcome three key limitations. First, establishing standardized imaging phenotypes is imperative for cross-study comparability. Second, researchers must adopt dynamic exposome assessments to capture longitudinal shifts in lifestyle and residence, reducing misclassification bias. Third, adopting interpretable mixture analysis is essential to unravel the "cocktail effects" of real-world co-exposomes. Addressing these gaps will provide the credible evidence needed to inform precision public health policies for exposome-related ocular diseases.

7.2 Conclusions

In summary, the transition from conventional environmental epidemiology to ocular exposomics represents a paradigm shift in understanding the complex etiology of vision-threatening conditions. By shifting the focus from isolated pollutants to a comprehensive, life-course assessment of cumulative exposomes, this field provides a robust framework for identifying novel exposome stressors and their synergistic interactions. Ocular exposomics serves as a critical bridge connecting exposome science with precision eye health. Translating high-dimensional exposomic evidence into implementable preventive strategies enables the formulation of targeted public health policies and personalized interventions. Amid the growing global burden of exposome induced ocular diseases, integrating exposome approaches into clinical practice will be indispensable for preserving visual function in a rapidly changing world.

Declarations

Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

All data used for this review are provided in the supplementary materials.

Code Availability

All code used for this review are provided in the supplementary materials.

Ethics

Not applicable.

Declaration of Generative AI Use

During the preparation of this work, the authors used DeepSeek to assist in editing the manuscript for readability in English. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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Figure legends

Figure 1. Framework for the effects, mechanisms and protection of exposomes on ocular diseases.

The core exposomes included in this paper include air pollution, climate conditions, light, ionizing radiation, etc. The main ocular diseases caused by these factors, organized in anatomical order, are ocular surface diseases (dry eye disease, keratitis, conjunctivitis, pterygium), cataract, refractive error, glaucoma, and retinal diseases (age-related macular degeneration, diabetic retinopathy, etc.). This paper introduces from two aspects: evidence and controversies. The core shared mechanisms through which exposomes act on the eye include oxidative stress, cell response and inflammatory reaction, with extensive crosstalk. The paper also introduces methods of causal inference in the context of exposure-related eye diseases and puts forward suggestions for future research. Eventually, this review summarizes targeted preventive measures, which require joint efforts from both patients and clinicians. Meanwhile, policy support is also needed in aspects including air quality monitoring, urban planning and greening, climate early warning, and occupational protection. Created in BioRender (https://BioRender.com).

Figure 2. Overview of exposome and eye disease.

This figure summarizes the current state of research on the key diseases and exposomes highlighted in this paper. The size of each circle represents the number of studies (both clinical and preclinical) investigating different diseases under a specific exposome. Based on the impact of exposome on ocular diseases, the effects are categorized as either beneficial or harmful, with color gradients indicating the strength of the evidence (purple #A020F0 to blue #0000FF indicate protective factors, white #FFFFFF represents weak evidence, and the color shifts from yellow #FFFF00 to red #FF0000 as risk factors increase). Our scoring criteria are as follows: for clinical studies, evaluation is based on two dimensions, study design and sample size (prospective studies receive 3 points, while retrospective studies receive 1 point; sample sizes over 10,000 earn 3 points, those between 1,000 and 10,000 earn 2 points, and those under 1,000 earn 1 point); for preclinical studies, the primary consideration is whether a complete mechanism is elucidated (6 points are awarded if the mechanism is revealed, whereas 2 points are given if only phenotypic observations are made in animal or cell models). The total score is the sum of the clinical and preclinical scores. As shown in the figure, air pollution has received extensive attention, while conditions such as cataracts and refractive errors appear to be more closely linked to light exposure. Furthermore, the impact of exposome like urbanization varies significantly across different diseases. This figure was generated using R version 4.5.0.

Figure 3. Core mechanisms of exposomes and their interaction with eye diseases.
A multitude of shared mechanisms are involved in the process by which exposomes induce ocular diseases. $PM_{2.5}$, cigarette smoke, blue light, UV and ionizing radiation can directly or indirectly induce the generation of ROS. Initially, the cellular antioxidant mechanism can be activated to a certain extent, but once exceeding the compensatory limit, consequences such as lipid peroxidation will be triggered, leading to oxidative stress and extensive cellular damage. In terms of cellular responses, cigarette smoke, blue light and other factors can lead to the production of caspase and initiate apoptosis; induce pyroptosis by forming membrane pores via GSDMD; disrupt cell membranes through extensive lipid peroxidation to cause ferroptosis; and also trigger uncontrolled proliferation via the MAPK and NF-κB signaling pathways. Exposomes such as heavy metals can directly initiate inflammatory responses, induce the NLRP3 inflammasome, and ultimately produce and release inflammatory factors including IL-6 and IL-8. The occurrence of many diseases is also associated with abnormal production and degradation of ECM, neovascularization, and infiltration of immune cells. There are numerous interactions among these mechanisms: for example, ROS can initiate inflammatory responses, immune cell infiltration can promote inflammatory responses, and inflammatory responses can lead to neovascularization, and so on. Created in BioRender (https://BioRender.com).
Abbreviations: ECM, extracellular matrix; $PM_{2.5}$, fine particulate matter < 2.5 μm in diameter; MMP, matrix metalloproteinase; SVCT2, sodium vitamin C transporter 2; VEGF, vascular endothelial growth factor; GSDMD, gasdermin D; YAP, Yes-associated protein; SOD, superoxide dismutase; ROS, reactive oxygen species; NLRP3, NOD-like receptor thermal protein domain associated protein 3; IL-1β, interleukin 1 beta; TNF-α,

tumor necrosis factor alpha; GPX4, glutathione peroxidase 4; GSH, reduced glutathione; GSSG, oxidized glutathione; GSR, glutathione-disulfide reductase; NADPH, nicotinamide adenine dinucleotide phosphate hydrogen.

Figure 4. Causal inference framework in observational studies.
The framework is organized into three domains: (1) What is Causality – Bradford Hill criteria (e.g., temporality, dose–response, biological plausibility) and methodological approaches (directed acyclic graphs, propensity score matching, inverse probability weighting, instrumental variables); (2) Evidence Generation – highlighting study designs including prospective cohort studies (human, longitudinal), preclinical studies (animal models), and natural experiments (policy-driven exposure variation); and (3) Limitations and Future Directions – emphasizing the need for high-quality imaging (color fundus photography, optical coherence tomography), repeated measures of exposure and outcome, and investigation of mixture exposomes (e.g., $PM_{2.5}$, PFAS, UFP, EDC) in causal pathways of ocular diseases. Created in BioRender (https://BioRender.com).
Abbreviations: UFP, ultrafine particle; $PM_{2.5}$, particulate matter < 2.5 μm in diameter; PFAS, per- and polyfluoroalkyl substances; EDC, endocrine disrupting chemicals; O_3, ozone.