TFOS Lifestyle Report: Impact of environmental conditions on the ocular surface

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ABSTRACT

Environmental risk factors that have an impact on the ocular surface were reviewed and associations with age and sex, race/ethnicity, geographical area, seasonality, prevalence and possible interactions between risk factors are reviewed.

Environmental factors can be (a) climate-related: temperature, humidity, wind speed, altitude, dew point, ultraviolet light, and allergen or (b) outdoor and indoor pollution: gases, particulate matter, and other sources of airborne pollutants. Temperature affects ocular surface homeostasis directly and indirectly, precipitating ocular surface diseases and/or symptoms, including trachoma. Humidity is negatively associated with dry eye disease. There is little data on wind speed and dewpoint. High altitude and ultraviolet light exposure are associated with pterygium, ocular surface degenerations and neoplastic disease. Pollution is associated with dry eye disease and conjunctivitis. Primary Sjögren syndrome is associated with exposure to chemical solvents. Living within a potential zone of active volcanic eruption is associated with eye irritation. Indoor pollution, "sick" building or house can also be associated with eye irritation. Most ocular surface conditions are multifactorial, and several environmental factors may contribute to specific diseases.

A systematic review was conducted to answer the following research question: "What are the associations between outdoor environment pollution and signs or symptoms of dry eye disease in humans?" Dry eye disease is associated with air pollution (from NO_2) and soil pollution (from chromium), but not from air pollution from CO or PM_{10}.

Future research should adequately account for confounders, follow up over time, and report results separately for ocular surface findings, including signs and symptoms.

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1. Introduction

Climate change and modern living modify weather patterns and the distribution and types of airborne particles and allergens in our atmosphere. These changes affect our exposure to air pollutants and other emissions. Local temperature, precipitation levels and distribution, air composition, wind speed and direction may influence atmospheric chemical processes, along with interactions on local and global-scale environments [1]. A wealth of evidence has been collected on the impact of air pollution on health [1,2]. Exposure to particulate matter, chemicals and gases can exacerbate chronic diseases, alter immune responses, trigger inflammation, lead to premature death, and contribute to a myriad of diseases. Indeed, environmental issues have gained increasing relevance in the context of climate change. Environmental illness can reduce work capacity, aggravate existing conditions, and negatively impact on quality of life [3–5]. This report is part of the Tear Film & Ocular Surface Society (TFOS; www.tearfilm.org) Workshop, entitled 'A Lifestyle Epidemic: Ocular Surface Disease,' which was undertaken to establish the direct and indirect impacts that everyday lifestyle choices and challenges have on ocular surface health."

1.1. Environmental conditions

The environment comprises of a broad range of conditions in constant and direct contact with the ocular surface. Environmental conditions encompass factors, such as sunlight, temperature, humidity, along with different types of pollutants, that include particulate matter, harmful gases, and aerosols [6] (Fig. 1).

Ocular surface homeostasis relies on an integrated, functional system that involves healthy corneal and conjunctival epithelial layers, tightly regulated tear film composition and stability, ocular surface innervation, adnexal glands, and blink frequency. Environmental hazards can disrupt the integrity of this ocular surface system, triggering symptoms and diseases [7,8] and multiple factors may contribute to certain ocular surface diseases. Distinct environmental conditions may increase risk and/or aggravate certain conditions, such as dry eye disease [3] which is readily impacted by exposure to certain climate factors [9], and ocular surface irregularities seen in pterygium or inflammatory cascades triggered in allergy. Indoor and outdoor environments may be somewhat linked but may also differ due local exposures, such as indoor occupational chemical pollutants or effects of air conditioning, and consequently the opportunities for ocular surface exposure are broad (Fig. 2).

1.2. The subcommittee report scope

This report aims to review evidence of environmental risk factors that have an impact on the ocular surface. Environmental conditions were divided into two groups: (a) climate-related: temperature, humidity, wind speed, altitude, dew point, ultraviolet radiation, and allergens and (b) outdoor and indoor pollution: gases, particulate matter, and other sources of airborne pollutants. Since many risk factors in daily living are not independent of each other, such as temperature and humidity, exposing the role of each risk factor can be challenging and often must be inferred.

Most ocular surface diseases are multifactorial and, even when related to environmental hazards, there is frequently more than one associated factor. Thus, a third section broadly discusses the role of environmental risk factors on specific ocular surface diseases. For the purpose of this Workshop, the 'Ocular Surface' is defined as the cornea, limbus, conjunctiva, eyelids and eyelashes, lacrimal apparatus and tear film, along with their associated glands and muscular, vascular, lymphatic and neural support. 'Ocular Surface Disease' includes established diseases affecting any of the listed structures, as well as etiologically related perturbations and responses associated with these diseases, including dry eye disease, allergy, pterygium, chemical and thermal exposures, infection, and degenerative and neoplastic ocular surface diseases. Where evidence was available, correlations with age and sex, race/ethnicity, geographical areas (rural vs urban), seasonality, prevalence and possible interactions among risk factors have been discussed.

1.3. Evidence search

The evidence summarized in this report was derived from two different strategies. A narrative review provides a broad overview of the risk factors and OSDs associated with environmental exposures. The quality of evidence from each study was considered and the report aimed to include reliable evidence based on high-quality systematic reviews, wherever available [10]. This was achieved by the Evidence Quality Subcommittee providing a comprehensive database of appraised systematic review evidence, judged to be of potential relevance to the report [11]. A systematic review was also conducted to answer the following research question that had been prioritized by the subcommittee: "What are the associations between outdoor environment pollution and dry eye disease, symptoms, and signs in humans?" Relevant literature was systematically identified, selected, appraised, and

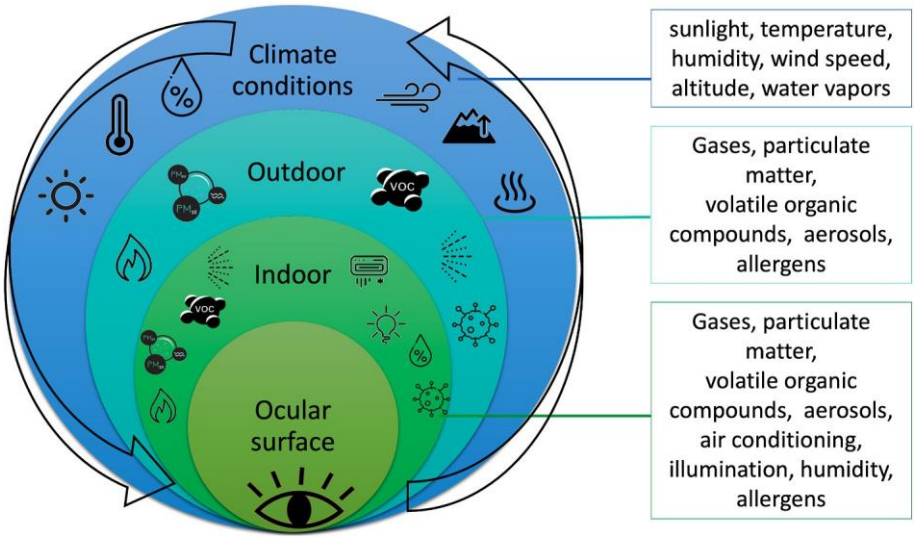

Fig. 1. Environmental conditions: climate factors and pollutants.

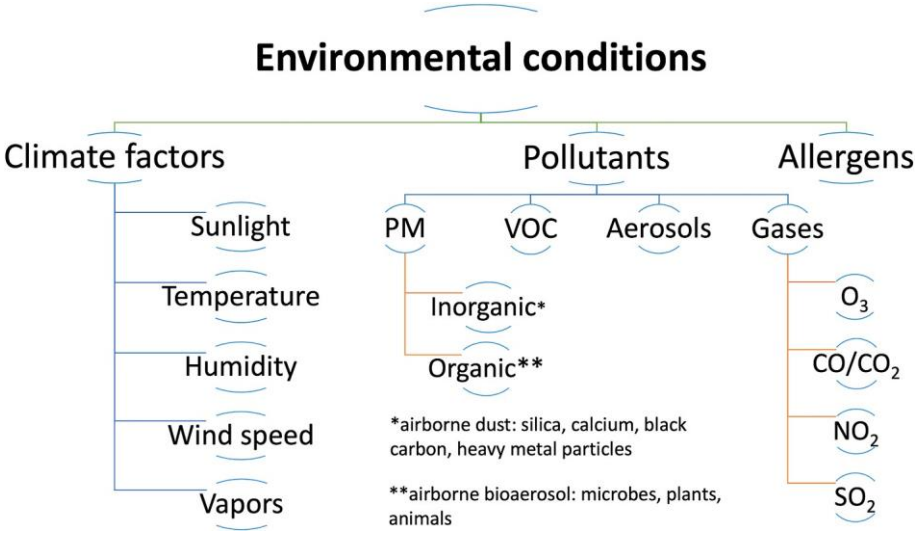

Fig. 2. Environmental conditions affecting the ocular surface.
PM: particulate matter; VOC: volatile organic compound; O_3: ozone; CO/CO_2: carbon monoxide/carbon dioxide; NO_2: nitrogen dioxide; SO_2: sulfur dioxide.

synthesized. To promote transparency in the process, a protocol for the systematic review was prospectively submitted to PROSPERO, an international database of prospectively registered systematic reviews (CRD42021297238).

1.4. *Repositories and data resources*

Meteorological and air pollution data in epidemiological studies were derived from a variety of sources. Broadly, these sources include satellite data [12,13], air quality monitors [14–21], statistical model estimations [22,23], and national meteorological/pollution monitoring/environmental protection centers [24–34]. Most epidemiological studies have used the latter method to obtain air quality data; a summary of examples of those studies, along with the pollutants monitored, are summarized in Table 1.

There are also open-access, publicly available air quality data sets and repositories that provide real-time and or historic data on various pollutants around the world (e.g., OpenAQ, https://openaq.org; World Air Quality Index Project, https://waqi.info).

1.5. *Challenges*

One of the major challenges for the evaluation of the studies included herein was the lack of clear definitions of diseases and classification systems for environmental hazards. In evaluating risk factors, it was found by the subcommittee that many published studies, but a limited number of well-designed population-based studies exist. Most studies were of case-control or cross-sectional designs, with small sample sizes. The Evidence Quality Subcommittee (EQS) provided a comprehensive list of Level 1 evidence for each subtopic in this report, which was evaluated and included whenever possible. Unfortunately, there remains a lack of robust and consistent studies and many areas of the globe are devoid of information regarding potential associations between environmental exposures and ocular surface diseases. Such risk factors have been neither equally substantiated nor comparably evaluated by the different studies included in this report. Of note, there is some overlap between the content covered by this subcommittee and other subcommittees in this workshop. For instance, digital environment and indoor exposure/sick building syndrome, cosmetics and allergy, societal challenges and occupation and outdoor exposure, lifestyle challenges and smoking.

2. Environmental conditions

2.1. *Climate risk factors*

There has been increasing interest in the effects of climate on general and ocular diseases. This reflects concerns about climate change as well as improvements in the use of climate information to better understand disease mechanisms and develop mitigation strategies. Many climate factors vary in time and space and might be considered and adjusted in the study designs to avoid confounders related to the social or environmental context. Associations between meteorological variables and health are likely to depend on local characteristics and have also evolved over time.

2.1.1. *Temperature*

Global variations in average temperatures are largely due to latitude, continentality, seasonality, solar radiation, ocean currents and wind speed. Temperature can affect ocular surface homeostasis and directly and indirectly precipitate distinct forms of ocular surface diseases and symptoms.

Trachoma is a neglected tropical disease caused by *Chlamydia trachomatis* and is considered one of the main causes of infectious corneal blindness. Trachoma is an important cause of chronic ocular discomfort in over 57 endemic countries, mainly in Africa. Both active and inactive stages involve the ocular surface, ranging from acute follicular conjunctivitis and inflammation to scarring, trichiasis and corneal opacity. A high air temperature is a common denominator in the transmission of acute trachoma, as the distribution of eye-seeking flies may be related to high air temperature. A systematic review quantified the association between climate factors and acute or chronic trachoma. This review highlights the lack of high-quality observational evidence studies exploring these potential associations and the poor quality of the climate data. There is very little information on the role of temperature on the distribution or prevalence of active trachoma, and even less evidence regarding chronic trachoma and blindness. Overall, the prevalence of trachoma appears to be higher in semi-arid Savannah areas where the climate is characterized by a winter dry season, short rainy summer season, and high year-round temperatures [36].

Extremely high or low temperatures in the outdoor and indoor environments are associated with dry eye disease [7]. A monitored cooler indoor environment between 22.2 and 25.6 °C was used in a crossover study evaluating indoor exposure and ocular and respiratory symptoms. A 1 °C decrease in temperature improved eye dryness symptom report in

Table 1
Summary of air pollution and meteorological data sources.

Study	Country	Data source	Pollutants and environmental parameters
Fu *et al.* 2017. Air pollution and outpatient visits for conjunctivitis: A case-crossover study in Hangzhou, China [35]	China	Environmental Protection Department of Zhejiang Province	$PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, O_3
		Meteorological Administration of Zhejiang Province	Temperature, relative humidity, atmospheric pressure
Szyszkowicz *et al.* 2016. Air pollution and emergency department visits for conjunctivitis: a case-crossover study [28]	Canada	Environment Canada's National Air Pollution Surveillance Program	O_3, NO_2, $PM_{2.5}$, SO_2
		Environment Canada	Temperature, relative humidity
Kim *et al.* 2020. Different adverse effects of air pollutants on dry eye disease: Ozone, $PM_{2.5}$, and PM_{10} [29]	South Korea	Korean Ministry of Environment	O_3, $PM_{2.5}$, PM_{10}
		–	Humidity
Lu *et al.* 2019. Short-term exposure to air pollution and conjunctivitis outpatient visits: A multi-city study in China [30]	China	China National Environmental Monitoring Center	$PM_{2.5}$, PM_{10}, NO_2, SO_2, O_3
		China Meteorological Administration	Temperature, relative humidity, windspeed
Malerbi *et al.* 2012. Ambient levels of air pollution induce clinical worsening of blepharitis [31]	Brazil	Companhia de Tecnologia de Saneamento Ambiental de São Paulo	CO, PM10, NO2
		Companhia de Tecnologia de Saneamento Ambiental de São Paulo	Temperature, relative humidity
Mu *et al.* 2021. Associations Between Air Pollution Exposure and Daily Pediatric Outpatient Visits for Dry Eye Disease: A Time-Series Study in Shenzhen, China [31]	China	Shenzhen Municipal Ecological Environmental Bureau	SO_2, CO, NO_2, O_3, $PM_{2.5}$, PM_{10}
		Meteorological Bureau of the Shenzhen Municipality	Temperature, relative humidity
Nucci *et al.* 2017. Pediatric conjunctivitis and air pollution	Italy	Regional Environmental Protection Agency of Lombardia	PM_{10}, $PM_{2.5}$
exposure: prospective observational study [32]		N/A	N/A
Bao *et al.* 2021. Association between short-term exposure to ambient nitrogen dioxide and the risk of conjunctivitis in Hefei, China: A time-series analysis [34]	China	Anhui Provincial Environmental Protection Department	NO_2, SO_2, CO, $PM_{2.5}$, PM_{10}, O_3
		Anhui Provincial Meteorological Administration	Temperature, relative humidity
Berg *et al.* 2020. Climatic and environmental c orrelates of dry eye disease severity: a report from the Dry Eye Assessment and Management study [35]	U.S.	National Centers for Environmental Information	O_3, CO, NO_2, NO_x, NO_y, SO_2, $PM_{2.5}$
		National Centers for Environmental Information	Temperature, relative humidity, windspeed, dewpoint
Kim *et al.* 2019. Short-term effects of ground-level ozone in patients with dry eye disease: a prospective clinical study [36]	South Korea	Korea Ministry of the Environment	O_3
		N/A	N/A
Chang *et al.* 2012. Relationship between air pollution and outpatient visits for nonspecific conjunctivitis [37]	Taiwan	Taiwan Environmental Protection Administration	PM_{10}, $PM_{2.5}$, NO_2, SO_2, O_3, CO
		Taiwan Environmental Protection Administration	Temperature, rainfall, relative humidity
Bourcier *et al.* 2003. Effects of air pollution and climatic conditions on the frequency of ophthalmological emergency examinations [38]	France	AIRPARIF	NO, NO_2, O_3, SO_2, PM_{10}
		Meteo-France	Temperature, humidity, atmospheric pressure, windspeed and strength
Mo *et al.l* 2019. Impacts of air pollution on dry eye disease among residents in Hangzhou, China: A case-crossover study [39]	China	Environmental Protection Department of Zhejiang Province	$PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, O_3
		Meteorological Administration of Zhejiang Province	Temperature, humidity, atmospheric pressure
Zhong *et al.* 2018. Association between dry eye disease, air pollution and weather changes in Taiwa. [40]	Taiwan	Taiwan Air Quality Network	CO, NO_2, O_3, $PM_{2.5}$, PM_{10}, SO_2
		Taiwan Air Quality Network	Temperature, relative humidity
Hong *et al.* 2016. Ambient air pollution, weather changes and outpatient visits for allergic conjunctivitis: A retrospective registry study [41]	China	Shanghai Key Laboratory of Meteorology and Health	PM_{10}, $PM_{2.5}$, NO_2, O_3, SO_2
		Shanghai Key Laboratory of Meteorology and Health	Temperature, relative humidity, wind speed
Li *et al.* 2016. The effect of air pollution on the occurrence of nonspecific conjunctivitis [42]	China	State Environmental Protection Administration of China	PM_{10}, $PM_{2.5}$, NO_2, SO_2, O_3, CO
		N/A	N/A
Mimura *et al.* 2014. Airborne particulate matter (PM2. 5) and the prevalence of allergic conjunctivitis in Japan [43]	Japan	Japan Ministry of the Environment	$PM_{2.5}$ Ox, NO, NO_2, NO_x, CO, CH_4, non methane hydrocarbons, total hydrocarbons
		Japan Meteorological Agency	Temperature, wind speed, humidity
Galor *et al.* 2014. Environmental factors affect the risk of dry eye syndrome in a United States veteran population [24]	U.S.	National Aeronautics and Space Administration	Aerosol optical depth (non-specific)
		National Climatic Data Center	Temperature, wind speed, relative humidity, visibility, atmospheric pressure

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Table 1 (*continued*)

Study	Country	Data source	Pollutants and environmental parameters
Yu *et al.* 2019. Air pollutants are associated with dry eye disease in urban ophthalmic outpatients: a prevalence study in China [44]	China	School of Environment, Tsinghua University –	CO, NO_2, O_3, PM_{10}, $PM_{2.5}$, SO_2 Humidity, temperature, atmospheric pressure
Aik *et al.* 2020. The burden of acute conjunctivitis attributable to ambient particulate matter pollution in Singapore and its exacerbation during South-East Asian haze episodes [45]	Singapore	National Environment Agency, Singapore Meteorological Services Singapore	SO_2, NO_2, $PM_{2.5}$, PM_{10}, O_3, CO. Temperature, relative humidity, rainfall
Cakmak *et al.* 2002. Effect of airborne allergens on emergency visits by children for conjunctivitis and rhinitis [46]	Canada	Environment Canada Environment Canada	O_3, NO_2, SO_2, coefficient of haze, sulfates Temperature, humidity, atmospheric pressure
Yang, C.Y., 2006. Effects of Asian dust storm events on daily clinical visits for conjunctivitis in Taipei, Taiwan [47]	Taiwan	Taiwanese Environmental Protection Administration Central Weather Bureau's Taipei Observatory	SO_2, NO_2, CO, O_3, PM_{10} Temperature, humidity
Hwang *et al.* 2016. Potential importance of ozone in the association between outdoor air pollution and dry eye disease in South Korea [48]	South Korea	Korea Ministry of Environment –	PM_{10}, O_3, NO_2, SO_2. Humidity

PM: particulate matter; O_3: ozone; CO: carbon monoxide; NO_2: nitrogen dioxide; SO_2: sulfur dioxide.

19% of participants [9]. In a human study using a controlled environment chamber, the mean tear evaporation rate was increased from 0.056 ml/min at 5 °C to 0.17 ml/min at 25 °C, however, the mean non-invasive tear break-up time also increased significantly from 7.3 sec at 5 °C to 12.4 sec at 25 °C and lipid layer thickness was also significantly lower at 5 °C and markedly higher at 20 and 25 °C [37]. The ocular surface temperature was reduced as the ambient temperature decreased, with a mean ocular surface temperature reduction of 4 °C as ambient temperature decreased from 25 °C to 5 °C [37]. Low corneal temperature has been associated with dryness symptoms and signs and onset of subjective discomfort sensation onset is reported earlier in patients with dry eye disease compared with controls after eye opening [38]. A temperature near 40 °C can change the properties of meibomian gland lipids and disrupt the tear film. In a South Korean population, diagnosis of dry eye disease was positively associated with outdoor temperature (1 °C increase in temperature was associated with an Odds Ratio (OR) of 1.076; 95% Confidence Interval (CI) 1.009–1.148) [39].

Akin to other allergic conditions such as asthma and rhinitis, temperature variations may be implicated in allergic conjunctivitis. By comparing meteorological data in a cohort of patients with allergic conjunctivitis in the USA, the odds of a health care visit for allergic conjunctivitis were statistically significantly associated with temperature (OR 1.028, $p < .001$), as well as temperature-variations (OR 1.054, $p < 0.01$), and temperature-humidity interaction (OR 1.0003, $p < 0.01$) [40]. However, the magnitudes of these estimates are small.

A cool air current lowers the ocular surface temperature [41]. Increased ocular surface temperature is associated with ocular blood flow from ocular surface inflammation [42]. A positive correlation between the room temperature and ocular surface temperature has also been reported [43,44].

2.1.2. Humidity

Multiple logistic regression analyses in South Korean population-based studies have revealed a negative association between relative humidity and risk of symptoms and diagnosis of dry eye disease [39]. Among a cohort of office workers, self-reported ocular dryness, irritation, and itching severity scores were lower while working in a higher indoor humidity (30–40%) environment than in "natural" indoor humidity (20–30%) [45]. Healthy subjects exposed to a controlled environment chamber with a constant ambient temperature of 21 °C and relative humidity ranging from normal to desiccating environment (40% versus 5% relative humidity), found a significant worsening in dry eye symptoms and signs (non-invasive tear break-up time, lipid layer thickness and tear production) after exposure to the desiccating environment [46]. Low relative humidity is associated with increased ocular irritation and alteration of the precorneal tear film, and these effects may be exacerbated during visual display unit work [47]. Moisture goggles can increase periocular humidity. A study compared commercially available uniformed moisture chamber spectacles to 3D personalized goggles. The mean periocular humidity was 37.7 ± 9.0% and 52.1 ± 3.0% after applying commercial and 3D personalized goggles, respectively although the mean relative humidity of the external environment was 15.7 ± 1.2% [48]. Increased periocular humidity using moisture goggles increased ocular comfort and decreased tear evaporation rate in patients with dry eye disease [48,49]. Another US study showed that relative humidity significantly impacts tear film evaporation regardless of the presence of dry eye disease, and likely accounts for the aggravation of dryness symptoms reported in conditions of low humidity such as deserts, airplane cabins, and dry seasons [50]. Caution should be taken in the interpretation of Schirmer tests results because of a clear decrease in wetting length as relative humidity of the environment is reduced [51]. Conversely, caution in interpretation is warranted as increased humidity has been associated with an increase in the number of microbial colonies, and individuals with higher microbial counts in the home exhibited more severe meibomian gland dropout, similarly leading to symptoms and evaporative dry eye disease [52].

In a US study, the risk of allergic conjunctivitis was negatively associated with relative humidity (OR 0.998, $p < 0.001$), and was positively associated with increased temperature (OR 1.028, $p < .001$), SD of temperature (OR 1.054, $p < 0.01$), and temperature-relative humidity interaction (OR 1.0003, $p < 0.01$). Local climate data were obtained from the National Climatic Data Center, comparing seasonality and geographical localization. The association between the environment and allergic conjunctivitis relies on the fact that such conditions facilitate air particulate and aeroallergen dispersion and tear film instability [40]. A South Korean study reported that the rate of unspecified conjunctivitis in outpatients was increased as temperature and humidity were increased [53]. A cross-sectional hospital-based study including 2,488,819 patients in India, reported that the environmental parameters of humidity ($r^2 = 0.65$, $p < 0.001$), and wind speed ($r^2 = 0.56$, $p < 0.01$) were significantly negatively correlated with the temporal pattern of adenoviral-presumed epidemic keratoconjunctivitis in the population, whereas there was no significant correlation with temperature [54]. A South Korean population-based, cross-sectional study found that pterygium was not related to humidity [55].

2.1.3. Wind speed

The local evaporation-driven tear film rupture hypothesis was investigated in a one-dimensional model for thinning of the aqueous

component of the corneal tear film, based on elevated evaporation at the anterior surface and osmotic water influx at the posterior surface [56]. Higher wind speeds reduced the mass-transfer resistance in the air phase and led to higher evaporation rates [56]. The model predicted the effects of various perpendicularly oriented wind speeds of 0.1, 0.3, 1 and 10 m/s on the cornea that represented sequentially "sitting/reading", "indoor working", "walking", and "cycling", respectively. The model concluded that wind speed played an important role in tear film rupture time, especially at higher speeds. During minimal activity, tear rupture could be averted. This proposed model study reported that predicted roles of wind speed and relative humidity on tear film stability seemed to be comparable to clinical observations [56].

Changes in weather conditions have a causal relationship with the volume of patients or the incidence of ocular diseases encountered in hospital outpatient clinics or emergency wards [57]. A retrospective observational study investigated the incidence of ocular diseases and correlations with weather data, reporting a positive correlation between the weekly total patient number, the incidence of corneal foreign bodies and conjunctivitis and the meteorological data. The positive correlations were statistically significant for the weekly sunshine duration and the weekly average temperature, but no correlation was found for the weekly average of any disease with wind speed in that study [56]. The retrospective nature and lack of a longer observational period in this study have been acknowledged as limitations of the study which might have resulted in the lack of association between wind speed and any ocular disease. Conceivably, under extremely windy conditions, people are more likely to stay indoors. As the emergency department site in this study, was placed in a distant location and the ocular diseases evaluated were not life-threatening conditions, some discomfort could have been tolerated, avoiding the need to visit the hospital [56].

Sporadic case reports have identified corneal frostbite and desiccation keratitis in ultra-marathon runners with prolonged exposure to high-speed winds and sub-zero temperatures [58]. Corneal freezing has also been described in military free-fall parachutists exposed to freezing temperatures and high winds in a survey study of 394 subjects (out of 1, 200 mailed questionnaires). Despite a low response rate (32%) in this study, 79% of the respondents had lost their protective eyewear during the free fall and 69% of these subjects experienced ocular symptoms with a 30-fold increase in the duration of ocular symptoms in subzero temperatures and high winds compared with the same high wind speeds and above zero temperatures. Contact lens wear has no protective effect against extreme wind speeds of free-fall nor did a previous history of PRK have any detrimental effects [59].

The "Hamburg Weather Study" was initiated to assess the impact of air pressure and wind speed on the refractive and visual outcome of LASIK in myopic eyes undergoing surgery between 2010 and 2012 in Germany. The study included 1,052 consecutive first eye treatments in myopic patients during two meteorologically different seasons. No clinically relevant correlation between wind speed or air pressure and the overall outcome of LASIK were found. Interestingly, moderate and high wind speeds both resulted in statistically better postoperative spherical equivalent. The report assumed higher wind speed was usually related to uncomfortable weather conditions which might have forced indoor activity in the study population [60]. Lack of higher order aberration data, data beyond the first postoperative months and data on risk factors such as smoking status were recognized as the main limitations of the Hamburg study.

An incidence rate prediction model for dry eye disease was developed using air pollutants (PM_{10}, NO_2, SO_2, O_3, and CO), meteorological factors (temperature, humidity, and wind speed), population prevalence rate for dry eye disease, and clinical data for South Korea. Wind speed was positively correlated with PM_{10} and negatively correlated with temperature. While relative humidity was observed to have a strong association with the incidence of dry eye disease, no such association with wind speed was found [61].

An epidemiological study from Taiwan noted a higher occurrence of corneal ulcers in onion harvesters in Southern Taiwan, in a monsoon area with prevailing gusty winds [62]. Mannequin and guinea pig eye exposure studies found that wind velocity was significantly related to the occurrence of corneal injury from soil and onion particles. The study suggested that a wind velocity threshold of 7 m/sec was a cut-off threshold for work safety, and if the wind speed exceeded this threshold, harvesting activities should not be permitted or use of eye goggles would be recommended for the protection of onion harvesters [62].

A retrospective chart review study aimed to define the type of ophthalmology consultations immediately after Hurricane Harvey in Houston area between September–October 2017, compared to the same time interval in the previous year [63]. Infectious conjunctival and corneal diagnoses rose dramatically, increasing over 150% from 8 to 22, with an odds ratio of 4.43. In comparison, the odds ratio for traumatic eye diagnoses was 2.13. The majority of category 4 Hurricane Harvey's damage appeared to be related to flooding, rather than wind speed. The study suggested that flooding might correlate more closely with infectious eye diseases, while high wind speeds may cause more eye trauma but the need for further studies spanning over a longer follow up period was deemed essential [63]. A retrospective database study was conducted, based on the experience of field hospitals, comparing the ocular morbidity in the 2010 Haiti and 2015 Nepal earthquakes with the ocular morbidity of the 2013 Philippines Typhoon [64]. The Philippines typhoon had the least disaster-related diagnoses (10.4% of the study population) which included eyelid/eyebrow laceration, orbital fracture, exposure keratitis, keratoconjunctival foreign body (the most common diagnoses), subconjunctival hemorrhage and blunt trauma [64].

The effect of moist chamber spectacle wear on the ocular surface and tear functions was investigated in a controlled wind exposure environment. In this study, 14 participants with dry eye disease, were exposed to the wind at 7 m/sec for 10 min, without spectacles, with conventional spectacles and with moist chamber spectacle wear [48]. Mean dryness scores after wind exposure were significantly higher, as were tear evaporation rate and blink rate, when no spectacles were worn or when conventional spectacles with no moist chambers were worn, than with moist spectacle wear. There were no significant tear evaporation changes before and after moist chamber spectacle wear. The study concluded that moist chamber spectacles had favorable effects on dryness symptoms, tear stability, and blink rate in windy environmental conditions [48].

A controlled adverse chamber environment study evaluated healthy participants with no previous history of contact lens wear, comparing hydrogel and silicone hydrogel contact lenses following exposure to 20 min of fan wind of 1.2 m/sec for 20 min at 18 °C and 18% relative humidity. Tear instability, higher tear osmolarity, and increased tear evaporation with marked dry eye and visual disturbance symptoms were observed with non-adapted hydrogel soft contact lenses wear, suggesting that silicone hydrogel contact lenses may be more suitable for those living and working in cool, low-humidity, and windy environments [65].

The current literature provides some evidence about the effect of wind speed on ocular surface diseases, but most studies are limited to case reports or retrospective chart reviews which are limited by their retrospective nature, lack of controls for risk factors for ocular morbidity or for co-existing ocular morbidities.

2.1.4. Dew point

The dew point is defined as the temperature in which air must be cooled to reach maximum water saturation (i.e., 100% relative humidity). Since the dew point metric does not depend on air temperature, the dew point provides a more absolute measure of water vapor content in the air than compared to the relative humidity metric. While numerous studies have examined the relationship between relative humidity and OSD, only one study examined the impact of dew point on signs and symptoms. In this study, 535 participants from five distinct climates

were recruited and examined for the relationship between weather, climate, pollutants on Ocular Surface Disease Index questionnaire, tear film break-up time, and corneal and conjunctival staining. These observations were made at baseline, 3 months, 6 months, and 12 months. Dew point was positively correlated only with tear break-up time, suggesting that a higher dewpoint may be a protective factor for tear film stability [34].

2.1.5. Altitude

Altitude over 3,000 m is well known in the medical literature to cause biological effects on the human body. High altitude conditions are hypobaric, with strong UVR and a high number of sunshine hours (average 3,400 h per year). A high altitude environment is characterized by low air pressure, hypoxia, low oxygen saturation, dry and cold air, prolonged and increased exposure to sunlight, solar infrared light and ultraviolet radiation (which could be reflected off snow), and wind and dust [66,67]. At high altitude, the ultraviolet radiation impact is greater than at low altitudes, damaging almost all eye tissues from lids, cornea and conjunctiva to lens and retina [68,69]. The most common ocular surface disease related to altitude is pterygium, while cataract is the most common eye disease and the leading cause of reversible blindness in high altitude areas [70,71]. High altitude, similar to other environmental conditions, has short- and long-term effects on the ocular surface, including short-term effects on corneal thickness, and increased risk of photokeratitis, as well as long-term effects such as high risk of pterygium and dry eye disease [71,72].

Tibet has an average elevation approximately 14,370 feet (4,380 m) above sea level. In a population-based study in Tibet including 1,319 individuals, pterygium was the most frequently observed eye problem. Farmers and construction workers had a significantly higher prevalence (36.1% and 28.6%, respectively) compared to those who spend daytime hours indoors (7.5%), students (6.8%) and teachers (6.8%), indicating an effect of outdoor conditions [73]. Of note, the general prevalence of pterygium in this study was 10.1%, higher than the 5.2% that has been reported in the central part of India [74].

A Mongolian population survey performed in Henan, a high-altitude city in China, selected 2,486 participant and found an overall prevalence of pterygium of 17.9%, and suggested a relationship between exposure to sunlight and a high-altitude plateau climate [75].

Some preexisting conditions may predispose the ocular surface to complications or disease exacerbation in the hostile environment of high altitude, such as dry eye disease, contact lens wear, refractive surgery history, glaucoma and retinal diseases. Dry eye disease is a common complaint in outdoor activities and might be exacerbated by the dryness, glare, and windy conditions seen at high altitude. Climbers may benefit from properly fitted wraparound glacier goggles that protect the eye from the wind and ultraviolet radiation [69].

High altitude conditions are accompanied by dry air and cold temperatures that may induce dryness symptoms not only in people visiting high regions but also for people living there [76]. The Tubingen High Altitude Ophthalmology study reported changes in the quality of the tear film during high altitude exposure in healthy subjects (4,559 m), resulting in increased tear osmolarity and a reduced tear break-up time. Such changes were fully reversible after descent to baseline at 341 m [77].

Due to fogging of spectacles in cold weather or with moisture and snow obscuring vision, climbers generally opt for rigid or soft contact lenses or refractive surgeries. Maintaining proper contact lens hygiene can be difficult in high altitude remote environments due to lack of clean water. Also, contact lens solutions may freeze during high altitude exposure [69]. Conventional soft contact lenses must be cleaned nightly and reinserted for daily use. Uncleaned lenses may exacerbate ocular irritation and dryness. Thus, daily disposable soft contact lenses are preferable and are popular among climbers. However, their use during high winds and extreme cold as well as wearing them during sleep poses health risks. The overnight use of SCL is associated with a five to ten-fold greater risk of infectious keratitis [78,79].

Some studies evaluating patients who underwent radial keratotomy, reported progressive increases in hyperopia at 12,000 ft, and 17,000 ft [80] and at 14,000 ft [81]. These suggest that approximately 24 h of high-altitude exposure can produce a hyperopic shift, and the shift increases in magnitude over 3 days at this altitude. The hyperopic shift is reversible after descent to sea level [81]. Most of the oxygen supplied to the cornea comes from atmospheric air. Hypoxia induces edema and increases corneal thickness. With the corneal architecture being weakened by radial incisions, a hypoxic cornea may preferentially expand circumferentially in the periphery, leading to central corneal flattening, and a more hyperopic refraction [81] Conversely, neither LASIK nor PRK resulted in a refractive shift at high altitude. Studies including patients with LASIK show no vision changes even at 26,400 feet [82,83]. Occasional blurred vision after LASIK in climbers may not have been due to a refractive shift, but surface changes on the cornea [69]. PRK subjects at 14,000 feet for 3 days showed no changes in the corneal shape or visual acuity. PRK corneas thickened uniformly at high altitudes without affecting refractive error [69]. Refractive surgery is a risk factor for *de novo* or exacerbation of dry eye disease, and any dry eye disease post-refractive surgery should be controlled prior to ascending to high altitude areas.

2.1.6. Ultraviolet radiation exposure

Exposure to ultraviolet radiation can induce photooxidation and generate reactive oxygen species [84]. Reactive oxygen species may be a trigger in the pathophysiology of dry eye disease and other ocular surface diseases [85]. Human tears have ultraviolet-absorbing antioxidants [84,86]. There is no difference in the tear antioxidant content of tears between young and old subjects, while the tear flow rate in younger subjects is 3-4-fold higher than that of older subjects [84].

A population-based, cross-sectional study of dry eye disease was conducted on 9,735 participants aged ≥40 years old in plain, hilly, and coastal areas in India. The prevalence of dry eye disease was 26.2%, with a higher rate in plains (41.3%) compared to hilly (24%) and coastal sites (9%). Multi-logistic regression identified associations between environmental factors for indoor smoke exposure OR 1.3 (95% CI 1.1–1.5), smoking OR 1.2 (95% CI 1.03–1.3) and prolonged exposure to sunlight OR 1.8 (95% CI 1.5–2.2) [13].

Suprathreshold ultraviolet radiation exposure can cause photokeratitis. Ultraviolet radiation induces corneal epithelial cell apoptosis and epithelial shedding [87]. The evidence for associations between ultraviolet radiation and ocular surface disease was evaluated and concluded that, there is strong evidence that exposure to ultraviolet radiation is associated with the formation of eyelid malignancies, such as basal cell carcinoma and squamous cell carcinoma, as well as photokeratitis, climatic droplet keratopathy, pterygium and cortical cataract. However, evidence for an association between exposure to ultraviolet radiation and the development of pinguecula, nuclear and posterior subcapsular cataract, ocular surface squamous neoplasia, and ocular melanoma remain limited [88].

A systematic review of occupational exposure to solar ultraviolet radiationand its relationship with pterygium, published in 2018, showed that the prevalence of pterygium is higher at low latitudes with a higher mean annual ultraviolet radiation, particularly in outdoor workers [89]. However, this systematic review may be unreliable because of an inadequate literature search. Occupational exposure to solar ultraviolet radiation is one of the most important risk factors for developing pterygium, even at relatively high latitudes [89].

Artificially generated ultraviolet radiation can also impact the ocular surface. An observational study reported fifteen patients who had received 8-methoxy psoralen and long-wave ultraviolet light treatment for psoriasis, and subsequently developed a mild form of photokeratoconjunctivitis, which fully recovered 8 h later [90].

2.1.7. Allergens

The ocular surface is susceptible to allergens, has a unique conjunctival-associated lymphoid tissue, and is highly vascularized, consequently, it is a common site for the allergic inflammatory response. Allergen-specific IgE antibodies in tears are produced locally rather than as serum exudates [91] There is a correlation between ocular allergy and IgE-mediated mast cell activation in conjunctival tissue, which causes the release of preformed mediators such as histamine and proteases, and the formation of cytokines. This triggers a cascade of cellular and molecular events inducing extensive migration and infiltration of inflammatory cells to the ocular surface [92].

Allergic conjunctivitis is mostly caused by airborne allergens: outdoor allergens, such as pollen grains, air pollution and fungal spores, and indoor spores, such as house-dust mite. Allergic conjunctivitis is estimated to affect 6–30% of the general population; it is observed in over 30% of the pediatric population, alone or in combination with allergic rhinitis [93]. Conjunctivitis triggered by allergens may be associated with systemic clinical manifestations such as asthma and allergic rhinitis, being found in 30–71% of patients with allergic rhinitis [93].

Indoor and outdoor environments have been affected by urban development, industrialization, and climate change. EXtreme weather conditions, increasing temperatures and precipitation have resulted in longer pollen seasons and allowed for higher concentrations of indoor and outdoor mold spores. Consequently, exposure to such aeroallergens grows, making the management of allergic rhino-conjunctivitis a significant challenge. Several aeroallergens, with homogeneous distribution in different areas of the world, play a relevant role in ocular allergies, due to direct sensitization as well as cross-reactivity [94–96]. Seasonal allergic conjunctivitis onset usually coincides with regional and seasonal increases in circulating allergens, as tree pollens in early spring, then grasses and weed pollens, and outdoor molds during the fall [97]. The symptoms in perennial allergic conjunctivitis can result from singular and/or multiple indoor allergens, such as animal dander, molds, and dust mites [98].

This section aims to offer information about some allergens, including grasses, weeds, and tree pollen, house-dust mite, and pet dander, which play a role in ocular allergies, and are clinically and epidemiologically relevant, at least in some areas of the world.

2.1.7.1. Grasses and weeds pollen. Grass pollen allergy is one of the most common pollen allergies worldwide with sensitization rates up to 30% depending on climate and region [99]. Grass pollens are among the most clinically important allergen sources, arise from three separate subfamilies including the temperate *Pooideae* (e.g. *Phleum pratense*; Timothy, or Lolium perenne; Ryegrass), the subtropical *Chloridoideae* (e. g. Cynodon dactylon; Bermuda grass) and the subtropical *Panicoideae* (e. g. *Paspalum notatum*; Bahia grass) subfamilies [100]. Although the distribution of temperate and subtropical grasses fits with the latitudinal climate gradients, it co-exists in temperate climates. Moreover, the distribution of subtropical grasses is likely to increase with global warming. Many grass species are present in the same geographic location, and, therefore, an individual can be sensitized simultaneously to pollens from many different species. Moreover, grass pollen has been shown to have a significant cross-reactivity, in some cases even between pollens belonging to different subfamilies (e.g. Chloridoid pollen and Pooid pollen cross-react with Panicoid pollen) [101].

A recent study, based on crowd-sourced symptom data of users of the patient's hay fever diary in Vienna, showed that grass pollen allergy sufferers have highly individual symptom severity profiles, and that the complexity of the grass pollen season clinical impact might be better explained by a combined cross-species, multi allergen, system rather than linking symptom profiles with cross reactivity of grass pollen allergens alone [99]. Most of the studies of allergic sensitization are based on serum IgE. However, grass pollen specific IgE antibodies in tears seem to be produced locally and strongly correlate with clinical manifestations of allergic conjunctivitis [91].

Other very common grass pollen sources, such as ragweed (*Ambrosia artemisiifolia*) and mugwort (*Artemisia vulgaris*) are not true grasses (*Poaceae*) but belong to the *Asteraceae* plant family (weeds). Native to North America, ragweed and mugwort are also common in Europe, in the Mediterranean regions and in parts of Asia. Interestingly, the actual expansion of ragweed in formerly mugwort-dominated areas is concomitant with an increase of weed pollen allergies in those regions [101]. In general, ragweed pollen sensitization has been increasing in the last decades, with sensitization rates up to 30% in the general population and up to 70% in atopic patients, and it is considered a major health problem in several areas of North America, Europe and Asia [101].

The major epidemiological relevance and the large body of studies on specific allergens responsible for sensitization to *Poaceae* and *Asteraceae* led to the development of different types of immunotherapies. Sublingual immunotherapy is, at present, the most prescribed treatment of seasonal allergic rhino-conjunctivitis in Europe, although randomized clinical trials and meta-analyses showed conflicting data about the magnitude of the benefit of grass/weed pollen sublingual tablets in reducing symptoms and in decreasing the use of symptom medication [102,103].

2.1.7.2. Tree pollen

2.1.7.2.1. Birch (Betulaceae family). Birch pollen is one of the major sources of allergens. Birch trees grow in many natural plant communities as well as in urban areas as ornamental plants. Pollination occurs from spring to early summer. Meteorological conditions such as temperature, humidity and sunlight have a strong influence on the concentrations of airborne pollen [104]. Birch pollen is the most common tree pollen in Northern and Central Europe. Due to its high allergenicity, it is a leading cause of rhino-conjunctivitis and asthma. In patient-based studies, the prevalence of positive skin prick testing results for birch in pollen-allergic patients in Europe has ranged from 5% in the Netherlands to 57% in Denmark [105,106].

Some ecological studies have investigated birch (*Betula verrucosa*), alder (*Alnus glutinosa*), hazel (*Corylus avellana*), hornbeam (*Carpinus betulus*) and oak (*Quercus* alba), which are members of the birch homologous group based on cross-reactivity among these pollen extracts [107]. There has been an increase in levels of birch pollen in the last few decades; also, longer periods of exposure have been observed due to climate change. Consequently, the prevalence of birch pollen sensitization has risen [105].

Caillaud *et al*. conducted a modeling regression and found a variation in clinical responses to natural exposure to birch pollen in sensitized patients during the Betula pollen season. The threshold was observed at the beginning of the season; throughout the season, the relationship proved to be linear for nasal, ocular and bronchial symptoms until a saturation point was reached, followed by a plateau [108]. The risk of sensitization to birch pollen and symptoms of atopic disease in children with atopic heredity was higher when mothers were exposed to this pollen during pregnancy [109].

A clinical trial revealed that a birch sublingual immunotherapy tablet mitigates rhino-conjunctivitis symptoms triggered by birch and oak pollens and induces IgG4 to allergens from all species within the birch homologous group [110]. A multicenter, randomized, double-blind, placebo-controlled trial was conducted to analyze 3 vac- cines in 134 adults with birch pollen allergy: recombinant birch pollen allergen vaccine (rBet v 1a), licensed birch pollen extract, natural pu- rified birch pollen allergen (nBet v 1) and placebo. The study confirmed the safety and effectiveness of the rBet v 1-based vaccine to treat birch pollen allergy and to induce a highly specific immune response [111].

2.1.7.2.2. Hazel (Betulaceae family). Hazel is a deciduous, wind-pollinated, and monoecious understorey shrub that can grow to heights of 4–8 m with a lifespan of 80–90 years. It begins flowering in

early spring, even before the leaves appear. Hazel trees can be found in Europe, North Africa, Asia Minor and North America. Hazel pollen concentrations are mainly influenced by weather factors such as humidity, temperature, sunlight exposure, precipitation and wind speed [112]. Notably, most patients with type I allergy to tree pollens also present with intolerance to nuts. A randomized, double-blind, place- bocontrolled study found a larger skin prick test area and higher spe- cific IgE values in patients with hypersensitivity to nuts and apples. Thus, the hypersensitivity to nuts was an indicator of more severe al- lergy in patients with rhinitis or conjunctivitis caused by birch pollen [113]. Common allergenic structures in hazel pollen and hazelnuts are likely to explain the sensitivity to hazelnuts in patients allergic to tree pollen [114].

2.1.7.2.3. Alder (Betulaceae family). Alder trees can be found across Europe, near rivers and in lakeside forests, even at higher elevations. A variety of species can be identified, namely black or common alder, green alder, grey or speckled alder and a hybridization type. In temperate climates, the start date for the alder pollen season is quite variable, ranging from December to March or April [115]. It shows moderate to high levels of allergenicity and cross-reactivity to hazel and birch pollens [116].

2.1.7.2.4. Ash (Oleaceae family). Ash is widely distributed in Europe (Great Britain, Ireland, Scandinavia, Russia, Central and Southern Europe) and America, where is frequently grown as a source for hardwood timber [117,118]. In Europe ash blossoms from March to May and it has been reported that almost 20% of pollen-allergic patients are sensitized to ash pollen, which has been recognized as a relevant allergen source, particularly in spring [119]. Clinical observations have shown cross-reactivity between ash pollen and olive, birch pollen, grass pollen and weed species [120–122]. A study carried out skin tests on a total of 1,500 pollinotic patients using an extract of Fraxinus pollen and showed a sensitization frequency of 59% [123].

2.1.7.2.5. Japanese cedar (Cupressaceae family). Japanese cedar is native to Japan and the coastal provinces of China and is often cultivated in Europe and North America. This is one the most relevant aeroallergens in Japan, with a high, although heterogeneous, sensitization rate in the resident population. Data from Northeast Japan showed antigen specific IgE in 41.5% and 20.5% of elementary school students in mountainous and coastal areas, respectively [124]. A recent study on healthy participants in Tokyo reported specific IgE prevalence, in the 20–29 years of age group, of 80% and 65% in males and females, respectively [125]. Other studies from Japan highlighted that, even after adjustment for confounders, the prevalence of allergic rhinoconjunctivitis was positively associated with cedar pollen counts in children [126] and that the peak of schoolchildren' rhino-conjunctivitis incidence was in March and April, which coincides with the release of Japanese cedar pollen [127]. An interesting study, conducted during the peak pollen season, found that half of the patients with Japanese cedar pollinosis reported a 25% reduction in productivity compared with the non-pollination season and that "itching eyes" was a significant independent risk factor for lost work time [128].

2.1.7.2.6. Horse chestnut (Sapindaceae family). The horse chestnut tree, native to Europe and particularly common in the Balkans and in Britain, is now cultivated throughout temperate zones, including Mexico, Turkey and the USA. It is common in urban settings because it has not been considered of allergological relevance and it has been recommended for planting in avenues [129]. A cross-sectional study compared children in urban Vienna and in a rural area, showing the presence of serum IgE specific to horse chestnut pollen in 12.6% and 1.9%, respectively. Moreover, the sensitization to pollen of other species, especially to that of plane trees, significantly raised the odds for sensitization to chestnut pollen [129].

2.1.7.3. House dust mite. House dust mites, including a variety of species with heterogeneous distribution, are important sources of allergens. If *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus* are inhabitants of homes worldwide [130], other species, as *Blomia tropicalis*, are prevalent in the tropics and subtropics [131]. Microenvironment modifications, including changes in temperature, humidity, and air pollution have a significant impact on dust mite growth, survival, and allergen production. In general, peculiarities of the different mite species, a warm and humid environment, typical of tropics but progressively expanding, are ideal conditions for dust mite growth and multiplication. With this in mind, the last decades of global warming and increasing urbanization might play a r role in the growing rate of sensitization to house dust mites [132]. Studies from tropical/subtropical urban settings reported very high rates of dust mites sensitization among atopic children, ranging from 71% [133] to over 90% (Taipei City, Taiwan and Kolkata, India) [134,135]. Moreover, a study performed in Northeastern India showed significant seasonal variations in HDM count, with maximum concentration when the atmospheric temperature, relative humidity, and rainfall were maximum [136].

Given the relevant role of temperature and humidity, houses with high-efficiency dehumidifiers and air conditioning provide a good control of dust mites number and allergens seasonal peaks [130]. Studies from Korea, comparing the 1990s and the 2010s, investigated the allergen sensitization in patients with respiratory allergies [137] and in patients with allergic rhinitis [138]. Skin reactivity to house dust mite was inversely related to age, with a peak between 10 and 30 years of age, and rates were not different between the 1990s (55.2%) and the 2010s (55.6%) [137]. In the allergic rhinitis population, higher rates of skin reactivity to house dust mites, increased from over 60% in the 1990s to over 70% in the 2010s [138]. Similarly large cohort study performed on Swiss young adults (medical students) between 2007 and 2015, reported a house dust mite sensitization rate of 17.5% [139].

The house dust mite is typically considered the main causative allergen in perennial allergic conjunctivitis, based on data from the 1980s [140,141]. A recent German retrospective study found in subjects monosensitized to house dust mites, the prevalence of itching and red eye was 23% and 5%, respectively. These percentages raised to 45% and 9%, respectively, in polysensitized patients [142]. Interestingly, data from The Danish Allergy Research Center cohort study showed that transient early-life sensitization to house dust mites is associated with a significantly increased risk of rhino-conjunctivitis in 14-year-old subjects (OR 3.33 95% CI 1.29–8.66) [143].

2.1.7.4. Cat and dog dander. Allergies to cat and dog dander are common in the Western world, and the prevalence of pet dander sensitization has increased in the last decades in both Europe and the United States [144]. Several allergen molecules have been described in cats and dogs, increasing the chances to perform molecular allergy diagnostics. Molecular studies demonstrated that individual sensitization patterns strongly mirror current or previous pet ownership except for Fel d 1 (cat allergen), which regularly causes sensitization also in non-owners [145]. The role of pet sensitization in ocular allergy is particularly relevant in but not limited to perennial allergic conjunctivitis [146]. A retrospective study analyzed 762 Japanese patients with allergic conjunctivitis and showed that 14% were positive for cat or dog antigen specific IgE [147]. Interesting studies from South America showed that, although not typical of tropical areas, sensitization to cats and/or dogs were frequent in patients with allergic conjunctivitis, which correlated with disease severity in children affected by vernal keratoconjunctivitis [148,149]. A large population-based study in the Netherlands showed that having a cat or a dog as a pet is not a risk factor for dry eye disease. After adjusting for multiple possible confounding factors, owning cats (OR 0.95 95% CI 0.89–1.00) and dogs (OR 0.92 95% CI 0.86–0.98) as pets, appeared to be a minor but significant protective factor for dry eye [150].

2.2. Outdoor risk factors and pollution

Air pollutants may adversely affect general health and the ocular surface. There are distinct sources of such pollutants, namely gases [carbon monoxide (CO), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), ozone (O_3), particulate matter (PM) from natural sources (volcanic eruption, rock debris, forest fire, salt spray, wind and dust storms, reactions between gaseous emissions and soil erosion), man-made sources such as fuel combustion, industrial (e.g., fossil fuel–fired electric power plants and manufacturing facilities), petroleum foundries, cement, smelting, mining operations, fly-ash emissions from power plants, soil pollution, burning of coal, transportation (vehicles emissions), agricultural sources (e.g., methane and pesticides) and indoor sources (e.g., air-conditioning systems, home gas and oil burners and wood stoves). The ocular surface is constantly exposed to indoor or outdoor air pollutants that are not mutually exclusive. Gases, bioaerosols and PM can freely exchange between outdoor and indoor environments through opening sites of windows and doors upon certain meteorological and airflow conditions [151,152].

Air pollution is the mixture of toxic chemicals or compounds in the air at levels that present a risk to health. Across the globe, air pollution-related diseases pose a massive threat to human health. An estimated 3.1 million people die prematurely each year because of air pollution [153]. Epidemiological investigations have revealed the short and long-term associations between high concentrations of air pollutants and increased health problems, including stroke, heart disease, lung cancer, diabetes and chronic lung disease [154].

The overall burden of disease is assessed using the disability-adjusted life year measure [155], which combines years of life lost due to premature mortality and years of life lost due to time lived in states of less than full health, or years of healthy life lost due to disability. One disability-adjusted life year represents the loss of the equivalent of one year of full health. Using this measure, the burden of diseases that cause premature death, but little disability can be compared to that of diseases that do not cause death but do cause disability. Disability-adjusted life years are expressed per 100,000 population.

Fig. 3 displays disability-adjusted life years attributable to worldwide ambient air pollution according to World Health Organization data sources.

https://www.who.int/images/defaultsource/maps/global_aap_dalys_2016. Disability-adjusted life years expressed per 100,000 population, latest World Health Organization report (2016).

The World Health Organization Ambient Air Quality Guideline offers quantitative and health-based recommendations for air quality management [156]. Exceeding the quality guideline levels for pollutants is associated with significant risks to public health. The guideline forms an evidence-informed tool that can be used to inform legislation and policy. The purpose of this document is to provide evidence-based information, to raise awareness of the impact of the air quality on health worldwide among the public and patients and to join national and international advocacy efforts to policy discussions. Table 2 shows recommendation of the 2021 Ambient Air Quality Guideline for levels of air pollutants.

[a] 99th percentile (i.e., 3–4 days exceeded per year); [b]Average of daily maximum 8-h O_3 concentration in the six consecutive months with the highest six-month running-average O_3 concentration. PM particulate matter.

Notably, according to World Health Organization reports, most ambient air pollution-attributable deaths occur in the South-East Asia

Table 2
World Health Organization Ambient Air Quality Guideline on air pollutants.

Pollutant	Average time	2021 AQG level
$PM_{2.5}$ Mg/m^3	Annual	5
	24-h[a]	15
PM_{10} Mg/m^3	Annual	15
	24-h[a]	45
O_3 Mg/m^3	Peak season[b]	60
	8-h[a]	100
NO_2 Mg/m^3	Annual	10
	24-h[a]	25
SO_2 Mg/m^3	24-h[a]	40
CO Mg/m^3	24-h[a]	4

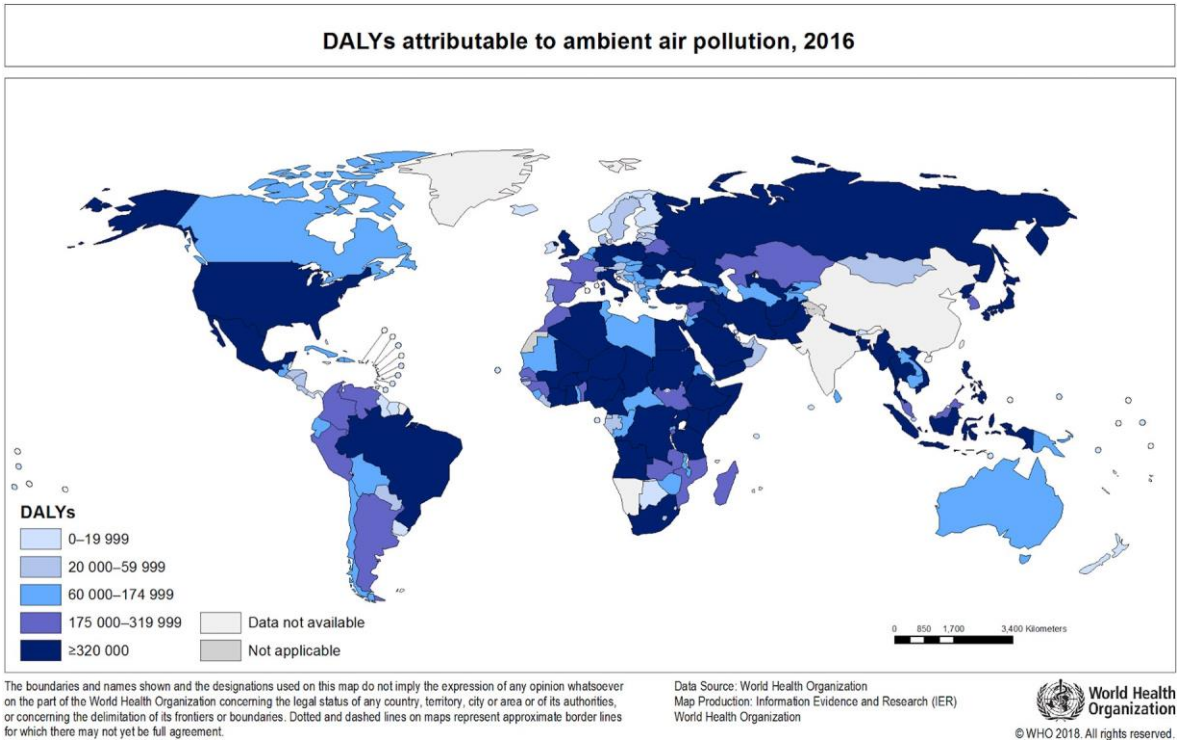

Fig. 3. DALYs attributable to worldwide ambient air pollution.

and Western Pacific regions with 2.4 and 2.2 million deaths, respectively. Approximately 980,000 deaths are attributable to air pollution in Africa each year, along with 475,000 deaths per year in the Eastern Mediterranean region, 348,000 in Europe and 233,000 in the Americas. Fig. 4 displays estimates of ambient pollution deaths per 100,000 population per year according to the latest World Health Organization report (2016).

https://www.who.int/data/gho/data/indicators/indicator-details/GHO/ambient-air-pollution-attributable-deaths. Number of deaths expressed per 100,000 population, latest World Health Organization report (2016).

2.2.1. Urban pollution (gases and particulate matter)

Traffic-induced air pollution has become increasingly common in urban populations. Such pollution is commonly assessed by particulate matter and NO_2 levels [157]. Although NO_2 can be created when oxygen or ozone in the air oxidizes nitrogen monoxide, the main source of NO_2 in outdoor air is fuel combustion, mainly from motor vehicles and then from power stations and factories [158]. The main source of particulate matter in urban areas is road transport, in addition to the burning fuels in power stations and factories. Traffic-derived particulate matter includes components from engine emissions, brake and tire wear, and dust from road surfaces [159].

A population-based, cross-sectional study (n=16,824) carried out in Korea reported the effects of outdoor pollution on the ocular surface [160]. This study was conducted over a period of 3 years (2010–2012), using a multistage stratified cluster sampling method based on official demographic data. Environmental data was collected at 283 atmospheric monitoring stations. There were 6,263 participants living in urban areas and 7,560 living in a rural environment. Outcome measures were symptoms of dry eye disease and/or a previous diagnosis of dry eye disease. Increased ozone levels and reduced humidity were associated with dry eye disease after adjusting for sex, dyslipidemia, thyroid disease, subjective health awareness and previous ocular surgery. Increased ozone levels of 0.003 ppm were significantly associated with symptoms and diagnosis of dry eye disease (symptoms: OR 1.17 95%CI 1.02–1.34 and diagnosis: OR 1.27 95%CI 1.09–1.48). Importantly, NO_2, not particulate matter <10 mm, was associated with dry eye disease. Although the concentrations of particulate matter <10 mm in this study were higher than the levels recommended by the World Health Organization (20 μg/m^3), the authors speculated that reflex tearing might have protected participants from the adverse environmental effects [160].

Another multidisciplinary prospective, population-based cohort investigated the health of 79,866 participants living in northern Netherlands. There was a strong positive correlation between dry eye disease and air pollutants, particulate matter <10 mm and NO_2. The effects of particulate matter <10 mm and NO_2 were reduced after further adjustment for comorbidities, resulting in a significant correlation between dry eye disease and NO_2 only. This would suggest that the associations between air pollutants and dry eye disease are likely mediated by a higher prevalence of other diseases that have been directly linked to air pollution, such as allergies and atopic diseases, atherosclerosis, and diabetes [150].

A systematic review and meta-analysis explored the relationship between air pollution and conjunctivitis [161]. Twelve studies, including 30,103,982 cases of conjunctivitis from 10 countries/regions across the globe, were included. Six common air pollutants showed positive associations with conjunctivitis, but statistical significance was only found for NO_2 and O_3. Patients under 18 years of age and female subgroups were at higher risk for conjunctivitis caused by air pollution. This review reported that the pooled relative risk of conjunctivitis for 10 μg/m^3 increase of air pollution was: 1.0006 (95% CI 0.9993–1.0019) for CO, 1.0287 (95% CI 1.0120–1.0457) for NO_2, 1.0089 (95% CI 1.0030–1.0149) for O_3, 1.0004 (95% CI 0.9976–1.0032) for particulate matter <2.5 mm, 1.0033 (95% CI 0.9982–1.0083) for particulate matter <10 mm, and 1.0045 (95% CI 0.9908–1.0185) for SO_2 [161].

Several researchers investigated spatial variations in exposure to traffic-related air pollution. A study evaluated the association between air quality and the prevalence of child respiratory and ocular morbidity. Respiratory symptoms such as wheezing, sneezing, running nose, tearing, and itchy eyes had positive and strong association with concentrations of particulate matter <10 mm and NO_2 (0.70–0.87,

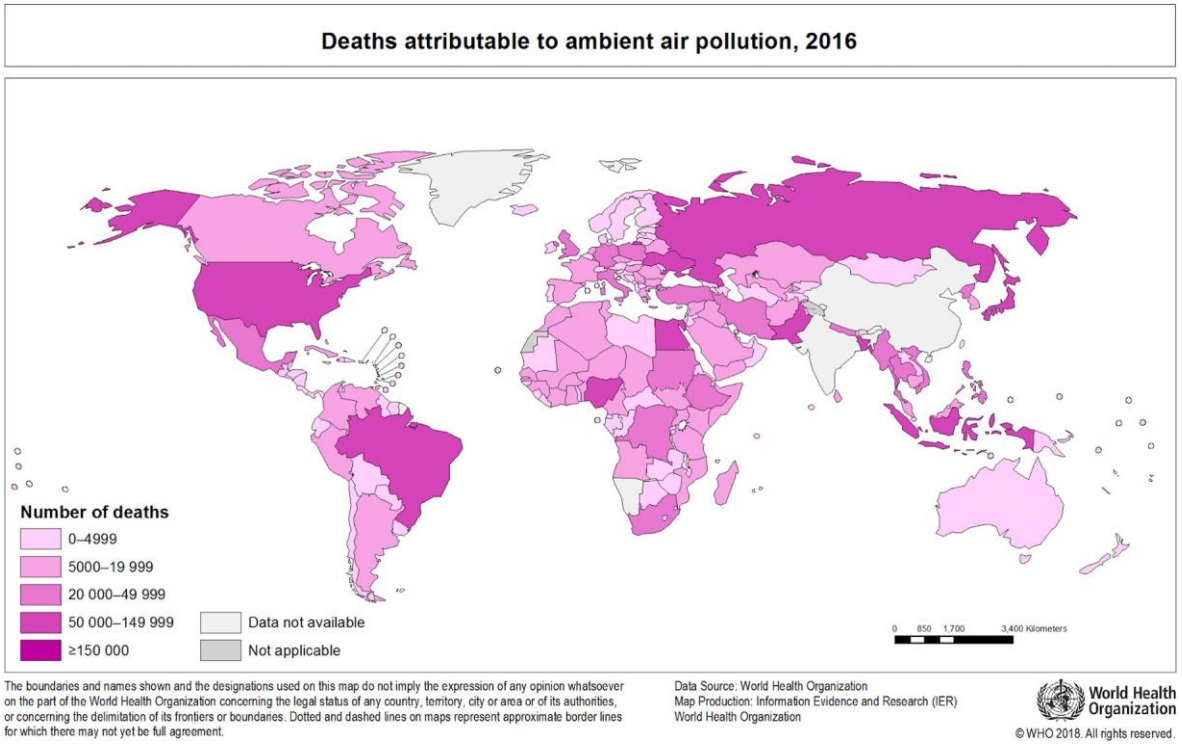

Fig. 4. Estimates of ambient air pollution attributable deaths worldwide.

respectively). Interestingly, the frequency of some symptoms was lower in study areas close to urban forest [162]. A study in Delhi compared ocular symptoms and signs of 441 subjects who commuted through highly polluted areas daily for at least two years with a control group of 79 subjects, who lived on campus and traveled from their houses to their workplaces within the campus facilities. Those in the study group presented with ocular symptoms, such as redness, watering, irritation, strain, blurring and photophobia, more frequently compared to the control group [163]. Schirmer test was 13.4 ± 6.7 mm in the group exposed to pollution compared to 16.0 ± 6.1 mm in the control group ($p < 0.001$). Similarly, tear break-up time was 13.0 ± 6.1 s and 19.2 ± 5.0 s in subjects exposed to traffic daily and controls, respectively [163]. Annual mean concentration range of suspended particulate matter, respirable suspended particulate matter, and NO_2 were 210–360, 180–200, and 40–90 μg/m^3, respectively, which were much higher than those recommended by the World Health Organization guidelines [164].

In Argentina a cross-sectional study included 78 participants exposed to different levels of particulate matter in either an urban (n = 44) or industrial zone (n = 34). The particulate matter size <2.5 mm level was significantly higher in the industrial zone group than in the urban area group. Ocular surface parameters, including bulbar redness, eyelid redness, staining with fluorescein and lissamine green, were higher in the industrial zone group compared to the urban area group [165]. Fifty-five healthy participants who had been living in the study area of São Paulo city for at least 5 years, received monitoring apparatus for detecting passive NO_2, to be carried for a period of daily activities. Notably, the rise in exposure to NO_2 was associated with the increased frequency of symptoms of irritation consistent with dry eye disease, as well as lower tear break-up time and increased frequency of meibomian gland dysfunction in a dose-response pattern [18]. These findings are also supported by another study that confirmed an association of combustion-derived pollutants with increased meibomian gland dysfunction and eyelid debris, associated with blepharitis. The authors suggest that the mechanism may be overloading of antioxidative defense system on the eyelid margin causing changes in the structure of essential fatty acids and chronic inflammation [29]. A study evaluated the mean individual levels of exposure to NO_2 for 24 h and to particulate matter <2.5 mm, as well as clinical findings from 71 taxi drivers and traffic controllers from São Paulo. TBUT values were reduced; particulate matter <2.5 mm and tear film osmolarity levels were significantly and negatively correlated [21]. The same group of authors also quantified goblet cells and mucin 5AC gene expression on the conjunctiva of healthy subjects exposed to traffic-derived air pollution in outdoor environments. There was an increase in mucin 5AC expression on the ocular surface, probably because of increased goblet cell density in response to airborne pollutants [166].

The particulate matter <10 mm exposure value was significantly higher in pediatric participants with conjunctivitis of unknown origin (33.5 ± 5.4 μg/m^3), and the most common symptoms and sign of conjunctivitis of unknown origin were foreign body sensation (37/48) and conjunctival hyperemia respectively, in a study conducted in Italy [31]. The prevalence of dry eye disease was greater in the industrial zone where particulate matter <10 mm levels were higher, and the population exposed to a higher level of particulate matter <10 mm had a significantly increased proportion of tear film long-chain fatty acid, a higher proportion of saturated fatty acid, and lower proportion of unsaturated fatty acid compared with an control group [165]. In China, outpatient visits in 5,066 participants with dry eye disease were significantly associated with increased air pollutants (particulate matter <10 mm, particulate matter <2.5 mm, SO_2, NO_2, and CO), but ozone level was not associated with dry eye disease [27] In a prospective, observational study in South Korea, including 43 patients with dry eye disease who had used the same topical agents for treatment, increased ozone and particulate matter <2.5 mm exposure led to greater ocular discomfort, and increased particulate matter <10 mm concentration, reduced tear film stability [27].

A large multiarea study in Taiwan found that increased NO_2, SO_2, O_3, and particulate matter <10 mm concentration were associated with outpatients' visits for nonspecific conjunctivitis, and the effects were stronger for O_3 and NO_2 [167]. Increased NO_2 levels were associated with ocular surface irritation and damage, and with abnormal tear stability in both Sjogren patients and normal control groups. Those with Sjogren syndrome were also more affected by NO_2 pollution [168]. Traffic-related CO and NO_2 were positively associated with dry eye disease in a systematic sampling cohort database in Taiwan, while O_3, particulate matter <10 mm, and particulate matter <2.5 mm were not associated with dry eye disease [169]. O_3 as a single air pollutant led to increased ocular discomfort and decreased tear secretion with short-term exposure in patients with pre-existing dry eye disease in South Korea [170]. In 27,605 female participants from the Taiwan Biobank data, ambient NO_2 concentration was significantly associated with increased prevalence of dry eye disease, but other air pollutants (particulate matter <12.5 mm, SO_2, O_3) and relative air humidity were not associated with dry eye disease [22]. Single-day lag exposures to NO_2, O_3, particulate matter <2.5 and < 10 mm were associated with outpatient visits in children for dry eye disease, and there was a dose dependent effect on the relative risk of dry eye for each air pollutant type [30]. Fig. 5 displays studies evaluating effects of air pollution on the ocular surface worldwide.

Conversely, a study from Greece compared participants exposed to dry air and heavy pollution to a control group exposed to a humid, cool, and low pollution. Tear secretion (Schirmer test) and tear film stability (tear break-up time) were higher in humid climates, but neither was associated with atmospheric pollution [171].

There were a greater number of inflammatory cells in conjunctival cytology sample in participants in Italy (Bologna), living in towns with heavy pollution compared to those living in the countryside, regardless of patient sex [172]. Most metropolitan areas in the US have relatively high concentration of air pollution (aerosol optical depth, an indicator of concentration of both solid and liquid aerosol particles in the air), and relatively higher rates of dry eye disease [23]. Increased air pollution from the burning of biomass is associated with increased tear film instability, ocular surface staining, and irritating ocular symptoms [14].

There is a significant association between the development of primary Sjögren syndrome and exposure to occupational chemical solvents (chlorinated solvents and aromatic solvents), but no association with biocides including ammonia, formaldehyde, and crystalline silica [173].

Ocular irritation is considered a marker of exposure to formaldehyde commonly present in occupational environments (industry, construction, laboratories) and domestic environments. A systematic review concluded that the maximum exposure to avoid ocular irritation is 0.0014 mg/m^3 of formaldehyde, much lower than the 0.1 mg/m^3, recommended by the World Health Organization [174].

2.2.2. Volcanic ash

Nearly 9% of the global population lives within a zone of potential active volcanic eruption. A systematic review estimated 550 active volcanoes are in close vicinity of urban centers or areas experiencing rapid population growth [175]. Short-term surges in trauma-related injuries emanating from traffic accidents and falls, and morbidity related mainly to ocular irritation and respiratory symptoms, have been reported. Changes in prevalence of communicable diseases and long-term health effects have not been attributed to volcanic eruptions. However, eruption-associated morbidity is likely underestimated [175]. However, this systematic review may not be reliable because a study risk of bias assessment was not reported. Current studies on ocular morbidity provide data from Mount St. Helens and Mount Kilauea eruptions in the US, Mount Sakurajima and Miyakejima island eruptions in Japan, Mount Etna eruptions in Italy, Holuhraun and Eyjafjallajokull eruptions in Iceland [176–182].

A survey of ophthalmologists in four US states affected by ash fall after the Mount Saint Helens eruption was undertaken. The study also

Fig. 5. Studies of worldwide air pollution.

compared the ocular findings between loggers working in the ash fall zone and loggers working in areas without ash exposure [176]. There were no cases of visual loss nor long-term ash exposure effects, but conjunctivitis was reported in more than 50% of patients and kerato-conjunctival foreign bodies in less than 20%. The study identified contact lens use (especially rigid contact lens) and dry eye disease as factors leading to aggravated symptoms. The survey was limited by a low response rate and lack of clarity in the study reporting period. There was a higher report of self-limiting ocular foreign body sensation and irritation in loggers working in exposure zones which disappeared within 1–2 days after exposure. The loggers working in high exposure zones also experienced more mucus discharge and lid crusting in the morning. There were no differences in conjunctival inflammatory cells on brush cytology between the two group of loggers. Limitations of this study include the absence of information on the type of ash, standardization of mask wear guidelines and failure to control for the effects of allergy in the participants [176].

The Kilauea Volcano Adult Health Study was the first cross-sectional, population-based environmental epidemiological study determining prevalence of cardiorespiratory symptoms, self-reported symptoms and diagnosed diseases in the region. There were higher concentrations of air SO_2 and fine aerosols (<0.3 μm) in the ash/air pollutant exposure zones, which showed a significant positive correlation with self-reported eye irritation. A limited air sampling period, lack of medical report confirmation of systemic or ocular diseases via medical reports and "healthy-resident-survivor effect" issues were the major limitations of this study [177]. A retrospective, non-comparative case series study was carried out of patients who lived in Oahu for more than 7 years and complained of eye irritation during a 3-month period of visible 'vog' period [181]. The authors coined the term 'vog' for volcano and fog, where they described the chemicals in vog that cause respiratory and eye irritation as SO gases, sulfate aerosols such as H_2SO_4, NH_4HSO_4, and $(NH_4)_2SO_4$. All patients displayed conjunctival hyperemia, discharge, papillae and punctal edema. Eyelid chemosis was noted in 73.3% of the participants. Itchiness, foreign body sensation, tearing and burning sensation were the most frequently reported symptoms. The signs and symptoms were proposed to be caused by a combination of toxic and allergic reactions. In addition to the disease severity descriptors not being defined, the retrospective nature of the investigation limit the generalizability of the findings. Milder cases were reported to respond to ice compresses and antihistamine eye drops within 1–2 days, while the more severe cases responded only after more than one week of treatment with topical steroid and antihistamines [181].

A retrospective cross-sectional 10-year survey investigated the effects of volcanic ash exposure in 10,380 school children between 6 and 15 years of age, examined annually each September in the decade from 1994 to 2003, after the Mt. Sakurajima eruption in Japan [178]. The study compared the frequency of positive ocular symptoms in years with and without active volcanic eruptions and in subjects living close or far away from the volcano. Ocular symptoms were determined to have been directly influenced by volcanic eruptions in subjects living in areas less than 4 km from the volcano's crater. The concentration of eruption related air pollutants such as SO_2 and NO_2 was not quantified, and seasonal allergic conjunctivitis was not controlled for, presenting the remaining limitations in the study [178]. Another study evaluating the impact of Sakurajima volcanic eruptions did not reveal differences in ocular symptoms between females living close to (25 km) and far away (50 km) from the eruption site [183]. As a strength of the study, air pollutants were quantified, but the authors acknowledged that occupation may be a confounding factor, as some subjects, who were farmers, living far away from the volcano during the summer months, who had higher symptoms, which was caused by sweat entering the eye. The Miyakejima volcano eruption study surveyed respiratory and ocular symptomatology in 611 healthy officials working to restore the island after the whole population was evacuated. Respiratory symptoms correlated with mean SO_2 concentrations, while there were equivocal findings for eye irritation, and males and cigarette smokers had a higher risk of ocular symptomatology [179].

The Holuhraun eruption study from Iceland studied acute symptoms in 32 government officials who volunteered to work at the eruption site. From the participants, 48% reported eye irritation despite facemask wear but the masks wear times were not controlled. Small study size, loss to follow-up needed to study long term effects, lack of air SO_2 data, possibility of mask removal for brief periods during work, and delay in last exposure to clinical examination were the weaknesses of the Holuhraun study [182]. The Eyjafjallajokull volcano eruption study investigated the differences between two populations resident in between the north (510 subjects, lower exposure zone) and south Icelandic territories (1148 subjects, higher exposure zone). Twice as many in the exposed population had two or more symptoms involving the nose, eyes, or upper respiratory tract (24% vs 13%). These individuals were also more likely to experience psychological effects compared with

individuals with no symptoms. Most symptoms exhibited a dose-response pattern within the exposed population, with severity corresponding to low, medium, and high exposure to the eruption. An important strength of this study was that it included the overall population of the exposed region and a matched sample from a nonexposed region. The response rate was 72%. A limiting factor was that the study relied on self-reported symptoms and that the degree of exposure was based solely on proximity of residency to the eruption [182].

The Etna eruption study in 2002 determined a significantly higher frequency of hospital visits in Catania related to ocular symptoms due to diseases that could be related to volcanic ash exposure [180]. The study lacked comprehensive information on the nature of ocular symptoms and signs for the hospital visits. In addition, the effects of pre-existing ocular diseases and the air pollutant concentrations were not controlled for.

In summary, volcanic eruptions appear to cause a variety of ocular symptoms which may be self-limiting or mostly responsive to symptomatic treatment. Contact lens wearers and patients with pre-existing dry eye disease appear to suffer more symptomatology and ocular surface abrasions. However, no chronic or visually disabling ocular adverse effects from volcanic ash have been reported in the literature. It should be noted that systematic reviews and volcanic eruption-related ocular surface studies face numerous limitations. The effects of volcanic eruptions appear to be the subject of gross approximations with considerable imprecision. For a significant number of events, no data are reported for injured, displaced, and affected populations; this likely contributes to a substantial underestimation of the impacts of volcanic activity on human populations. Inconsistencies and errors appear to be common in data files from different sources, and in some cases inclusion criteria were not ideal for the purposes of systematic reviews, all of which creates a challenge in reconciling event lists. The relative paucity of primary research focusing on the ocular surface health-related topics significantly limits the conclusions that can be drawn about volcanic impacts on the ocular surface of human populations. A principal limitation of the literature review is the fact that only English language publications are included, which likely contributes to incomplete coverage of studies published in other languages originating from low- and middle-income countries.

2.2.3. Dust

Coal dust exposure was associated with reduced tear secretion and tear break-up time in a Chinese study comparing coal miners and general workers [184]. In a study from Japan, the presence of Asian dust particles (composed by particles of aluminosilicate, SiO_2 and $CaCO_3$, with organic compounds and inorganic nitrate coated on the surface) on the ocular surfaces was correlated with higher conjunctivitis scores. The majority (44 of the 45 samples) were positive for silicone and aluminum which are components of Asian dust particles [185]. Direct contact with a coal mine and smoke were associated with reduced tear break-up time and tear secretion [186]. Street sweepers in Nigeria had higher odds of developing dry eye disease compared to office cleaners (OR 2.09 95% CI 1.11–3.93, $p = 0.02$) (Nigeria) [187].

2.2.4. Other pollutants

High blood mercury levels have been associated with symptoms of dry eye disease in a nationally representative South Korean population (OR 1.32 95% CI 1.06–1.66) [188]. The incidence and prevalence of Sjögren syndrome were significantly increased (3.6-fold) in areas where soils contained high levels of chromium, however lead, copper, and arsenic in soils did not show a significant association in studies performed in Taiwan [189,190].

2.3. Indoor risk factors

2.3.1. Sick building syndrome

Sick building syndrome, sometimes called building-related symptoms, describes a situation in which the occupants of a building experience acute health effects or discomfort that can be linked directly to the time spent in the building. The effects may be related to humidity, illumination, temperature, air velocity, air conditioning, toluene and paint thinners, construction materials, particles, and mold, as well as gaseous and particulate indoor air pollution. In 1982, greater attention was paid to sick building syndrome, after the World Health Organization expert group defined it as a combination of nonspecific general symptoms. Symptoms include mucous membrane irritation (eye, throat and nose), neurotoxic effects (headaches, fatigue, lack of concentration, feeling heavy-headed and difficulty concentrating), respiratory symptoms (shortness of breath, cough, and wheezing), skin symptoms (rash, pruritus, and dryness in the face, hands or scalp) and chemosensory changes (enhanced or abnormal odor perception and visual disturbances) and others, such as dizziness and nausea [191,192] (Table 3). Sick building syndrome has emerged as an occupational and environmental health issue. Nonspecific complaints appeared to be linked to a particular room or zone or can be widespread throughout buildings.

According to the United States Environmental Protection Agency, it is crucial to distinguish between building-related illness and sick building syndrome. Major indicators of sick building syndrome do not include specifically defined causes of the symptoms experienced by occupants of the building. Symptoms seem to be linked directly to the time spent in the building because most of the complainants reported relief soon after leaving the building. In contrast, the main indicators of building-related illness include symptoms that could be clinically defined and have clearly identifiable causes. Certain building-related illnesses conversely, may require prolonged recovery times after leaving the building. Common building-related illnesses include asthma, hypersensitivity pneumonitis, inhalation fever, rhinosinusitis, conjunctivitis, laryngopharyngitis and infection, such Legionnaires' disease [192].

The prevalence of sick building syndrome symptoms was assessed based on large population-based, cross-sectional studies.

The National Institute for Occupational Safety and Health studied 2,435 respondents from 80 office buildings in the USA and estimated that 19% of the study population met the criteria for multiple sick building syndrome symptoms (at least three of the following: dry or irritated eyes, sore or dry throat, stuffy or runny nose, unusual tiredness or fatigue, and headache) [193–195]. The USA Environmental Protection Agency conducted the Building Assessment Survey Evaluation Study, a systematic survey of 4,326 employees from 100 randomly selected USA office buildings, in the 1990s, and 45% of the work force

Table 3
Sick building syndrome symptoms [191,192].

Sick building syndrome symptoms	
Mucous membrane irritation	Eyes: irritated, red, burning, inflamed, dry, swollen, painful, watering, itchy eyes and tearing. Nose: irritation, blocked stuffy or runny nose, and sneezing. Throat: hoarse, dry throat, irritated throat, burning, dry mouth, phlegm, and mucus.
Respiratory symptoms	Shortness of breath, cough, wheezing, chest tightness, breathing difficulty, and flu-like symptoms.
Skin symptoms	Rash, pruritus, and dryness involving face, hands or scalp; dry or flushed facial skin; scaling or itching scalp or ears; itching/stinging/tightness or burning sensation in facial skin; itching on the body without any rash; rough, irritated, dry, red, itching, spotty, or flaking skin; spotty skin rash; and brittle nails
Neurotoxic effects	Headaches, fatigue, unusual tiredness, lethargy, lack of concentration, feeling heavy-headed and difficulty concentrating, dizziness, nausea, irregular heartbeat, and tachy-/bradycardia
Chemosensory changes	Enhanced or abnormal odor perception, visual disturbances, and sensation of getting a cold

reported at least one work-related health symptom and 20% reported at least three recognized building-related symptoms [196,197]. The authors of the California Healthy Building Study involving 880 participants from 12 buildings estimated that more than 40% of the workers reported that work-related eye, nose, or throat irritation occurred often or always. Additionally, the prevalence of cases with at least three symptoms was approximately 20% or greater [198].

The European Health Optimization Protocol for Energy-Efficient Buildings and the European Audit Project covered 6537 occupants from 56 office buildings in 11 European countries (the Netherlands, Denmark, France, Belgium, United Kingdom, Greece, Switzerland, Finland, Norway, Germany, and Portugal). The three most prevalent building-related symptoms for the month preceding the building audit were lethargy or tiredness (52%), headache (42%), and dry eye disease (39%) [199,200]. A cross-sectional study involving 1,885 employees of 9 offices in the UK, reported that the prevalence of symptoms varied among buildings, from <5% to over 50% [201]. The Danish Town Hall Study was conducted to characterize sick building syndrome among the population of office employees in Demark. The 4,369 participants working in 14 different buildings had reported a prevalence of 28% of work-related mucosal irritation and 36% reported general symptoms in the form of headache and abnormal fatigue or malaise [201,202]. Additionally, an epidemiological study conducted in the Netherlands (7, 043 office workers from 61 office buildings) indicated that sick building syndrome is common, with the most frequently reported health complaints affecting the eyes (19.5%), nose/throat (23.5%) and nervous system (20.3%) [203]. The mean number of symptoms reported in the Whitehall II Study varied from 1.2 to 3.2. Only 25% of men and 15% of women reported no symptoms, and 14% of men and 19% of women reported five or more relevant symptoms. The Whitehall II Study included 4,052 participants aged 42–62 years working in 44 buildings in London (UK) [204]. The ProKlimA Project started in February 1995 in Germany, aimed to understand the phenomenology and etiology of sick building syndrome and involved 4,596 office workers from 14 office buildings. Overall, 22–55% of the occupants were affected, with the young and less well-educated reporting more symptoms and irritations [205]. Recently, the results of the European Union project OFFICAIR were published. The OFFICAIR (meaning "on the reduction of health effects from combined exposure to indoor air pollutants in modern offices") was a European collaborative project. OFFICAIR Europe was a large cross-sectional study performed during the winters of 2011 and 2012, gathering data from 167 office buildings in eight European countries (Greece, France, Finland, Hungary, Italy, Portugal, Spain and the Netherlands) simultaneously with questionnaire data from 7,441 office workers. Based on this study, an extensive database was created, which included both physical office building characteristics and individual sociodemographic data (e.g., age, sex, and educational level), lifestyle (e.g., smoking and alcohol intake), work-related data (e.g., computer use), psychosocial environment (work-related stress), and health symptoms [206–210]. The most prevalent symptoms reported were "dry eyes" (31%) and "headache" (29%). Ocular symptoms were generally very common, and at least one in five workers experienced eye-related symptoms, such as "burning or irritated eyes" (20%) and "watering or itchy eyes" (18%) [207,209].

In a nationwide study of 3,335 employees in 320 offices in Japan, the occurrence of at least one of 19 possible symptoms of sick building syndrome occurred in 24.9% of participants. The prevalence of frequent eye irritation, general symptoms, upper respiratory symptoms, lower respiratory symptoms, and skin symptoms strongly related to the work environment was 12.1%, 14.4%, 8.9%, 0.8%, and 4.5%, respectively [211]. In another large epidemiological study of 2,856 office workers in 56 office buildings in Singapore, symptoms typical of sick building syndrome were reported in 19.6% of the participants [212].

Studies from Brazil reported a high prevalence of general and mucous membrane-related symptoms among occupants of buildings. The most prevalent symptoms among 2500 office workers in São Paulo were nasal symptoms reported by over 60% of workers [213]. In another study of 1,736 office workers in a sealed office building and 950 office workers in a non-sealed office building, both in downtown Rio de Janeiro, the most prevalent reported symptoms were "lethargy" (58.5% sealed vs. 50.5% non-sealed) and "dry throat" (42% and 36%, respectively) [214].

Exposure to such indoor conditions is common in the general population, affecting children and adults, workers and nonworkers, and office and domestic environments. Affected workers may experience lost productivity because of irritating and chronic symptoms, which could cause absence due to sickness. Since sick building syndrome is not a clearly defined disease but rather a combination of nonspecific symptoms affecting multiple organs, the diagnosis is challenging and usually based on self-reports and the lack of pathophysiological abnormalities and the absence of any other specific diagnosis. There is no final accepted unified clinical set of symptoms for sick building syndrome and a broad variation exists among published studies. The symptoms severity may vary from person to person, even within the same building. Occupants might have different perceptions, even if they are exposed to the same environment. Additionally, the percentage of dwellings or offices with building-related problems may change depending on the definition of the condition used.

Another challenge in assessing sick building syndrome is the impact of technical development on the indoor environment during the last forty years. Heating, ventilation, and air conditioning systems have used various technologies to control the temperature, humidity, and purity of the indoor air since the 1980s. Many factors related to office standard equipment have changed (i.e., photocopiers, electronic devices, and type of paper). Moreover, the building environmental design standards have changed and could also differ significantly between countries. It is worth mentioning that non-industrial indoor environments almost always have multiple subliminal exposures and sources. Additionally, studies were conducted in different climate zones, and the causes of indoor environment alterations could be different in different climate zones. Finally, epidemiological studies can be significantly affected by information and selection bias. Data from most studies were collected through self-administered questionnaires without objective environmental measures, such as temperature, humidity, lighting, air velocity, carbon dioxide concentrations or monitoring of environmental agents such as volatile organic compounds and specific bioaerosols, such as molds or particulates. Only a few studies combined self-questionnaires of building occupants with indoor or outdoor environmental measurements [198,203,204,214–216].

Ocular symptoms associated with sick building syndrome are described as "tired or strained eyes," "dry, itching, or irritated eyes" and "watering eyes". These symptoms are general but may also be a sign of a specific ocular condition or disease, such as dry eye disease, refractive error, or conjunctivitis, which indicates a building-related illness rather than sick building syndrome. It should also be noted that dry eye disease was first defined as a disease rather than a disorder and sick building syndrome was listed as a modifiable risk factor for dry eye disease by the TFOS DEWS II Epidemiology Committee [217].

The relationship between the results of objective ocular surface analysis and the self-reported complaints has not been fully explored in sick building syndrome. Objective tests, including the Schirmer test and fluorescein tear break-up time were performed in 87 workers from a modern air-conditioned building (the sick building), and 76 working in three traditional office buildings (comparator buildings). The stability of the tear film was significantly reduced ($p < 0.01$) in the employees in the sick building compared with the employees in the naturally ventilated buildings [218]. In the ProKlimA Project conducted in Germany [205], participants were surveyed and objective ocular surface tests, such as tear break-up time, lipid layer thickness, lissamine green staining of conjunctiva and the presence of foam at the eyelid or canthus, were conducted. Tear break-up time appeared to be the best indicator for self-reported eye complaints accompanying sick building syndrome

[219]. Another study suggested that tear break-up time may be significantly confounded by other factors, such as a history of eye disease and female sex and may not necessarily be an independent objective indicator of sick building syndrome, and proposed that tear lipid layer thickness was a reliable eye-related indicator of the indoor environment [220]. No further studies clearly distinguished objective ocular signs as indicators for sick building symptoms.

Most sick building studies, especially in the 1990s, focused on office buildings, and only a few considered the domestic environment or other specific environments, such as hospitals [216,221–227]. Most studies have considered the prevalence of sick building syndrome in adults, but a limited number have reported prevalence in the pediatric population [228–230].

There are numerous possible causes and risk factors for sick building syndrome, and usually cross-sectional studies do not give strong evidence of causal relationships. The majority of sick building syndrome studies are surveys, with only a few longitudinal studies. Previous studies have all shown that the relationships between environmental conditions and human well-being in office buildings are complex and not easy to expose. Sick building syndrome is more likely to be caused by a combination of factors, which could be categorized as indoor environment-related, related to the occupant or worker in the building and outdoor environment-related. There was considerable inconsistency between the risk factors identified in cross-sectional studies and prospective analyses. In Denmark, a study found no clear evidence of sick building syndrome symptoms related to specific factors in the indoor environment in a one-year longitudinal study including 1,402 office workers [231]. However, exposures in the indoor environment were assessed via questionnaire without any objective environmental measurements. Other associations between indoor environment conditions (measured or reported) and sick building syndrome symptoms confirmed by longitudinal studies, include female sex [216,232], history of asthma or parental asthma [215,229], pollen or pet allergy [215, 229], biomarkers of allergy and inflammation [232], humidity [215], dampness [197,232,233], mold and fungal spore concentrations [230, 232], concentrations of benzene, toluene, ethylbenzene, and xylenes [216], elevated levels of indoor aldehydes and aliphatic hydrocarbons [232], lack of office cleanliness, floor dust, crowded office conditions, and low job satisfaction [230], indoor painting [232,234], lifelong smoking and environmental tobacco smoke exposure [216,234], and outdoor environmental pollution [215,229]. Possible sick building syndrome risk factors are presented in Table 4.

Table 4
Possible risk factors for sick building syndrome.

Risk factors for sick building syndrome	
Indoor environment Related	air temperature
	humidity
	air conditioning
	ventilation rate
	poor indoor air quality (IAQ)
	CO_2, NO_2, SO_2, and particulate matter smoking and
	environmental tobacco smoke (ETS)
	building dampness
	mold and fungal concentrations
	microbial VOC (MVOC) and bioaerosols
	volatile organic compounds (VOCs)
	concentrations of benzene, toluene, ethylbenzene,
	and xylenes (BTEX)
	aldehydes and aliphatic hydrocarbons
	floor dust
	newer buildings and renovations
	exposed concrete and/or plaster
	indoor painting
	synthetic materials in building
	new furniture
	wall to wall carpeting and laminated floor
	window condensation
	absence of operable windows
	frequency of cleaning
	visual display unit (VDU) work
	use of carbonless paper
	crowded office
	presence of cockroaches, rats, and mosquitoes/flies
Occupant of the building Related	female gender
	age
	allergic disorders: pollen or pet allergy and atopy
	parental asthma/allergy (heredity)
	biomarkers of allergy and inflammation
	perception of odor
	personality trait
	work stress and psychosocial stress
	socioeconomic status
	working conditions
	low job satisfaction
	depression
	skin type
	social and economic factors
	perceived control over indoor climate
	perceived dry air (not equivalent to low humidity via objective measures)
Outdoor environment Related	outdoor air pollution
	SO_2, NO_2, O_3, and particulate matter climatic factors
	temperature, humidity, and wind speed
	traffic - living near a main road or highway

Underlined factors are those derived from longitudinal studies.

2.3.2. *Sick house syndrome*

Sick house syndrome occurs in residential dwellings and has a similar definition to sick building syndrome. Symptoms are experienced when the person is in the house and are alleviated when away from the domestic environment for a period of time. Most of the knowledge about sick house syndrome, is based on studies from Sweden, Japan and China. A Swedish study, which investigated 14,235 dwellings in the 1990s, revealed that the prevalence of sick building/house symptoms among the adult population was relatively high, with "tiredness" occurring in 24% of responders, followed by nasal symptoms in 13% [215]. Additionally, in Sweden, a large population-based, cross-sectional study (3, 000 randomly selected Swedes, aged 18–64 years) was conducted with the main aim of measuring the prevalence of general, mucosal, and skin symptoms in the Swedish adult population. "Fatigue" was the most frequently reported symptom, which occurred in 36.3% of responders. The second most frequently reported symptom was "dry facial skin", which occurred in 17.6% of responders. The most common mucosal symptom was ''irritated, stuffy, or runny nose'' reported by 8.8% of responders. The general risk of developing SBS, defined as an individual reporting at least one general symptom, one mucosal symptom, and one skin symptom every week over three months, was estimated to be 4.3% of workers and 4.8% of nonworkers in the Swedish population aged 18–64 years. Office workers did not report sick building syndrome symptoms more frequently than those not working in offices. This observation changed the perception of sick building syndrome, as it was no longer limited to non-industrial or office workplaces [235]. Another longitudinal population study conducted in Sweden, evaluated sick building syndrome symptoms and domestic environmental conditions in a population sample of 1,000 adults aged 20–65 years with a 10-year follow-up period (1991–2001). For the 427 responders at the follow-up, the cumulative incidence of subjects with new onset of at least one symptom of SBS in each group was highest for mucosal symptoms (28%), 25% for general symptoms and 12% for skin symptoms. The prevalence of mucosal symptoms remained unchanged, while general and any skin symptoms decreased within the observation period [236]. The Buildings, Energy use, Technical Status and Indoor environment (BETSI) Study was commissioned by The Swedish National Board of Housing, Building and Planning in 2006 and studied 821 single-family houses. Almost one quarter (23%) of responders reported having at least one weekly sick building syndrome symptom during the last three months. In total, 17% reported general symptoms, 8.4% re- ported mucosal symptoms and 6.3% reported skin symptoms [233]. As

part of the European Community Respiratory Health Survey (ECRHS study), a random sample of 1800 men and 1800 women aged 20–44 years during the years 1990–2002, from the population in Sweden were surveyed for sick building syndrome symptoms. The 10-year incidence (onset) of general, mucosal, and skin symptoms in the population of 452 participants, was 8.5%, 12.7%, and 6.8%, respectively [234].

A nationwide study conducted in Japan, covered six areas of northern and southern Japan, including 2,297 dwellings. The percentage of households with either one or more residents showing symptoms of sick house syndrome ranged from 1.4% to 5.7%, with a mean of 3.7% [216]. A longitudinal study also conducted in Japan identified approximately 14% and 12% of subjects as having sick building syndrome symptoms in the first and second years of the study, respectively [223].

The China, Children, Homes, Health Study was a large multicenter study of asthma, allergies and sick building syndrome among parents and children and associations with the domestic environment in China [237]. The sick building syndrome results were based on cross-sectional studies performed in certain subgroups. Parents (n = 5,299) of 3–6-year-old children from 54 randomly selected kindergartens in Chongqing reported that the prevalence of adult sick building symptoms at least once every week was 11.4% for general symptoms, 7.1% for mucosal symptoms and 4.4% for skin symptoms [221]. Analysis of a further subgroup including parents (n = 4,530) of 1–8-year-old children from randomly selected kindergartens in Chongqing, the prevalence of adult sick building syndrome SBS symptoms reported weekly or sometimes was as high as 78.7% for general symptoms, 74.3% for mucosal symptoms and 47.5% for skin symptoms [221]. The prevalence of weekly sick building syndrome symptoms in the entire China, Children, Homes, Health Study cohort, including 36,541 adults, was: 2.8% for eye symptoms, 4.1% for throat symptoms, 4.8% for skin symptoms, 3.0% for headache and 13.9% for fatigue [238]. The questionnaire survey subgroup of the China, Children, Homes, Health Study, included 7,865 families with infants, and 14% of adults reported general symptoms, followed by 11% for mucosal symptoms and 9% for skin symptoms [228].

Limited data are available regarding the prevalence of sick building syndrome in schools and universities, including in children and students [229,230,232]. A systematic review of studies reporting the effects of indoor school environments and the performance of children, concluded that little direct scientific evidence of high quality was available. Nevertheless, even the incomplete findings provide suggestive evidence that indoor conditions commonly found in schools (low ventilation, dampness, microbiological and chemical exposures) have adverse effects on the general health and academic performance of schoolchildren [224]. A cross-sectional study of 10,851 children (1–6 years old) in Sweden reported a high prevalence of symptoms (rhinitis 11.1%, eczema 18.7%, and wheezing 18.9%), possibly related to indoor environmental conditions, especially dampness [232]. Two 2-year prospective studies among pupils of junior high schools in Taiyuan, China, reported prevalence and possible risk factors for sick building syndrome in children. The first study included 1,993 pupils at baseline and 1,143 after a period of two years. The prevalence of mucosal and general symptoms was 33% and 28%, respectively, at baseline and increased at follow-up to 40% and 44% ($p < 0.001$) [229]. The second study comprised 2,134 pupils who participated at baseline, and 1,325 pupils at follow up, who used in the same classrooms throughout the study period (2010–2012) also reported a high prevalence of sick building symptoms. The prevalence of mucosal and general symptoms was 22.7% and 20.4%, respectively, at baseline, and the prevalence also increased during follow-up to 29.7% and 35.6% ($p < 0.001$) [230].

2.4. Other risk factors

2.4.1. Use of masks - Covid 19

Face mask wear became endemic in the COVID-19 pandemic. A systematic review of 172 observational studies across 16 countries included 25,697 patients with COVID-19, Severe Acute Respiratory Syndrome or Middle East Respiratory Syndrome and summarized the best of available evidence to support the use of masks, as well as physical distancing to reduce the risk of contamination by coronaviruses and this recommendation and such strategies were consequently recommended worldwide [239]. There is an increasing awareness of mask-associated dry eye, due to leakage of air and limitations to lower lid movements from inappropriate mask fitting [240]. Where used, tape adhering to the skin of the nose and upper cheek may also interfere with movement of the lower lid, which may cause secondary entropion and lagophthalmos [240,241]. A study from Italy reported that 18.3% of 3,605 participants experienced mask-associated dry eye, and there was a positive association between those with mask-associated dry eye and females and those who undertook retail work [242]. A study from Croatia reported that mask-associated dry eye was more prevalent in subjects with a history of dry eye disease, those wearing a mask for longer than 3 h a day, and subjects who were female. There was no association between age and mask-associated dry eye in these studies [242,243]. A study including 31 patients with moderate-to-severe dry eye in Spain, reported that mean non-invasive tear break-up time with face mask wear was 12.3 ± 4.8s and increased to 13.8 ± 5.0s without a mask ($p = 0.006$) [244]. Ocular consequences of pandemic mitigating measures are described in detail in the systematic review of the Societal Challenges Report [245].

2.4.2. Exposure

2.4.2.1. Biochemicals and bioterrorism. Bioterrorism is terrorist action involving the intentional release or dissemination of a biological warfare agent, which includes some bacteria, viruses, *Rickettsiae*, fungi or biological toxins. The US Center for Disease Control and Prevention has categorized Biological Weapons Agent Sampling, based on the risk to national security, into three categories: Category A (highly toxic and high-priority agents), Category B (relatively easy to disseminate, resulting in low mortality rates and mild morbidity rates) and CategoryC (emerging pathogens that could in future be engineered for mass exposure because of ease of production and dissemination, availability, and potential for high mortality and morbidity).

The ocular surface, in the context of Biological Weapons Agent Sampling is not considered to be a main target, because most biological agents are designed to affect the lower respiratory tract. However, short- and long-term ocular adverse effects can occur. Examples of agents with ocular surface involvement include *Bacillus anthracis*, Monkeypox virus, mycotoxins and enterotoxins [246]. Another example of induced ocular surface damage is the use of the so-called "yellow rains" containing Trichothecene mycotoxins (Category B). These myotoxins cause multiple general symptoms involving dyspnea, wheezing, tachycardia, nausea, vomiting, diarrhea, vascular and hematologic changes. Contact with the ocular surface results in an immediate ocular pain, followed by conjunctivitis and blurred vision [246,247]. Trichothecene mycotoxins are likely to have been used in combination with sulfur mustard, so called 'yellow rain'. Sulfur mustard (SM - bis(2-chloroethyl) sulfide) is a chemical agent, which affects the ocular surface causing epithelial defects, chronic inflammation, neovascularization and permanent corneal limbal stem cell deficiency. *Staphylococcus aureus* enterotoxin type B (Category B) is another potential biological weapon causing possible ocular effects. It may be absorbed by the conjunctival mucous membranes, and subsequently cause systemic immune activation [246,248]. The aerobic Gram-positive rod *Bacillus anthracis* (Category A) is considered as the most efficient agent for large-scale biological attack and can cause potentially lethal diseases affecting different organs [246,247]. Although rare, palpebral involvement may occur in about 4% of cases and lead to sight-threatening complications, such as ectropion, lagophthalmos and corneal scars [249,250]. Monkeypox virus is classified as Category C and there are rising concerns about its potential use as a bioterrorism agent [251]. Ocular involvement is as high as 25% for

conjunctivitis and unknown for complicated blepharoconjunctivitis. Serious ocular complications include corneal abrasions and ulcers, which ultimately lead to corneal scarring [252].

2.4.2.2. Infectious aerosols and bioaerosols. An infectious aerosol is defined as "a collection of pathogen-laden particles, such as viruses, bacteria, and fungi in air" [253], which usually contains pathogens accompanied by body fluids, transmitted through coughing or sneezing, normal human speech or because of medical procedures [254,255].

Infectious aerosol transmission has been mainly attributed, but not limited to following pathogens: *Neisseria meningitidis*, *Mycobacterium tuberculosis*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Mycoplasma pneumoniae*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Middle-East Respiratory Syndrome-associated Coronavirus*, *Severe Acute Respiratory Syndrome Coronavirus*, *Varicella Zoster virus*, *Ebola virus*, *Norovirus*, *Influenza virus*, [253,256–259]. Evidence supports the existence of trans-ocular transmission for several pathogens including: *Respiratory Syncytial virus*, *Influenza virus* and *Severe Acute Respiratory Syndrome Coronavirus* [260–264]. Respiratory droplets containing different serotypes of adenovirus have also been postulated as a possible means of contamination causing epidemic keratoconjunctivitis and pharyngoconjunctival fever, although in the case of adenoviruses, direct contact with ocular secretions is the most common mode of transmission [265,266].

Infectious aerosols can be included in the general group of bioaerosols, which includes not only pathogenic bacteria, fungi and viruses but also non-pathogenic live or dead bacteria and fungi, viruses, high molecular weight (HMW) allergens, bacterial endotoxins, mycotoxins, peptidoglycans, β (1 → 3)-glucans, pollen and plant fibers [267]. Bioaerosols may have infectious, allergic and toxic effects on human health. It is worth underlining that bioaerosols are subject to the same physical laws as other airborne particulate matter in the outdoor and indoor environment and particle size is the most important determinant of aerosol behavior [268]. Moreover, factors such as temperature, humidity and sunlight exposure can all act to inactivate free-floating, airborne infectious organisms [269].

Mucous membrane irritation including ocular surface may be caused by several bioaerosol agents as fungi, bacteria, actinomycetes, endotoxin, β (1,3)-glucans, peptidoglycans, mycotoxins, and probably many other currently unidentified plant and amicrobial components. Environmental exposure of bioaerosols might be related to agriculture and industry activities, such as slaughterhouses, wood industry, paper production, fermentation industry, metal machining industries, garbage collection and composting and buildings with contaminated heating, ventilation and air conditioning systems [267,270]. Several effects of bioaerosols on ocular surface signs and symptoms have been studied in experimental and epidemiological studies. In a study including 368 students, a reduced tear film stability was associated with the concentration of total fungal DNA and Aspergillus/Penicillium DNA in dust vacuumed from the school classrooms [271]. Results of longitudinal studies have linked molds, fungal DNA and bacterial component concentration to ocular symptoms. A 1-year prospective study suggested that total culturable fungal concentrations in floor dust may have nonlinear correlations with eye irritation, although these associations did not persist after controlling for the amount of floor dust [272]. In a 10-year longitudinal study in a Swedish population, dampness or indoor molds at baseline was a predictor of the incidence of mucosal symptoms (RR 2.28 95% CI 1.46–3.55) [234]. Another longitudinal study suggested a protective effect of bacterial compounds in settled dust relative to the incidence of mucosal symptoms. Associations between fungal DNA levels and symptoms were equivocal; the onset of indoor environmental symptoms was positively associated with total fungal DNA, but total fungal DNA was also unexpectedly positively associated with remission of mucosal symptoms [230].

The certainty of the currently available evidence regarding the exact effect of different bioaerosols on ocular surface signs and symptoms is low. Further studies are necessary in this field.

2.4.3. Smoking

Smoking is a common form of recreational drug use. Nearly a quarter of the global population (22.3%) smokes tobacco, making it the most popular form of smoking. Less commonly smoked drugs are cannabis, opium, and crack (cocaine) [273]. Tobacco use sickens and kills millions of people every year, over eight million people died from tobacco-related diseases in 2019 [274]. Tobacco cigarettes can produce over 6,000 chemical constituents, including NO_2, CO_2, volatile com- pounds, phenolic compounds, nitrosamine compounds, aromatic amines, polycyclic aromatic hydrocarbons, as well as varying amounts of metals, identified as toxins and carcinogens. Active and passive smoking creates numerous health problems that affect the cardiovas- cular and respiratory systems [275].

Tobacco smoke exposure has negative effects on the ocular surface, often triggering lipid layer changes, apoptosis, inflammation, reactive oxygen species-mediated DNA oxidation and impairment of autophagy [276,277] (See also Lifestyle Report [278] and Societal Challenges Report [245]). Clinical evidence has also linked smoking with various ocular surface alterations. Although epidemiological studies play a key role in the assessment of ocular surface risks, there is a dearth of large well-controlled studies evaluating the harmful effects of cigarette smoking on the ocular surface and cornea. Currently, it is assumed that tobacco smoke causes instability of the tear film by increasing tear evaporation rate and reducing tear film lipid spread time, which promotes ocular surface damage in chronic smokers [279]. Mucin changes and a reduction in goblet cell density, reported in some studies [280–282], also explain the lower tear break-up time commonly observed among tobacco smokers. Contact lens wearers presented with decreased tear break-up time after passive smoke exposure but with no change in the mean tear evaporation rate or vital staining scores [283].
Perhaps counterintuitively, given these ocular surface effects, in large epidemiological studies [150] and in a meta-analysis of published studies [284], there was no association between current smoking and dry eye disease.

It is well established that gas phases of tobacco smoke contain numerous oxidizing substances, which expose inhalers to an excessive free radical load and make corneal epithelial cells more susceptible to apoptosis and damage [285]. The deleterious effects of even short passive tobacco smoke exposure on the tear film and ocular surface is evidenced by an increase in lipid peroxidation products, tear inflammatory cytokines, as well as a decrease in mucosal defenses, causing tear instability and damage to the ocular surface epithelia [280]. More recently, alterations in the anatomy and function of meibomian glands have been described among tobacco smokers, including abnormal meibum quality, alterations of the lid margins and a decrease in meibomian gland density, confirmed by *in vivo* confocal microscopy and meibography [286,287]. Of note, *in vivo* confocal microscopy among chronic smokers revealed decreased corneal basal epithelial density, anterior and posterior keratocytes density, endothelial cell density and sub basal nerve count [286]. Smoking also enhances the risk of squamous metaplasia of the cornea and bulbar conjunctiva [288], as well as keratitis by delaying corneal wound healing in smokers, thus preventing epithelial regeneration and ulcer healing [289,290].

Vaping, i.e., the use of electronic cigarettes has risen in popularity, showing an increase from seven million to over 41 million users worldwide from 2011 to 2018. In electronic cigarette devices, heat is used to produce an aerosol that contains nicotine (the highly addictive chemical found in tobacco products), flavorings and other substances that are inhaled by the user. Electronic cigarettes are alleged to be a safer alternative to cigarettes. However, the current literature suggests that these may pose a real threat to ocular surface health and advises utmost caution on their use. Exposure to electronic cigarette vapor can cause corneal staining, with nicotine and acrolein potentially triggering an

inflammatory response in corneal epithelial cells [291].

Several other recreational drugs may also produce lasting ocular surface alterations, such as the Crack Eye Syndrome, whose spectrum of clinical features includes microbial keratitis, corneal epithelial defects and superficial punctate epithelial keratopathy [292]. A recent systematic review of case reports of ocular complications after the use of crack cocaine proposed several pathophysiologic mechanisms, including: 1) a direct toxic effect of crack cocaine smoke on the structural and functional properties of the corneal epithelium; 2) the anaesthetizing effect of the crack cocaine vapors which may delay the normal blinking reflex and result in exposure keratopathy; 3) devitalization of the corneal nerves due to chronic exposure to crack cocaine may lead to reduced neurogenic support of corneal epithelial integrity; 4) repeated exposure to crack cocaine smoke an alkaloid form of cocaine could create a chronic low-grade chemical burn that might result in corneal epithelial defects; and 5) mechanical trauma from eye rubbing may be related to corneal epithelial defects [293]. According to a review of case series, corneal disease caused by smoking crack had two clinical manifestations: 1) relatively painless vision loss, redness and purulent discharge in one or both eyes; and 2) painful vision loss, redness, photophobia and tearing associated with sterile epithelial defects due to eye rubbing [294]. A systematic review found that the majority of cases (63%) had bilateral involvement; 83% of all cases with microbial culture results had corneal infections. Even with aggressive treatment, 22% remained with significant visual impairment [293].

There is robust evidence of the ill-effects of tobacco and other illicit drug use. To solve to this global health issue, there is a pressing need to increase knowledge and create more awareness about mortality risks as well as to support and promote smoking cessation.

3. Environmental-related ocular surface diseases

3.1. Dry eye disease

Dry eye disease is considered a multifactorial disease of the ocular surface characterized by ocular symptoms, tear film abnormalities, inflammation, and damage to the ocular surface. It is mainly classified into aqueous deficient dry eye and evaporative dry eye, however mixed disease also evidently exists [295].

Dry eye disease is the most common ocular surface disease in the world, with prevalence based on symptoms and signs ranging from 5 to 50%. In assessing the prevalence of dry eye disease based on severe symptoms of dryness and irritation and/or a physician's diagnosis of dry eye (Women Health Study criteria), 4.3% was reported as an age-adjusted result in American male subjects (median age 64.4 years old). In Asian studies using the Women Health Study criteria, the overall prevalence based on symptoms only, ranged from 14.4 to 24.4% (South Korea: 14.4–17.7%, Japan: 11.5–24.4%, China: 23.7%) [217]. The prevalence of dry eye disease based on symptoms and signs ranged from 8.7 to 30.1% Prevalence appears to be higher in Asian than in Caucasian populations. The prevalence of meibomian gland dysfunction, based on population-based studies, ranged from 38 to 68% in those older than 40-years. The prevalence of dry eye disease mostly increased signifi-cantly and showed a positive association with age and the prevalence of MGD increased by 5.3% per decade. The increase in prevalence for signs of dry eye disease with age showed a greater change than for symptoms [217]. Demographic factors in dry eye disease are described in detail in the Societal Challenges report [245].

Environmental exposures are listed as consistent risk factors of dry eye disease along with age, female sex, Asian race, meibomian gland dysfunction, connective tissue disease, Sjögren syndrome, androgen deficiency, and modifiable factors including computer use, contact lens wear, hormone replacement therapy, hematopoietic stem cell transplantation, and medications (antihistamines, antidepressants, anxiolytics, isotretinoin) [217]. The economic burden of dry eye disease includes direct medical care spending, the loss of productivity, and impact on quality of life [217,296,297]. In addition, dry eye disease can reduce overall quality of life, and the related components are ocular pain and irritation, and decreased well-being, and visual performance [217]. Patients with mild and severe dry eye disease experience a reduction in quality of life at a level similar to that experienced as result of mild psoriasis or moderate-to-severe angina [298]. In everyday life, such as driving, reading, carrying out professional work, using a computer, and watching television, those with dry eye disease reported three times more difficulty than those without [299]. Risk factors associated with dry eye disease are explored in detail in the Lifestyle Report [278].

Symptoms of dry eye disease can be confirmed by symptom questionnaires such as the 5-item dry eye questionnaire (DEQ-5) or Ocular Surface Disease Index (OSDI) (with cut-off values of ≥ 6 or ≥ 13, respectively) [300]. Visual disturbance can be assessed subjectively with either the DEQ-5 or Ocular Surface Disease Index questionnaire. Other dry eye questionnaires available to quantify symptoms include the Standard Patient Evaluation of Eye Dryness and Assessment in Dry Eye instruments. Tear film instability is a key diagnostic measure. Tear break-up time is preferably performed using a non-invasive method, or with fluorescein if a non-invasive measure is not available. Tear volume is also an important diagnostic component in aqueous deficient or mixed dry eye disease. Schirmer test and tear meniscometry are common diagnostic methods for tear volume. The Schirmer test with a cut-off level of $\leq$ 5 mm has a reported 84% sensitivity and 58% specificity, and the topographic tear meniscus height, optical coherence tomography-based assessment of tear meniscus height, radius of tear meniscus curvature, and tear meniscus area, have been used increasingly in more recent years for evaluating dry eye disease [300]. Tear osmolarity testing is another important diagnostic method, with high correlation to disease severity. Tear osmolarity of $\geq$308 mOsm in either eye or an interocular difference of osmolarity>8mOsm has become a widely accepted cut-off level for dry eye disease [301]. Ocular surface staining is a common feature in dry eye disease, frequently assessed using sodium fluorescein and/or lissamine green dye. The van Bijsterveld system, the National Eye Institute/Industry Workshop guidelines, the Collaborative Longitudinal Evaluation of Keratoconus schema, the Oxford Scheme, the area/density combination index, and the Sjögren's International Collaborative Clinical Alliance ocular staining score, among others, can be applied for internal consistency in recording of ocular surface staining, noting the different systems are not interchangeable [302–307]. Ocular surface inflammation is related with pathophysiological mechanism in dry eye disease; however, inflammation is not specific to dry eye disease Conjunctival redness and ocular surface immune markers (for example, HLA-DR expression in immunocytochemistry of impression cytology samples) have been used as diagnostic tests. In addition, the level of tear matrix metalloproteinases can also be of diagnostic value in dry eye disease. A commercial 'point of care' diagnostic test that assays tear matrix metalloproteinase-9 levels is clinically available and levels $\geq$40 ng/ml indicate ocular surface inflammation. Interferometry of the tear film, meibography, meibomian gland expressibility/duct assessment, and blink/lid closure analysis are also diagnostic tools for assessing the tear film, presence and severity of meibomian gland dysfunction, and tear distribution [300].

The core mechanism of dry eye disease is a desiccating environmental stress causing hyperosmolar tissue damage on the ocular surface. Consequently, aggravation of ocular surface inflammation provokes the vicious inflammatory cycle of dry eye disease. Conjunctival goblet cell loss and decreased tear secretion from abnormality of the lacrimal functional unit are also triggered. Pain and decreased visual function can also be accompanied by tear hyperosmolarity, loss of lubrication, inflammatory mediators and neurosensory factors, and tear and ocular surface irregularity [308].

Most patients with dry eye disease experience acute episodic flares, associated with various environmental stresses, typically associated with rapid exacerbation of ocular discomfort, and aggravation of inflammation. The adaptive immune reactions are already activated,

and acute flares can lead to rapid increase in inflammation at much lower thresholds in chronic dry eye disease than in a normal eye [309]. Environmental exposure mechanisms for dry eye disease also include oXidative stress and its impact on inflammation. Several outdoor and indoor environmental pollutants may also induce changes in epigenetics, the ocular surface microbiome, immune tolerance, and normal defense mechanisms [310]. However, there is a critical limitation, particularly in human studies, that exposures from environmental pollutants are difficult to measure and standardize. It may be possible to establish a more controlled environment in animal studies, but the levels of exposure are often extreme, and it is not matched with real-world human life exposures. Additional or synergistic ocular surface aggravation from combinations of pollutants should be also evaluated. More advanced technology in measuring of environmental factors and identification of susceptible individuals requiring early treatment of dry eye disease are needed.

3.2. *Allergy*

Ocular allergy is a broad term encompassing various IgE- and non-IgE-mediated ocular surface hypersensitivity disorders [311]. As highlighted by the Task Force Report from the European Academy of Allergy and Clinical Immunology Ocular Allergy Interest Group on Diagnosis and Management of Ocular Allergy, pathogenesis, and clinical manifestations, together, can be used to classify these disorders. Typical IgE-mediated allergic diseases include seasonal and perennial allergic conjunctivitis, while a complex pathogenesis, miXing IgE-mediated and non-IgE-mediated allergic reactions, is a key feature of vernal and atopic kerato-conjunctivitis [311].

Despite the large body of literature on the incidence and prevalence of systemic allergic diseases, evidence on the epidemiology of ocular allergy is relatively poor [311,312]. Published studies show marked heterogeneity with respect to their design, population, geographical area, and disease identification approach (including interviews, questionnaires and ophthalmological examinations) [312].

A web-based survey, performed in 2017 in Japan, reported that, in the general population, the prevalence of seasonal allergic conjunctivitis, perennial allergic conjunctivitis, atopic keratoconjunctivitis and vernal keratoconjunctivitis in the general population was 45.4%, 14.0%, 5.3%, and 1.2%, respectively [312]. The only large population-based study on adults, adopting interviews as the survey method, reported a prevalence of allergic conjunctivitis of 40% [313]. This report, based on data extracted from The National Health and Nutrition EXamination Survey III, performed between 1988 and 1994 in the US, defined those reporting at least 1 occurrence of ocular allergic symptoms in the previous 12 months as cases.

Population-based studies performed on children and adolescents, have reported prevalence rates of allergic conjunctivitis ranging from 17.5% [314] to 39.9% [315] The lower value (17.5%), arose from a large (n = 33,902), population-based survey performed in Japan on elementary school children (6–12 years) through 1992, 2002, and 2012 [314]. The study was published in Japanese, but the results are summarized in a recent review [312]. Another large survey conducted in Japan, on 13,215 school children (7–15 years) in Kyoto, reported that a lifetime prevalence rate of allergic conjunctivitis of 30% in 2006, versus 24.5% in 1996 [315].

A cross-sectional study performed on school children in Karachi, Pakistan, one of the most populated cities in the world, reported a prevalence of active ocular allergy, identified on the basis of symptoms and slit-lamp examination, of 19.2% [316]. The highest prevalence of allergic conjunctivitis in children and adolescents was reported by a study conducted in Kumasi Metropolis, Ghana. In this cross-sectional study, based on symptoms and slit-lamp examination, 39.9% of 1,571 students had active ocular allergy [315].

Given the frequent association between ocular and nasal allergic manifestation, several studies investigated the prevalence of rhino conjunctivitis. The French population-based study, performed in 2006 on 4,019 adults, reported 16.5% of prevalence of rhino conjunctivitis symptoms [317]. The International Study of Asthma and Allergies in Childhood Phase Three Study Group reported the outcomes of a large questionnaire-based survey covering all the major regions of the world and involving 1,059,053 subjects of 2 age groups (13–14 years and 6–7 years), in 98 countries [318]. In 13-14-year-olds, the average prevalence of current rhino-conjunctivitis symptoms was 14.6%, ranging from 9.2% in Northern & Eastern Europe to 17–18% in Latin America and Africa. In 6-7-year-olds, the average prevalence of current rhino conjunctivitis symptoms was 8.5%, ranging from 4.2% in the Indian subcontinent to 12.7% in Latin America with larger variations among countries. Smaller but most recent questionnaire-based surveys performed on adolescents in Italy and Kuwait, reported a prevalence of 20.5% and 28.6%, respectively [319,320].

The most severe forms of ocular allergy, vernal and atopic keratoconjunctivitis, although rarer, deserve specific focus, given their major impact on quality of life and their potential for devastating visual complications. The prevalence of vernal keratoconjunctivitis in Europe was estimated by a study analyzing questionnaires completed by 776 ophthalmologists from 6 different countries [321]. This study reported prevalence ranging from 0.003% to 0.3%, with higher values in Italy and lower values in other northern European countries. This analysis was based on several assumptions, including that all patients with vernal keratoconjunctivitis were referred to ophthalmologists, potentially leading to underestimating the disease prevalence. Most ophthalmological examination-based surveys on vernal keratoconjunctivitis have been conducted in African countries, reporting prevalence from 4% (in 3,041 school children in Rwanda) [322] to 11.1% (in 574 school children in Ethiopia) [323].

The previously described Japanese web-based survey is the only population-based published study reporting prevalence of atopic keratoconjunctivitis; 5.3% in the general population were affected [312]. Ophthalmic patient-based surveys reported that the proportion of atopic keratoconjunctivitis relative to all ocular allergy ranges from 4.7% [324] (in 455 Thai patients of all ages) to 7% [93] (in 3,545 Italian patients of all ages). Nevertheless, a study design based on the requirement for an ophthalmologist consultation might potentially lead to an overestimation of the proportion of severe forms of allergy such as atopic keratoconjunctivitis.

Among children and adolescents, the literature suggests an association between ocular allergic manifestations and increasing age. Together with the previously mentioned International Study of Asthma and Allergies in Childhood Phase III study on rhino conjunctivitis [318], other smaller cross-sectional studies have reported similar age-related changes in allergic conjunctivitis [315,316]. Other than vernal keratoconjunctivitis, which shows a significant male predominance in several studies [323,325,326], data on the sex-distribution of allergic conjunctivitis and rhino conjunctivitis are equivocal [314,316,319,320].

Interestingly, a large study performed in schoolchildren in Kyoto, reported an increase in both allergic conjunctivitis and allergic rhino conjunctivitis during the spring cedar pollen season from 1996 to 2006 (prevalence of 13% vs 25% and 3% vs 8%, respectively). Prevalence increased more in boys than in girls over the 10 years, reversing the female predominance seen in 1996 [327].

The increase in the prevalence of ocular allergy in recent decades, that is strongly supported by data from the International Study of Asthma and Allergies in Childhood studies, is consistent with the report from the World Allergy Organization (WAO) on the rising burden of allergic diseases worldwide, particularly in children [328]. The comparison of Phase III versus Phase I data (2002/2003 versus 1993/1997), shows a global increase of children and adolescents experiencing rhinoconjunctivitis [318].

Some forms of ocular allergy show seasonal variations in symptom prevalence and severity due to pollen count and weather variations. Airborne pollen is one of the most common triggers of allergic disease,

including rhino conjunctivitis [93,320,329,330], and pollen count plays an important role in defining the peak of active cases and anti-allergic drugs use observed in spring and fall in several regions with temperate or continental climate. An interesting longitudinal study performed on children sensitized to grass pollen, showed that eye symptom scores increased with pollen count beyond concentrations of about 70 grains/m^3 and did not plateau until about 140–150 pollen/m^3. These results, together with relevant variations observed in relation to respiratory allergy, suggest benefit in a traffic light model for directing public pollen warnings toward children [329]. However, as highlighted by studies focusing on cedar pollen in Japan, there are obvious discrepancies in the regional differences in the relationship between seasonal allergic conjunctivitis and pollen dispersion [312,331]. This suggests that other exogenous factors may serve as an adjuvant-like mechanism, leading to increased prevalence.

Growing evidence supports the association between ocular allergy, at least the more severe forms, and air pollution. The questionnaire-based cross-sectional study performed in Japan in 2017, involving 3,004 subjects, found that the prevalence of vernal keratoconjunctivitis was significantly associated with the levels of NO_2 and PM_{10} (ORs of 1.72 and 1.54 (per quintile), respectively) and the prevalence of atopic keratoconjuctivitis was significantly associated with NO_2 (OR of 1.23). Interestingly, other than seasonal allergic conjunctivitis, no other ocular allergic disease had significant associations with the degree of pollen dispersion, and when pollen count was included in multivariate analysis it had no impact on the air pollutants coefficients [331] A large Indian cross-sectional, hospital-based study found a strong, statistically significant, association between ground-level ozone and the temporal pattern of recent onset allergic eye disease [332].

Pollen dispersion and air pollution are environmental factors of great interest, particularly for the implications for public health policy. The literature suggests that a wide range of exogenous and endogenous risk factors play a role in ocular allergies. Furthermore, as highlighted by an Italian cross-sectional study, only about 20% of patients affected by ocular allergy report a single factor as the primary trigger of conjunctivitis [93].

Risk factors associated with a higher prevalence of ocular allergy include climate-related factors of high environmental temperature and low humidity [312,332], exposure to mold/dampness [319], dust particles [93,315,323], cigarette smoke [93,319], close household animal contact during childhood [320,323], and atopic parental history [93, 319,320].

The "hygiene hypothesis" (suggesting that childhood exposure to microorganisms might protect against allergies, including ocular allergy) [333], seems to be supported by studies reporting a significant inverse correlation between the prevalence of rhino conjunctivitis symptoms and the number of total and older siblings [320]. However, a recent sub-analysis of worldwide data from the International Study of Asthma and Allergies in Childhood studies Phase III study on asthma, rhino-conjunctivitis and eczema, showed that inverse associations with older siblings are mainly a phenomenon of more affluent countries, whereas greater severity of symptoms in larger families is globally more widespread [333].

Itching is considered as the hallmark symptom of ocular allergy, and thus has been required as an inclusion criterion in some studies [314]. Its high prevalence, ranging from about 73% [324] to 100% [315], is widely reported in the literature [93,316]. Besides itching, common symptoms and signs of ocular allergic disease are tearing (40%–95%), grittiness (54%–60%), discharge (54–66%), redness (71%–92%), papillae (47%–97%), chemosis and follicles [93,315,324,327]. Photophobia, reported in about 30% of patients with allergic conjunctivitis, is much more prevalent in vernal and atopic keratoconjunctivitis (about 80%) [93]. These severe forms of ocular allergy, together with classic manifestations of allergy (reported as more severe), show specific signs including eyelid skin involvement (reported in 37% of atopic keratoconjunctivitis patients), giant papillae, limbal infiltration, Horner-Trantas dots, and corneal involvement [93,315,324].

The severity of corneal involvement ranges from superficial epitheliopathy to shield ulcers. Keratopathy is widely reported as a complication of major clinical relevance, however data on its prevalence are highly heterogeneous, ranging from 1% to 15% [93,334–336], possibly because of differences in corneal exam accuracy and lack of standardization in defining the condition. Amblyopia is anecdotally reported as a possible complication of corneal involvement in children with vernal keratoconjunctivitis [337]. Vernal keratoconjunctivitis manifestations are described as tarsal, limbal or mixed, with highly heterogeneous relative prevalence [93,323–326,335,336].

Additional potential complications of severe forms of ocular allergy are those related to the use (and misuse) of steroids, including cataract and glaucoma. These complications are currently rare in Western countries but steroid-induced glaucoma in patients with vernal keratoconjunctivitis is a devastating condition in certain areas of the world. A recent dramatic report, retrospectively analyzing records of 4,062 patients with vernal keratoconjunctivitis who visited a tertiary center in India, showed a prevalence of glaucoma of 2.24%, with one-third requiring surgery and one-third bilaterally blind [338]. A possible complication of ocular allergy, which remains controversial, is keratoconus, possibly because of the combined effect of eye rubbing-related repetitive mechanical trauma and release of inflammatory mediators. However, three recent systematic reviews on this topic, published between 2020 and 2022 [339–341], reached highly contrasting conclusions, ranging from "eye rubbing, family history of keratoconus, allergy, asthma, and eczema being the most important risk factors for keratoconus", to no significant association being observed between KC and allergic eye disease, eye rubbing, or atopy". One of these three systematic reviews may be unreliable because of inappropriate meta-analysis methods [339].

A growing body of evidence supports the role of ocular allergy as a risk factor for dry eye disease. Ocular allergy, especially the most severe forms, can affect different key mechanisms of the vicious cycle in dry eye disease [342], including tear film instability [343], ocular surface inflammation and damage [343,344], and neurosensory abnormalities [343–345]. However, at present, the evidence on this topic is limited by the small size of existing case-control studies and the lack of standardization in diagnosis of dry eye disease (especially in children).

Clinical manifestations and complications of ocular allergy can significantly affect the quality of life of patients. Several studies reported a major impact of vernal keratoconjunctivitis on missed school days and difficulty in completing schoolwork [326,334]. Impairment of health-related quality of life in children with vernal keratoconjunctivitis has been assessed using standardized questionnaires [346,347], however reduced quality of life is not limited to severe forms of ocular allergy. In children with allergic rhinitis, having conjunctivitis doubled the risk of a "moderate/high" impact on quality of life [319], and children with seasonal or perennial allergic conjunctivitis and their parents have a significantly reduced quality of life [347].

3.3. *Pterygium*

A pterygium is a wing-shape fibrovascular degeneration of the conjunctiva that advances over time across the cornea [348]. Clinical presentation and symptoms include irritation, dryness, irregular astigmatism, decreased vision and aesthetic issues [349,350]. Long term ultraviolet radiation exposure has recently been confirmed as the most significant risk factor for pterygium [351–358]. Other reported risk factors for pterygium are: age [359–362]; male sex, [89,363,364]; outdoor occupations [89,362,365]; farming [73], low education [366], rural residency [364], low latitude [358,367] and darker skin complexion [353,362,366]. In a systematic review of 20 studies published in 2013, the general prevalence of pterygium was found to be around 10% [367]. However, this systematic review may not be reliable because of inadequately specified eligibility criteria, inadequate

literature searches, and inappropriate meta-analysis methods. Another recent systematic review included 68 studies and 24 countries found a global prevalence of 12%, pooling 415,911 participants from 24 countries. The lowest prevalence was reported in Saudi Arabia (0.07%) and the highest in China (53%) [368]. The most significant demographic risk factors from the systematic review were male sex, older age, rural residence and outdoor occupations (farmers, hunters, military personnel). The most important environmental risk factor was prolonged sunlight exposure (more than 5 h a day), compared to less than 5 h of daily exposure, increasing the risk up to 24 times. Neither outdoor exposure nor type of occupation are independent risk factors *per se* but become so in co-occurrence with radiation, constant exposure to sunlight and determinants such as age and sex [368]. However, caution in interpreting this systematic review is warranted because of suboptimal literature searching and poor concordance between its findings and conclusions.

In a North American study, the prevalence of pterygium was reported to be 2.5–3 times higher in the black population compared with whites [362]. Despite its worldwide distribution, pterygium is most common at latitude 40° around the equator [369]. Within this area, the prevalence rate of pterygium is reported to be more than 10 times that of higher latitudes [370], which strongly supports the role of UV radiation as a key risk factor [368]. A recent population-based study performed in the northernmost part of the Brazilian Amazon región, reported a high prevalence of pterygium of 58.8% [371], while among indigenous people living in the National Reserve of Xingu, further south in the Brazil, the prevalence was 10.8% [371]. Fig. 6 maps the prevalence of pterygium around the world.

The pathogenesis of pterygium remains elusive. Some studies suggest that it could be a premalignant disease [357,372,373]. The formation of pteygium implies limbal structural reorganization through the formation of pterygium cells, rather than a simple limbal failure. Such reorganization is related to genetic susceptibilities and/or ultraviolet radiation-induced damage [374,375]. Pterygium progression was considered to be the result of two limbal changes: disruption of the limbal barrier due to chronic ultraviolet radiation exposure, and consequently, conjunctivalization of the cornea [375,376]. Squamous metaplasia of the epithelium is a consequence of a wide variety of ocular surface diseases, including dry eye disease, vitamin A deficiency and ultraviolet radiation exposure. Squamous metaplasia has been reported to be present in more than 70% of pterygium cases [377]. The distribution of the squamous metaplasia varies over the bulbar conjunctiva: the most severe over the pterygium surface, and the interpalpebral and inferior conjunctiva. The superior conjunctiva under the upper eyelid (protected from ultraviolet radiation) shows minimal superficial epithelial changes. All cases show solar basophilic elastoid degeneration, vessels and fibrosis in the stroma. Approximately 50% of the cases show pigmentation of the epithelium, atributed to exposure to ultraviolet radiation [378,379]. Numerous other risk factors have been associated with the etiology of pterygium besides ultraviolet radiation [355, 356] such as environmental irritants (dust, wind) [376], viral agents [380,381], familial and hereditary factors [382] and immunological and inflammatory factors [375,383–385].

Ultraviolet A radiation causes indirect damage to DNA through inducing reactive oxygen species, and activation of transcription factors, which regulate the expression of multiple genes [386,387]. Ultraviolet radiation can also damage limbal stem cells [372], and induce inflammation [388] and change to the normal function of stromal fibroblasts [389]. A genetic predisposition in affected individuals may lead to an abnormal fibrovascular response to UV radiation [382,390,391]. Some potential targets of genetic studies have been identified but the genetic basis of pterygium still needs to be clarified [392].

Pterygium is associated with several ocular symptoms, such as irritation, redness, tearing, dryness, and decreased vision. The visual disturbance may be due to corneal visual axis involvement or with-the-rule induced astigmatism and tear film instability [393,394]. Pterygia are usually located in the interpalpebral zone, more often nasally than temporally, where the ultraviolet limbus irradiation is 20 times higher [369,395]. Topographical astigmatism is generally reversible or at least reduced following surgery [396,397]. The most important differential diagnoses are ocular surface squamous neoplasias, due to the same risk factors of ultraviolet radiation chronic inflammation, irritants like dust and oncogenic viruses and the manifestations range from mild dysplasia to invasive squamous cell carcinoma [372,398,399]. Although diagnostic suspicion is usually based on clinical signs such as feeder vessels, positive rose bengal staining, papilliform or leukoplakic appearance, inferior location in older individuals, biopsy with histopathological evaluation is the gold standard diagnostic test [400,401]. High-resolution optical coherence tomography may help to distinguish between benign and malignant lesions. Pterygia can be differentiated (with a sensitivity of 94% and specificity of 100%) by their normal thin epithelium with thickened subepithelial layer in contrast to the thick and irregular epithelium in ocular surface squamous neoplasia [382]. The coexistence of pterygium and ocular surface neoplasia is not uncommon. Australian studies reported a coexistence of between 5% and 10% with most cases being corneal intraepithelial neoplasia II [372,

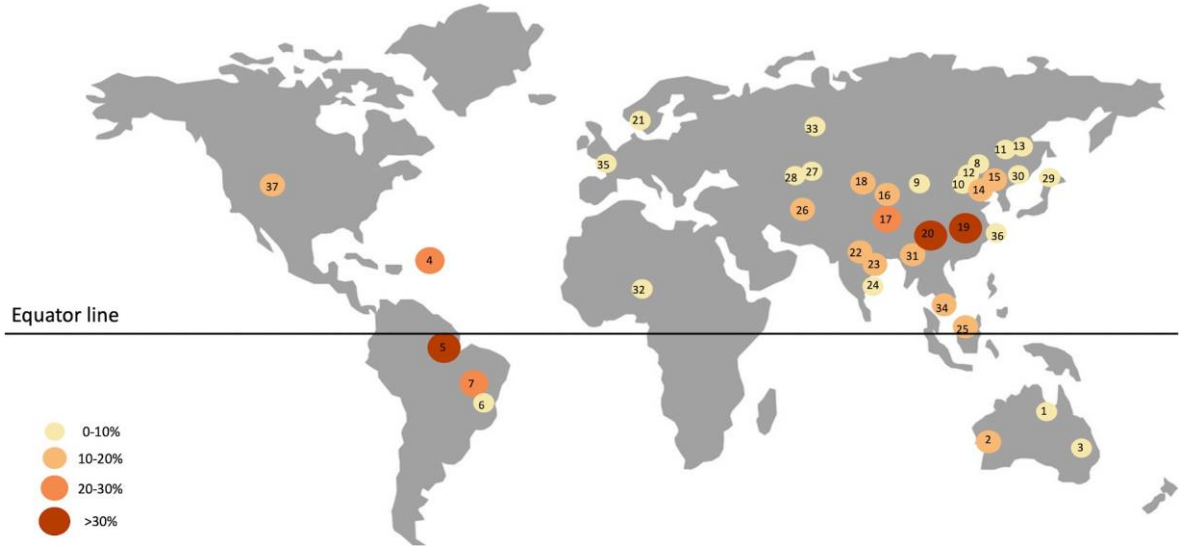

Fig. 6. Prevalence of pterygium around the world.

399], in Canada, up to 0–2% [398,402] and in the USA, 2% [401], with the North American studies finding most ocular surface neoplasia to be corneal intraepithelial neoplasia I. It is possible that pterygia diagnosed in regions with high ultraviolet exposure are more susceptible to coexistence with ocular surface neoplasia [379]. A recent study showed that pterygium greatly impacts on ocular surface parameters such as corneal topography, tear film stability and meiboscore; 88% of pterygium patients presented with meibomian gland alterations. Interestingly, meibomian gland dropout was coincident with the site of the pterygium in 54% of the upper and 77% of lower lids [403].

Sunlight protection and tear film care are mandatory in the management of patients with pterygium. Reducing ultraviolet radiation exposure and use of ultraviolet-attenuating sunglasses is advisable. Surgery remains controversial but is is generally indicated in progressive pterygium, where there is visual axis involvement, ocular movement limitation or the presence of atypical features. Meta-analyses have evaluated treatment options for pterygium. Limbal conjunctival autograft has a lower recurrence compared with pterygium excision with the bare sclera technique (OR 0.08 95% CI 0.04–0.17, $p < 0.01$), bulbar conjunctival autograft (OR 0.10 95% CI 0.04–0.23, $p < 0.01$), or intraoperative mitomycin C (OR 0.22 95% CI 0.09–0.52, $p < 0.01$). There was no statistically significant difference in the recurrence rates after limbal conjunctival autograft and amniotic membrane graft (OR 0.66 95% CI 0.26–1.70) [404] Another meta-analysis evaluated twenty randomized clinical trials with 1,866 participants (1,947 eyes) and concluded that surgical excision of pterygium combined with conjunctival autograft has a 46% lower risk of recurrence than excision combined with amniotic membrane graft. Pterygium recurrence after surgery ranged from 3.3% to 16.7% in the conjunctival autograft group and 6.4%–42.3% in the amniotic membrane graft group [405]. A network meta-analysis of 24 randomized clinical trials that included1,815 eyes of 1,668 patients and allowed direct and indirect comparison between 14 interventions. The optimum intervention based on the meta-analysis was excision with limbal conjunctival autograft, due to its lower recurrence rate and the bare sclera technique alone should be discontinued since it is associated with high recurrence rates [406]. Another study reported outcomes in 538 eyes and concluded that recurrence rates of amniotic membrane grafting were higher compared with limbal conjunctival autograft, but amniotic membrane grafting may be a good option for patients with extensive conjunctival scarring or in glaucoma patients to preserve the conjunctiva [407]. Risk factors for recurrence include: young age, fleshy pterygium body appearance, higher pterygium grade and inflammation.

3.4. *Pinguecula*

Pinguecula is a yellowish degenerative growth, often triangular, slightly elevated bulbar conjunctival lesion adjacent to the nasal or temporal side of the limbus. Pinguecula is considered a degenerative connective tissue disorder, generated by the accumulation of abnormal elastic material in the connective tissue, situated under the limbal-conjunctival epithelium on either side of the cornea, as a result of changes in sun-altered fibroblasts and elastic material [408]. Patients may report ocular hyperemia, irritation and tearing, but visión is rarely affected. Ocular surface elevation and staining may be present. Population-based studies report the prevalence of pinguecula at around 45% in the adult population. Men are at a higher risk [365,408–410]. In Spanish population above 40 years old, the prevalence of pingecula was 47.9% and pterygium 5.9% [365]. In a prevalence study that included 7, 774 individuals (3,850 urban, 3,924 rural) aged over 40 in a South Indian population, the prevalence of pinguecula and pterygium was 11.3% and 9.5% respectively, and rural residency was a risk factor [351]. The prevalence of pinguecula was higher in the younger age groups(15–29 years) with reduced rates in eldery [411]. Some studies propose that pinguecula may be a risk factor for and can eventually develop into a pterygium [365,412,413]. Alcohol consumption was also strongly associated with pinguecula [365].

Treatment for pinguecula is rarely required. Patients with discomfort due to pingueculitis are generally managed with mild anti-inflammatory drops or artificial tears. Contact lens fitting and wear experience might be suboptimal. Sunglasses to protect from ultraviolet radiation exposure, wind and dust are recommended. In cases of severe or recurrent inflammation, excessive growth or cosmetic disfigurement surgery may be considered [414].

3.5. *Climatic droplet keratopathy*

Climatic droplet keratopathy is a progressive corneal degenerative condition characterized by corneal opacification due to accumulation of globular deposits in Bowman's layer and anterior stroma associated with abnormal corneal sensitivity, which affects predominantly males over 40 years old [415–417]. It is also known as Bietti's band-shaped nodular dystrophy, spheroidal degeneration, chronic actinic keratopathy, Labrador keratopathy, elastoid degeneration, keratinoid corneal degeneration and oil droplet degeneration.

The etiopathology is unknown, although it is considered a multifactorial disease related to environmental factors, such as intense constant winds, low humidity and ultraviolet radiation exposure, independent of hot or cold arid climates [418]. More severe forms of climate droplet keratopathy have been described in regions with high heat and dryness [419], compared with cold regions [420,421]. Climate droplet keratopathy is considered a rural and outdoor disease, it is rare in urban individuals and frequently affects indigenous people in the Americas [417,422–424]. In a population study in China, the overall prevalence was 6.5%. Age and outdoor exposure were considered risk factors while vegetable intake and wearing a hat appear to be protective factors [424]. Nevertheless, climate droplet keratopathy varies widely in different regions and ethnic groups [418,421,425].

The pathogenesis of climate droplet keratopathy probably involves enzymatic glycosylation and inflammatory dysregulation associated with ultraviolet radiation exposure [416,426]. Some studies have reported a correlation between vitamin C/ascorbic acid concentration in the cornea and protection against ultraviolet radiation damage. A study conducted in Argentinean Patagonia, described climate droplet keratopathy as a rural disease. In this región, it generally affects sheep herders who work in a windy region with dry and sandy soil sparsely covered by small bushes. The inhabitants of this region exhibited abnormally low ascorbic blood levels and consequently, lifetime partial ascorbic acid nutritional deficiency because their main food source is almost exclusively lamb [422]. However, there were no reports of climate droplet keratopathy in Jujuy and Santiago del Estero and other regions in Argentina with similar weather conditions and activities [418]. In those areas, inhabitants tend to protect their eyes from ultraviolet radiation (by wearing sunglasses and hats) and have better levels of ascorbic acid in their diet. Apart from having moderate corneal abrasions, sheep from the same Patagonian region do not suffer from any subepithelial degenerative corneal conditions. It has been postulated that this may be because sheep, unlike humans, can synthesize ascorbic acid from grass. Climate droplet keratopathy is hypothesised to occur in "individuals with chronic corneal exposure to multiple unfavorable environmental conditions (e.g. excessive UV-B exposure, lack of vegetation/shade, dry/windy climate, particle bombardment, ascorbic acid partial nutritional deficiency, lack of eye protection and genetic factors) which would trigger inflammatory processes and oXidative stress, leading to progressive degradation and accumulation of proteinaceous material in Bowman's layer and superficial stroma [416,418,422].

There is no medical treatment for climate droplet keratopathy. Sun protection, in the form of sunglasses and hats is recommended. Corneal transplant (lamellar or penetrating) is the management of choice in advanced cases where there is severe visual impairment. Recurrences have been seen with the same original features [416].

In conclusion, exposure to ultraviolet radiation can lead to three possible degenerative processes. What is clear is that pterygium does not

correlate with climate droplet keratopathy. Although pingecula and pterygium show some association, there is no evidence that the relationship is causal and other factors are important in the development of pterygium.

3.6. Ocular surface chemical injury

Chemical injuries to the eyes, particularly from acid and alkaline chemicals, can range from mild irritation through to blinding cicatricial sequelae and corneal opacification. Chemical injury to the eyes was the second most common cause of work-related eye injuries treated in emergency departments in the USA., after foreign bodies [427–430]. Household injuries from various cleaning agents are also quite common, especially among young children [429,431].

The incidence of chemical eye injuries is 50–60 cases per million persons per year in the USA and United Kingdom. It is likely higher in developing countries due to limited education of individuals regarding the dangers of caustic chemicals and less frequent use of protective measures when such chemicals are used [432–434].

Direct environmental exposure seems to be an uncommon source of chemical injury, with minimal literature on the subject. The environment one lives and works in, however, can certainly increase the risk for acute chemical and thermal injuries to the eye, with accidental exposure being the most common cause. The sources of injury are varied and will be described in more detail below.

3.6.1. Large-scale exposures

Large-scale chemical exposures in the environment may occur from chemicals released into the air via industrial accidents or accidents involving trains or trucks that are transporting large quantities of chemicals. These are generally localized events and differ from the eye irritation that may occur from various air pollutants.

Ammonia is an alkaline compound that has widespread industrial-scale usage and is also a common component in household cleaning agents. As a result, it is the most common source of direct exposure injuries in the workplace and a common cause of household injuries. The wider public may also be exposed, in the case of large-scale industrial accidents and hazardous material spills from truck and train accidents [435].

Chlorine has many uses ranging from water disinfection to multiple industrial indications including solvent production, plastics production and as a bleaching agent in paper production. It is one of the top ten chemical substances produced in the USA, with approximately 25 billion pounds produced annually [435]. Chlorine gas can form hydrochloric acid and hydrochlorous acid and can cause significant respiratory symptoms. The concentrations in exposures are generally not significant enough to cause more than temporary eye irritation, however [436]. As with ammonia, the wider public may be exposed to chlorine gas through industrial accidents or during transport in vehicle or train accidents where compressed liquid chlorine is spilled and becomes gaseous. The gas is heavier than air and accumulates in low-lying areas [435].

Pesticide exposure may occur as an occupational hazard to farmworkers or as an airborne risk to those living in areas of agricultural activity. Ocular surface irritation is common, but longer-term sequelae are rare [437,438].

3.6.2. Occupational exposures

Factory and construction workers are the most likely group to suffer work-related chemical injuries. There is an approximately 6:1 male to female ratio amongst the injured with the average age being 35 years [439]. Alkaline chemicals account for approximately 60–70% of the injuries [440–442]. Inadequate education regarding the danger of the substances and the need for eye protection may play a role in the rate of injury, particularly in developing countries [443].

Alkaline agents generally cause worse injury due to higher intraocular penetration [435]. Common products containing alkaline substances include lime, plaster, mortar and various cleaning agents and detergents [427]. Acidic chemicals can also cause extensive damage to the ocular surface. Common products containing strong acids include toilet cleaner, battery fluid, swimming pool cleaner and bleaches [427]. Hydrofluoric acid, like strong alkalis, can penetrate the eye and is particularly injurious. It is found in rust remover, leather-tanning fluid, high octane gasoline and glass- or enamel-etching materials [427,444].

3.6.3. Criminal activity

Various types of criminal activity can increase the risk of chemical injury to the eyes. Ocular chemical injuries from assaults tend to yield more severe injury because ammonia (a strong alkali) is the most commonly used agent and means for rapidly irrigating the eyes are not as readily available in the setting of an assault [440,445,446].

Illegal methamphetamine labs are a potential source of both thermal and chemical injuries. Ammonia is a chemical used in the production of methamphetamine and the risk for explosions is significant. Such incidents may also expose neighboring residents to chemical irritant [435, 447].

Pepper sprays (most commonly oleoresin capsicum) are used for personal protection and by law enforcement personnel to subdue violent individuals. It can cause severe, temporary ocular surface irritation, but generally do not lead to longer term problems [448].

3.6.4. Household exposures

The age-specific risk for chemical ocular injuries in the household setting is highest in children aged 1–2 years old and household cleaning agents have been identified as the most common causative chemicals in large studies of emergency room and poison control center data in the USA [429,449]. Most of these injuries are preventable with safe storage of cleaning agents in areas that are out of reach of small children [433, 450]. In developing countries, delay in treatment of chemical eye injuries is a problem. Time between injury and presentation averaged 68.3 days in a study from India analyzing 134 pediatric patients with ocular chemical burns [451]. Individual liquid laundry and dishwasher detergent capsules (also called “detergent pods”) have emerged as a risk of acute chemical eye injury in young children [452]. The detergents within the water-soluble packets are more concentrated than in regular powder or liquid formulations. Children 4 years of age and younger are most affected, with the child either biting or squeezing the pod and then the detergent squirting into one or both eyes. Conjunctival irritation and corneal abrasions may result, but longer-term sequelae are rare [453–456].

More severe ocular chemical injuries may occur with other substances commonly found in households. In a large review of 319,508 calls to poison control centers in the USA from 2000 to 2016, bleach was the most common cause, accounting for 26% of cases [449]. The second and third most common sources of eye injuries in a residential setting were various floor and tile cleaners (13%) and disinfectants (11%) [449]. Ocular injuries occur in 8.4% of cleaning solution exposures [457], with that number rising to nearly 25% in the pediatric age group [458,459]. Especially serious injuries may occur with drain cleaners and oven cleaners due to the strong alkali components they contain (most commonly sodium hydroxide with pH values of 12 or higher) [449]. The vulnerability of young children and the preventable nature of the injuries emphasize the need for preventive measures includingchild-resistant containers, storage of potentially dangerous products outof the reach and sight of small children and increased public awareness. Hydrogen peroxide is a common chemical kept in households. Most solutions in this setting are 3% concentration and do not pose a risk of severe eye injury. Concentrations of 10% or greater, however, may cause corneal abrasions and ulceration [460].

Bottles of cyanoacrylate glue are occasionally mistaken for eye drops and inadvertently applied to the eyes and eyelids. The glue can cause significant irritation due to the granularity of the dried glue. It can also cause discomfort by sticking the eyelids and eyelashes together. It

generally does not lead to longer-term ocular surface damage, however [461].

Eye injuries from alkaline calcium hydroxide paste (lime) are a significant problem on the Indian subcontinent and in Southeast Asia. The paste, known as chuna in India, is mixed with chewing tobacco and causes small oral mucosal epithelial abrasions that enhance the absorption of chemicals released from the tobacco. It is often sold in small polythene packets that children may subsequently play with. The chuna packets are flimsy and burst easily, releasing calcium hydroxide onto the eyes. The average age at the time of injury is between 8 and 9 years [451,462]. The damage to the ocular surface can be severe and lead to significant long-term pain and vision loss. In one report, approximately one third of patients received no irrigation of the eyes at the time of injury and 70% did not present for eye care until at least 1 month after the injury. The scarring sequelae from these injuries can be blinding and are among the most challenging problems ocular surface surgeons face [462]. Further detail is provided in the Societal Challenges report [245].

3.6.5. *Ocular surface thermal injury*

As with chemical injuries, thermal injuries to the eyes are mostly accidental. The sources of injury may be a direct flame, scalding liquid, or burning hot items such as cigarettes, curling irons or fireworks [463]. The rapid blink reflex and eyelids protect the ocular surface in many cases, but eyelid burns may cause cicatricial sequelae such as entropion or lagophthalmos that can lead to longer term ocular surface issues [464,465]. Duration of exposure and intensity of the heat source are key features that determine the severity of ocular injury. Hot oils and greases tend to adhere to the ocular surface and cause more severe injuries [466]. Acids and alkalis may cause an exothermic reaction that adds an element of thermal injury to the chemical injury.

Airbag deployment in motor vehicle accidents can cause significant thermal and chemical injuries to the eyes [467,468]. The chemical reactions that induce the rapid inflation of the airbag also release high temperature gases (up to 500 °C) and produce alkaline corrosives such as sodium hydroxide. The alkaline particles may lead to severe chemical injury of the ocular surface. First responders to the accident scene may be focused on other injuries and not inspect and rinse the eyes. This may further worsen the severity of the chemical aspect of the injury [469].

Fireworks can cause both thermal and chemical injury to the eyes. Sparklers are a common source of injury, tending to cause only mild conjunctival irritation [470]. Though less common, more severe chemical and thermal injuries occur from Roman candles that launch a series of colored fireballs into the air. The fireball is a mixture of alkaline chemicals, so when one accidently hits the eye, the damage from both the heat and chemicals can be severe, leading to blinding sequelae such as limbal stem cell deficiency. Firework injuries are most common in young males, with bystanders also frequently injured [471]. However, this is based on a systematic review that may be unreliable because of the lack of a risk of bias assessment. The nature and severity of the injury may not be appreciated right away, which can further worsen the damage [472].

Wildfires are an increasing problem worldwide that could potentially lead to thermal and chemical injury in firefighters and other emergency personnel, as well as the public. Conjunctival irritation from smoke is the most commonly reported eye finding and may occur over wide geographic areas as the smoke is dispersed by the prevailing winds and carried long distances from the actual fires. More severe sequelae are rare, however, unless direct thermal injury to the face occurs. There is a growing literature on injuries resulting from wildfires, but the literature on significant direct thermal or chemical ocular injuries resulting from wildfires is currently minimal [473–475].

The personal protective equipment standard is defined separately for each segment of industry including, but not limited to, chemical industries, power plants, metal production, agriculture, health services, and utilities. It requires employers to provide employees with personal equipment designed to protect them against certain occupational hazards. Regarding the ocular surface, a systematic review showed that wearing eye protection device has a significant effect in reducing eye injuries among industrial workers, thus it is strongly recommended for various sectors of industry [476]. However, caution is warranted in interpretation of the review outcomes because of suboptimal meta-analysis methods.

3.7. *Ocular surface neoplastic disease*

Ocular surface squamous neoplasia ranges from dysplasia or conjunctival intraepithelial neoplasia or carcinoma *in situ* to invasive squamous cell carcinoma. Squamous cell carcinoma is the most common ocular malignancy with a high rate of recurrence [477–483], which generally affects the limbus of elderly individuals [481]. Patients commonly present with eye redness and ocular irritation [484], that ranges from asymptomatic to severe pain and visual loss. In some cases, squamous cell carcinoma can be life threatening [478,485–487]. Diagnostic suspicion is raised with clinical signs including feeder vessels, positive rose bengal staining, papilliform or leukoplakic appearance, inferior location, seen in older individuals. Biopsy with histopathological evaluation is the standard for confirming diagnosis [400,401]. Patients with a history of conjunctival intraepithelial neoplasia and squamous cell carcinoma should be followed up annually. Early diagnosis and follow up of conjunctival intraepithelial neoplasia is important to avoid progression to squamous cell carcinoma and metastasis [483,488].

The most important environmental predisposing factors for ocular surface squamous neoplasia include chronic solar ultraviolet B radiation and cigarette smoke exposure [478,479]. Other associations are, human papillomavirus infection, p53 expression, vitamin A deficiency, ocular surface injury, exposure to petroleum products, and chronic infection with human immunodeficiency virus, and hepatitis B and C virus [372,398,399,479,489]. Individual risk factors for ocular surface squamous neoplasia include, pale skin, pale iris, propensity to sunburn, more than 50% of exposure time outdoors in the first 6 years of life and living within 30° of the equator [490].

Squamous cell carcinoma is considered rare, with an incidence of 0.03 per 100,000 per year and is approximately five-fold higher among males and whites. There is a high rate of squamous cell carcinoma in tropical countries and there is an association between squamous cell carcinoma and ultraviolet B exposure. Regression analysis has suggested a link between ultraviolet B exposure and squamous cell carcinoma of the conjunctiva, which was as strong as the link between squamous cell carcinoma of the eyelid and ultraviolet B exposure, and much stronger than that for conjunctival melanoma [491]. The incidence of ocular squamous cell carcinoma declined by 49% for each 10° increase in latitude falling from 12 cases per million per year in Uganda (latitude 0.3(0)) to less than 0.2 per million in the United Kingdom (latitude 50 (0)). As solar ultraviolet radiation decreases with increasing latitude, the incidence of squamous cell carcinoma decreases by 29% per unit reduction in ultraviolet radiation exposure [492].

Ocular surface squamous neoplasia may coexist with pterygium in up to 10% of cases [372,379,398,399,401,402]. Data on sun exposure largely support squamous cell carcinoma rates, suggesting a dose-response effect [385,488,493]. However, this does not fully explain the difference in incidence in ocular surface squamous cell carcinoma in Uganda and the United Kingdom. A regression analysis [491] suggested that a link between ultraviolet B exposure and prevalence of squamous cell carcinoma is not specific enough to be interpreted as evidence of a significant link [488]. Promoter mutations in the telomerase reverse transcriptase gene have been identified in several cancers including cutaneous melanoma and squamous cell carcinoma. Telomerase reverse transcriptase gene promoter mutations were found in 44% of 48 samples of conjunctival ocular surface squamous neoplasia with mutational profiles supporting ultraviolet B radiation induction as the major source of the malignancy [494].

Conjunctival melanoma is a rare ocular malignancy, comprising approximately 5% of all ocular melanoma [495,496] with an estimated mortality of between 13 and 38% at 10 years, in adult studies [497,498]. It is approximately 18–40 times less common than uveal melanoma, with an estimated incidence of 0.012–0.08 per 100,000 in adults and 0.68% of cases in children younger than 14 years and increases in incidence have been noted in recent decades [479,496–498]. Conjunctival melanoma can occur on the bulbar, forniceal or tarsal conjunctiva, as well as the caruncle. It can arise *de novo* or from pigmented lesions [479,495,496]. An increasing incidence in Europe and among white American men may be related to increased ultraviolet radiation [499–501]. Other studies have failed to demonstrate such a correlation [502]. An immune response triggered by exposure to ultraviolet radiation might partially explain epidemiological findings of a higher incidence of ocular melanoma in sun-exposed patients [503–506]. Cumulative lifetime ocular ultraviolet B exposure was found not to be a risk factor for ocular melanoma [507]. Most of the studies and guidelines focus on adults, despite the higher incidence in children. Excision biopsy, using a "no-touch" technique is the optimal diagnostic and therapeutic modality [479,495]. Topical chemotherapy is useful when excision margins display atypia, although margins positive for melanoma require re-excision [508].

4. Climate change and OSD

Anthropogenic emissions of greenhouse gases are altering the Earth's climate, resulting in a global average increase in temperature of over 0.85 °C since 1880. For example, nineteen of the hottest years have occurred since 2000, and the year 2020 tied with 2016 for the hottest year on record. These rising temperatures result in stronger and more frequent extremes of weather, changes to precipitation patterns and arable land, greater ice melt, and disruptions to several other environmental processes. Climate change can affect human health through three pathways: i) changing frequency and severity of extreme weather events, such as heat, drought, and heavy rain; ii) altering the burden and pattern of distribution of vector-, water-, and food-borne diseases; iii) resulting in undernutrition (when climatic factors interact with global food markets), mental ill-health, and even violence and conflict. These factors are further explored in the Societal Challenges report [245].

Adaptation is "the process of adjustment to actual or expected climate and its effects" to reduce or avoid risks. Health adaptation to climate change can be categorized into 3 forms: i) incidental adaptation including actions taken within the health sector that aid climate change adaptation, but are not delivered for this express purpose; ii) linear adaptation activities including responses to specific climate threats through the implementation of adaptive practices that enable health systems to respond to identified risks; iii) building resilience which relates to system-wide changes that improve the ability of a system and society to cope with climate change.

The intriguing chain reaction of global warming in ocular health is ominous. Temperature rise because of ongoing climate change is of concern to patients with dry eye because of high tear evaporation rates. Climate change may also prolong the allergy season (typically spring and early summer) resulting in greater occurrence of allergic eye disease. Other ocular surface disease can similarly be associated with climate change: including inflammatory conditions (marginal keratitis, chronic episcleritis, corneal metaplasia, pterygium); infections and superinfections (corneal and conjunctival herpes simplex and herpes zoster, viral keratoconjunctivitis, infectious corneal injuries, contact lens-related injuries); tumor (epidermoid neoplasia of the ocular surface).

Even though the potential influence of climate on the ocular surface system has been recognized, there is only one study that has examined the association between weather and pollution changes from 2004 to 2013 and the first occurrence of dry eye disease. Temperature was associated with a relatively small increase in dry eye disease occurrence (~1%) per degree Celsius. In contrast, every 10% increment of relative humidity was related to approximately 6.7% reduction in dry eye occurrence [169].

Based on climate-related changes in environmental risk factors, an increase in the prevalence of OSDs may be expected in the near future. While the increased temperature resulting from climate change is difficult to manage, control of traffic emissions is relatively achievable in comparison. Therefore, efforts should be made to phase out polluters such as fossil fuel powered vehicles, making the air cleaner and improving health.

5. Impact of outdoor pollutants on dry eye: a systematic review

5.1. Introduction

As noted, the outdoor environment presents a broad range of pollutants that can be in constant and direct contact with the ocular surface. Exposure to air pollutants (e.g., from gases, particulate matter), soil pollutants (e.g., from metals), and water pollutants (e.g., from outdated irrigation systems) can challenge the ocular surface. In the context of climate change, exposures to such pollutants are expected only to increase. The associations between specific outdoor environmental pollutants and dry eye disease diagnosis, symptoms, and signs are not well known.

5.2. Objectives

The objective of this systematic review was to evaluate the associations between outdoor environment pollution and dry eye disease diagnosis, symptoms, and signs in humans.

5.3. Methods

This systematic review was prospectively registered on the systematic review protocol registry PROSPERO (registration number CRD42021297238). The Subcommittee members IJS, MA, MCM, EV and THW, conducted this systematic review.

5.3.1. Eligibility criteria

Studies involving any human population in any country, without restriction by age, sex, race, or other factors were included. Table 5 lists the specific pollutants of interest within the categories of gases, particulate matter from natural or man-made sources, pollutants measured by satellite-based measurements, and water pollution. Comparators could include no outdoor environmental pollutant, another environmental pollutant, or lesser degree of exposure to the same environmental pollutant. Outcomes of interest were incidence or prevalence of dry eye-related diagnoses (e.g., dry eye disease, xerophthalmia), signs (e.g., corneal staining, tear instability), or symptoms (e.g., irritation, dryness, redness), as defined by study authors.

Published comparative or single-group (noncomparative) studies, without restriction on sample size, were included. Conference abstracts were excluded. Comparative studies could include prospective or retrospective cohort, case-control, or cross-sectional designs. Analytically accounted for potential confounders were a requirement for comparative studies.

5.3.2. Search strategy

The search targeted primary studies in MEDLINE (via PubMed) and Embase, from inception to January 4, 2022. No date, language, or human restrictions were applied to the search. The search included MeSH (for PubMed) or Emtree (for Embase) controlled-vocabulary terms, along with free-text words, related to environmental pollution, and the specific individual pollutants (gases, particulate matter, satellite-based measurements, and water pollutants). Appendix A in- cludes the full search syntaxes for both databases; these were indepen- dently peer-reviewed. The reference lists of included studies were

Table 5
Environmental pollutants of interest for this systematic review.

Type of Pollution	Subtype of Pollution	Examples
Air Pollution	Gases	Carbon monoxide (CO), nitrogen oxide (NO), nitrogen dioxide (NO_2), nitrogen oxide + nitrogen dioxide (NO_x), all nitric oxides [[523], sulfur dioxide (SO_2), ozone (O_3)
	Particulate matter from natural sources	Volcanic eruption, Asian dust (yellow sand), wind/dust storms, forest fires, salt spray, rock debris, gaseous emissions, quarry
	Particulate matter from manmade sources/incinerated waste	Fuel/coal combustion, industrial processes, smoke, haze, petroleum foundries, cement/glass/steel manufacturing, smelting, mining, power plant fly-ash emissions, agricultural
Pollutants measured through satellite-based measurements	–	Aerosols measured through aerosol optical depth (AOD) measured by satellite instruments, such as Moderate Resolution Imaging Spectroradiometer (MODIS) and Multi-angle Imaging Spectroradiometer [524]
Soil pollution	From metals	Cadmium, chromium, lead
Water pollution	–	Pollution because of outdated water supply systems, tetrachloroethylene

scanned for additional eligible studies.

5.3.3. Screening

Duplicate records obtained were removed from the searches before screening. All investigators (IJS, MA, MCM, EV, and THW) participated in the screening process. After two rounds of pilot screening by all investigators, each abstract was independently screened by two investigators using Abstrackr (http://abstrackr.cebm.brown.edu/). All abstracts deemed potentially eligible were rescreened in duplicate in full text. At both stages, discrepancies were resolved by discussion and/or consultation with a third investigator.

5.3.4. Risk of bias assessment and data extraction

For study risk of bias assessment, items from the Newcastle-Ottawa Scale [509] were used for cohort, case-control, and cross-sectional studies. For cross-sectional studies, questions about follow-up were considered not relevant. When assessing risk of bias for comparative studies, participant age and sex were considered important confounders that studies should have accounted for. For single-group studies, quality-related questions from the National Heart, Lung, and Blood Institute ([510]) Quality Assessment tool were used.

Extracted data included publication-identifying information; funding source; study years; study design features; country; eligibility criteria; population characteristics (age, sex); environmental pollutant (exposure and comparator) names, amounts, and durations; and relevant outcomes and their definitions and results.

For each included study, one investigator extracted all data and assessed risk of bias into custom-developed and pilot-tested forms in the Systematic Review Data Repository Plus (http://srdrplus.ahrq.gov/). A second investigator verified all extractions and risk of bias assessments. All discrepancies were resolved by discussion and/or consultation with a third investigator.

5.3.5. Syntheses

For comparative studies, data from only adjusted analyses were extracted. For dichotomous outcomes, adjusted odds ratios (adjORs), adjusted relative risks (adjRRs), and/or adjusted prevalence ratios (adjPRs) were evaluated. For continuous outcomes, adjusted mean differences (adjMDs) were evaluated. It was planned that pairwise meta-analyses using random-effects models would be conducted if 3 studies reported results on the same outcome for the same exposure, provided the exposure and outcome were defined and analyzed similarly. However, the data did not allow for any appropriate meta-analyses.

5.3.6. Subgroup analyses

Subgroup analyses by important patient factors, such as age, sex, and geographic region, were planned but were unable to be conducted because the data did not allow for them.

5.3.7. Assessment of certainty of evidence

The certainty of the body of evidence was graded per the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) system [511,512]. Certainty was evaluated for the associations between each pollutant and three outcomes: diagnosis of dry eye (or, when reported, Sjögren syndrome), dry eye symptoms, and dry eye signs. For each certainty assessment, the number of studies and participants (as an index of the sparsity of the evidence), overall risk of bias and methodological quality, directness of the evidence, consistency of study results, precision of estimates of effect, and overall findings across studies were considered. Based on these assessments, a certainty rating of either high, moderate, low, or very low was assigned for each pollutant and outcome.

Outcomes with highly inconsistent findings across studies, or with data from only one study, were deemed to have very low evidence and therefore did not merit a conclusion. This approach is consistent with the concept that for imprecise evidence "any estimate of effect is very uncertain," the definition of very low certainty evidence as per the GRADE approach [512].

In accordance with Agency for Healthcare Research and Quality (AHRQ) guidance for describing effects of exposures/treatments [513, 514], when articulating conclusions, this systematic review incorporates qualifying language regarding certainty as follows: "may" for conclusion statements with low certainty, "probably" for conclusion statements with moderate certainty, and no qualifiers for conclusion statements with high certainty.

5.4. Results

5.4.1. Summary of screening process

Fig. 7 provides the PRISMA flow diagram for this systematic review. The searches yielded 2,493 unique records, of which 79 were screened as full-text articles and 19 articles (describing 19 studies) were included. The most frequent reasons for exclusion at the full-text stage were because the studies were comparative without adjusted analyses (n = 15), did not address dry eye disease diagnosis, symptoms, or signs (n = 14), or were available as conference abstracts only (n = 12).

5.4.2. Characteristics of included studies

The 19 included studies comprised one retrospective cohort study [513], one case-control study [22], two cross-sectional studies [515, 516], and 15 single-group studies [18,21,27,34,39,150,160,166,169, 170,189,190,517–519] (Table 6). Four studies were conducted in South Korea, four in Taiwan, three in Brazil, three in the USA, and one each in China, India, The Netherlands, Norway, and Thailand. None of the 17 studies that reported on funding sources were funded by industry. The studies were conducted between 2000 and 2018 and published between 2005 and 2021.

5.4.3. Characteristics of study participants

More than two-thirds of the studies (13/19) enrolled the general population of adults living in the study's geographical area, which

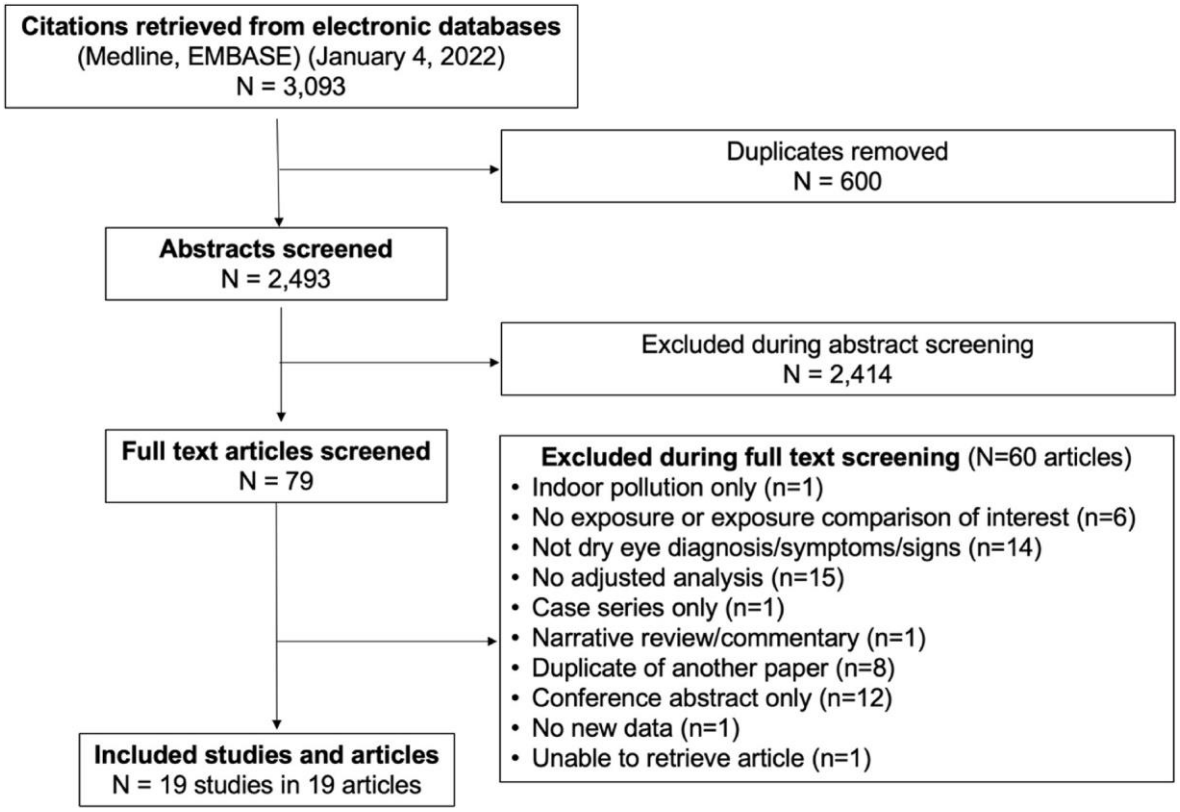

Fig. 7. PRISMA flow diagram for study records in this systematic review.

Table 6
Characteristics of included studies and outcomes reported in this systematic review.

#	Author, Year, Reference	Study Design	Country	Industry funded?	Study Years	Statistical Adjustment
1	Aschengrau 2015 [520]	Retrospective cohort	USA	No	2006–2008	Multiple regression
2	Chung 2021 [22]	Case-control	Taiwan	No	2006–2018	Multiple regression
3	Moen 2011 [515]	Cross-sectional	Norway	No	2008–2010	Multiple regression
4	Sahai 2005 [516]	Cross-sectional	India	NR	NR	Multiple regression
5	Berg 2020 [34]	Single-group	USA	No	NR	N/A
6	Hwang 2016 [160]	Single-group	South Korea	NR	2010–2012	N/A
7	Kim 2019 [170]	Single-group	South Korea	No	2016–2017	N/A
8	Kim 2020 [27]	Single-group	South Korea	No	2016–2018	N/A
9	Lee 2019 [190]	Single-group	Taiwan	No	2000–2001	N/A
10	Lian 2018 [189]	Single-group	Taiwan	No	2005–2009	N/A
11	Modi 2014 [518]	Single-group	USA	No	2001–2012	N/A
12	Novaes 2010 [18]	Single-group	Brazil	No	NR	N/A
13	Torricelli 2013 [21]	Single-group	Brazil	No	NR	N/A
14	Torricelli 2014 [166]	Single-group	Brazil	No	NR	N/A
15	Um 2014 [39]	Single-group	South Korea	No	2010–2012	N/A
16	Vehof 2021 [150]	Single-group	Netherlands	No	2014–2017	N/A
17	Wiwatanadate 2014 [519]	Single-group	Thailand	No	2008–2008	N/A
18	Yu 2019 [517]	Single-group	China	No	2013–2013	N/A
19	Zhong 2018 [169]	Single-group	Taiwan	No	2004–2013	N/A

AbbreviationsN/A = not applicable, NR = not reported.

ranged from town level to entire country level (Table 7) [18,21,22,39,150,160,169,189,190,515,516,519,520]. Four studies enrolled participants with dry eye [27,34,170,517]. One study enrolled war veterans returning to the USA from Iraq [518]. Another study enrolled taxi drivers and traffic controllers [166].

Sample sizes in the 18 studies that reported this information ranged widely, from 21 to 79,866 participants. Two of the 19 studies enrolled only males, one study enrolled only females, and two studies did not report sex data. The other 14 studies enrolled between 31% and 90% female populations. Participant ages also varied across studies, with means ranging from 29.4 to 58.0 years (among studies reporting age data).

5.4.4. Exposures assessed and outcomes reported

Most studies (16/19) reported on air pollution (Table 8). Exposures evaluated most frequently included various gases (SO_2, NO_2, NO_x, No_y, O_3, and CO) and participate matter (PM_{10}, $PM_{2.5}$, and incinerated waste). One study reported on high versus low levels of air pollution without naming specific pollutants. Outcomes evaluated in the 16 studies included various combinations of dry eye disease (or Sjögren Syndrome) diagnosis, dry eye symptoms, and dry eye signs.

Two studies reported on associations between soil pollution (with

Table 7
Characteristics of participants in included studies.

#	Author, Year, Reference	Inclusion Criteria	Exclusion Criteria	Sample Size	Sex	Age (years)	Age Categories (years)	
					Female %	Mean (SD) or Range	Category	%
1	Aschengrau 2015 [520]	Born 1969–1983 to married women living in one of 8 Cape Cod towns	NR	1,303	64%	29.4 (3.7)	NR	–
2	Chung 2021 [22]	Female, living at address for ≥5 years	History of cancer	6,880	100%	53.6 (9.9)	30–40 40–50 50–60 60–70	11% 21% 35% 33%
3	Moen 2011 [515]	Age 18–67 years	Contact lens use	519	36%	44 (13)	NR	–
4	Sahai 2005 [516]	Age >20 years	Acute ocular infections, corneal/conjunctiva pathology, contact lens use, extraocular/ intraocular surgery in past 6 months	500	55%	NR	21–30 31–40 41–50 51–60 61–70 >70	22% 20% 21% 18% 12% 7%
5	Berg 2020 [34]	Adults with ocular dryness for at least 6 consecutive months with moderate to severe symptoms (OSDI)	NR	535	81%	58.0 (NR)	NR	–
6	Hwang 2016 [160]	Sample of national residents	None	16,824	58%	50.9 (16.7)	19-29 30–39 40–49 50–59 60–69 ≥70	11% 18% 17% 19% 17% 17%
7	Kim 2019 [170]	Age ≥19 years, living in Incheon for ≥2 years, DED	Contact lens use, ocular surgery in past 3 months	33	79%	55.2 (10.5)	NR	–
8	Kim 2020 [27]	Age ≥19 years, living in Incheon during study period, DED	Contact lens use, ocular surgery in past 3 months, history of refractive surgery, another ocular surface abnormality, or used glaucoma drugs	43	72%	56.3 (10.2)	NR	–
9	Lee 2019 [190]	General adult population in different areas of Taiwan	NR	11,220	90%	NR	10–20 20–30 30–40 40–50 50–60 60–70 >70	1% 5% 12% 22% 29% 19% 14%
10	Lian 2018 [189]	Random sample of the National Health Insurance Research Database in Taiwan	NR	NR	NR	NR	NR	–
11	Modi 2014 [518]	Veterans returning from Iraq	NR	115	87%	33 (10)	NR	–
12	Novaes 2010 [18]	Living in the area for ≥5 years	Chronic illnesses, smoking, contact with chemical solutions, contact lenses use, ophthalmic surgery, pre-existing ophthalmic conditions	55	NR	20 to 52	NR	–
13	Torricelli 2013 [21]	Living in the area for ≥5 years	Smoking, contact lens use, ophthalmic surgery, ophthalmic diseases	71	0%	46.8 (9.7)	NR	–
14	Torricelli 2014 [166]	Living in the area for ≥5 years, taxi driver or traffic controller	Smoking, contact lens use, ophthalmic surgery, ophthalmic diseases or use of eye drops, any oral medication	21	0%	43.8 (7.2)	NR	–
15	Um 2014 [39]	Age ≥30 years	NR	16,431	58%	30 to NR	30–39 40–49 50–59 60–69 ≥70	21% 20% 22% 19% 19%
16	Vehof 2021 [150]	Living in the north of the Netherlands	NR	79,866	57%	50.1 (12.4)	NR	–
17	Wiwatanadate 2014 [519]	Age >14 years, nonsmoker, lived in Mae Rim for >1 year	NR	3,025	67%	15 to 91	NR	–
18	Yu 2019 [517]	≥1 of these: dryness, foreign body sensation, burning, eyesight fatigue, discomfort, vision fluctuation	Other eye diseases, e.g., conjunctivitis, glaucoma, ocular trauma	23,922	49%	NR	<25 25–45 >45	21% 46% 34%
19	Zhong 2018 [169]	DED using ICD-9 codes	Sjogren	25,818	31%	51.1 (17.7)	<18 18–49 ≥50	2% 45% 54%

Abbreviations: DED = dry eye disease, ICD-9 = International Classification of Diseases: Version 9, NR = not reported, SD = standard deviation.

Cd, Cr, Cu, Hg, Ni, Pb, and/or Zn) and dry eye disease (or Sjögren Syndrome) diagnosis. One study reported on the association between water pollution (with tetrachloroethylene) and dry eye diagnosis.

5.4.5. Risk of bias

Appendix B (Tables B-1 to B-4) provides details of the risk of bias assessments for the 19 studies, separately by study design. The retrospective cohort study [520]) was at overall moderate risk of bias due to a sizeable percentage of participants (45.5%) being lost to follow up. The case-control study was at overall low risk of bias [22]. The two cross-sectional studies were at overall moderate risk of bias due to lack of statistical adjustment for sex [515]) or participant self-report of pollutant exposure [516]).

Fourteen of the 15 single-group studies were at overall low risk of

Table 8
Pollutant exposures evaluated and outcomes reported in included studies.

#	Author, Year, Reference	EXPOSURES EVALUATED																		OUTCOMES REPORTED		
		Air Pollution																		DED or Sjogren diagnosis	DED symptoms	DED signs
		Gases						Particulate matter		Incinerated waste	Unspecified	Soil pollution							Water pollution			
		SO_2	NO_2	NO_x	NO_y	O_3	CO	PM_{10}	$PM_{2.5}$	Incinerated waste	Air pollution, unspecified	Cd	Cr	Cu	Hg	Ni	Pb	Zn	PCE			
1	Aschengrau 2015 [520]	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	Yes	–	–
2	Chung 2021 [22]	X	X	.	.	X	.	.	X	.	.	.	.	.	.	.	.	.	.	Yes	–	–
3	Moen 2011 [515]	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	–	–	Yes
4	Sahai 2005 [516]	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	Yes	–	–
5	Berg 2020 [34]	X	X	X	X	X	X	.	X	.	.	.	.	.	.	.	.	.	.	–	Yes	Yes
6	Hwang 2016 [160]	X	X	.	.	X	.	X	.	.	.	.	.	.	.	.	.	.	.	Yes	Yes	–
7	Kim 2019 [170]	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	–	Yes	Yes
8	Kim 2020 [27]	.	.	.	.	X	.	X	X	.	.	.	.	.	.	.	.	.	.	–	Yes	Yes
9	Lee 2019 [190]	.	.	.	.	.	.	.	.	.	.	X	X	X	X	X	X	X	.	Yes	–	–
10	Lian 2018 [189]	.	.	.	.	.	.	.	.	.	.	.	X	.	.	X	.	.	.	Yes	–	–
11	Modi 2014 [518]	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	–	Yes	–
12	Novaes 2010 [18]	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	–	Yes	Yes
13	Torricelli 2013 [21]	.	X	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	–	Yes	Yes
14	Torricelli 2014 [166]	.	X	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	–	Yes	Yes
15	Um 2014 [39]	X	X	.	.	X	X	X	.	.	.	.	.	.	.	.	.	.	.	Yes	Yes	–
16	Vehof 2021 [150]	.	X	.	.	.	.	X	X	.	.	.	.	.	.	.	.	.	.	Yes	–	–
17	Wiwatanadate 2014 [519]	X	X	.	.	X	.	X	.	.	.	.	.	.	.	.	.	.	.	–	Yes	–
18	Yu 2019 [517]	X	X	.	.	X	X	.	X	.	.	.	.	.	.	.	.	.	.	Yes	–	–
19	Zhong 2018 [169]	X	X	.	.	X	X	X	X	.	.	.	.	.	.	.	.	.	.	Yes	–	–

Abbreviations: Cd = cadmium, CO = carbon monoxide, Cr = chromium, Cu = copper, DED = dry eye disease, Hg = mercury, Ni = nickel, O_3 = ozone, Pb = lead, PCE = tetrachloroethylene, PM_{10} = particulate matter <10 μm in diameter, $PM_{2.5}$=particulate matter< 2.5 μm in diameter, NO_2 = nitrogen dioxide, NO_x = reactive nitrogen oxides, No_y reactive nitrogen compounds, SO_2 = sulfur dioxide, Zn = zinc.

bias. One study was at overall moderate risk due to participant self-report of pollutant exposure [518].

5.4.6. Organization of the rest of the results section

In the summary of findings table (Table 9), we provide GRADE certainty of evidence rating and justification for the ratings for each pollutant and outcome. The next subsections describe findings for each pollutant and refer to specific evidence tables in the Appendix.

5.4.6.1. Air pollution

5.4.6.1.1. Air pollution from gases: SO_2. The case-control study and six single-group studies reported on air pollution from SO_2 (Appendix Table C-1). Results were inconsistent for dry eye disease diagnosis and symptoms, and certainty of the evidence was very low for signs of dry eye disease.

- Five studies reported on the association between incremental increases in exposure and diagnosis of dry eye disease [22,39,160,169,517]. Although the other three studies reported no association, two reported an increased odds of diagnosis (adjOR 1.09, 95% CI 1.01 to 1.18 [39] and adjOR 1.64, 95% CI 1.50 to 1.79, respectively [517]).
- Four studies reported on dry eye symptoms [34,39,160,517,519]. Although two studies reported no association, two reported greater odds of symptoms; one study reported higher odds for general symptoms (adjOR 1.09, 95% CI 1.01 to 1.19) [39] and the second reported greater odds for ocular irritation (adjOR 1.26, 95% CI 1.09 to 1.47), ocular redness (adjOR 2.95, 95% CI 1.45 to 5.94), and blurred vision (adjOR 1.21, 95% CI 1.00 to 1.46) [519].
- One study reported no association between exposure and dry eye disease signs (conjunctival staining, corneal staining, tear film break-up time, and Schirmer test) [34].

5.4.6.1.2. Air pollution from gases: NO_2. One case-control study and 10 single-group studies reported on air pollution from NO_2 (Appendix Table C-2). Results were inconsistent for dry eye diagnosis. Exposure was associated with ocular irritation (but no other symptoms) and with lower tear break-up time (but no other signs).

- Six studies reported on the association between incremental increases in exposure and dry eye disease diagnosis [22,150,160,169,517]. Although the other three studies reported no association, increased odds of diagnosis were reported as follows; (adjOR 1.43, 95% CI 1.15 to 1.78) [22], (adjOR 1.12, 95% CI 1.02 to 1.23) [160], and (adjOR 1.08, 95% CI 1.04 to 1.11) [169].
- Seven studies reported on symptoms [16,18,21,34,39,166,519]. The studies generally reported the lack of an association of exposure with symptoms, except for ocular irritation. One study reported a trend ($p < 0.01$) for greater ocular irritation with increasing exposure [18] and another reported greater ocular irritation per 1 ppb increase in exposure (adjOR 1.05, 95% CI 1.03 to 1.07) [519].
- Four studies reported on dry eye disease signs [18,21,34,166]. The studies generally reported the lack of an association of exposure with signs, except for tear break-up time. Tear break-up time was negatively correlated with exposure in two studies (correlation coefficient −0.14, $p < 0.038$ [34] and −0.316, $P=0.019$ [18]). Other reported signs were corneal staining, conjunctival staining, Schirmer test, meibomitis, tear film osmolarity, tarsal goblet cell density, and mucin 5AC mRNA levels.

*5.4.6.1.3. Air pollution from gases: NO_x and NO_y *.* One single-group study in the USA reported on air pollution from NO_x and NO_y (Appendix Table C-3). High exposure was not associated with dry eye disease symptoms or signs, but higher NO_x was associated with somewhat lower corneal staining scores (correlation coefficient −0.08, $P < 0.0038$) and higher NO_y was associated with somewhat lower conjunctival staining scores (correlation coefficient −0.06, $p < 0.0038$) [34].

5.4.6.1.4. Air pollution from gases: O_3. A case-control study and eight single-group studies reported on air pollution from O_3 (Appendix Table C-4). Results were inconsistent for all three outcomes.

- Five studies reported on the association between incremental increases in exposure and diagnosis of dry eye disease [22,160,169,517]. Although the other three studies reported no association, increased odds of diagnosis were reported as follows; (adjOR 1.27, 95% CI 1.09 to 1.48) [160] and (adjOR 3.97, 95% CI 3.67 to 4.29) [517].
- Six studies reported on the association between incremental increases in exposure and dry eye disease symptoms [27,34,39,160,170,519]. Although the other three studies reported no association, worse symptoms with greater exposure were reported as follows; (adjOR for dryness/irritation per 0.01 ppm increment 1.17, 95% CI 1.02 to 1.34) [160], (adjMD for ocular surface disease index per 1 ppb increment 3.43, SE 9.92) [170] and (adjMDs for ocular surface disease index per 1 ppb increment ranging from 0.33 to 0.49 within the first month) [39].
- Three studies reported on the association between incremental increases in exposure and dry eye disease signs [27,34,170]. Results were inconsistent across studies. Signs evaluated were corneal staining, conjunctival staining, tear break-up time and Schirmer test.

5.4.6.1.5. Air pollution from gases: CO. Four single-group studies reported on air pollution from CO (Appendix Table C-5). Results were inconsistent for dry eye disease diagnosis but support a lack of an association between CO exposure and dry eye disease symptoms.

- Three studies reported on the association between incremental increases in exposure and dry eye disease diagnosis [39,169,517]. One study reported no association [39], one reported increased odds of diagnosis (adjOR 1.11, 95% CI 1.00 to 1.22) [169], and the third reported lower odds (adjOR 0.49, 95% CI 0.42 to 0.56) [517].
- Two studies reported on dry eye disease symptoms [34,39]. There was no association between increased exposure and symptoms.
- One study reported no association between exposure and dry eye disease signs (conjunctival staining, corneal staining, tear break-up time, and Schirmer test) [34].

5.4.6.1.6. Air pollution from particulate matter <10 μm. Six single-group studies reported on air pollution from particulate matter <10 μm (Appendix Table C-6). Generally, particulate matter <10 μm was not associated with dry eye disease.

- Four studies reported that incremental increases in exposure to particulate matter <10 μm were not associated with dry eye disease diagnosis [39,150,160,169].
- Four studies reported that incremental increases in exposure to particulate matter <10 μm were not associated with greater symptom occurrence [27,39,160,519]. Specific symptoms evaluated included dryness, irritation, redness, blurred vision, and ocular surface disease index total scores.
- One study reported on dry eye disease signs. A 1 ppb increase in particulate matter <10 μm was associated with lower tear break-up time at 1-week (adjMD −0.03, 95% CI -0.05 to −0.01), 1 day (adjMD −0.03, 95% CI -0.05 to −0.01), and 1-month (adjMD −0.02, 95% CI -0.03 to −0.01); however, it was not associated with corneal staining or Schirmer test scores [27].

5.4.6.1.7. Air pollution from particulate matter: particulate matter <2.5 μm. The case-control study and seven single-group studies reported on air pollution from particulate matter <2.5 μm (Appendix Table C-7). The findings were inconsistent across studies.

- Four studies reported on dry eye disease diagnoses [22,150,169,517]. Although three studies reported that incremental increases in exposure were not associated with diagnosis, one reported that participants exposed to ≥124 days a year when particulate matter <2.5 μm levels exceed "extreme value" in China were more likely to

Table 9
Summary of Findings in this Systematic Review.

Type	Subtype	Specific Pollutant	Outcome	N Studies	N Participants	Risk of Bias	Consistency	Precision	Directness	Other	Certainty of Evidence	Conclusions
Air	Gases	SO_2	Diagnosis	5	89,875	Moderate	Inconsistent	Precise	Direct	–	Very low	None (inconsistent results)
			Symptoms	4	36,815	Moderate	Inconsistent	Precise	Direct	–	Very low	None (inconsistent results)
			Signs	1	535	Low	N/A	Precise	Direct	Sparse	Very low	None
		NO_2	Diagnosis	6	169,741	Low	Inconsistent	Precise	Direct	–	Very low	None (inconsistent results)
			Symptoms	7	36,962	Low	Consistent	Precise	Direct	–	**Moderate**	**Associated with ocular irritation, but no other symptoms**
			Signs	4	682	Moderate	Consistent	Precise	Direct	–	**Moderate**	**Associated with lower TBUT, but no other signs**
		NO_x and	Diagnosis	0	0	–	–	–	–	–	–	None
		NO_y	Symptoms	1	535	Moderate	N/A	Precise	Direct	Sparse	Very low	None
			Signs	1	535	Moderate	N/A	Precise	Direct	Sparse	Very low	None
		O_3	Diagnosis	5	89,875	Low	Inconsistent	Precise	Direct	–	Very low	None (inconsistent results)
			Symptoms	6	36,891	Low	Inconsistent	Precise	Direct	–	Very low	None (inconsistent results)
			Signs	3	611	Low	Inconsistent	Precise	Direct	–	Very low	None (inconsistent results)
		CO	Diagnosis	3	66,171	Low	Inconsistent	Precise	Direct	–	Very low	None (inconsistent results)
			Symptoms	2	16,966	Moderate	Consistent	Precise	Direct	Sparse	**Moderate**	**Not associated with symptoms**
			Signs	1	535	Moderate	N/A	Precise	Direct	Sparse	Very low	None
	Particulate matter	PM_{10}	Diagnosis	4	138,939	Low	Consistent	Precise	Direct	–	**High**	**Not associated with DED diagnosis**
			Symptoms	4	36,323	Low	Consistent	Precise	Direct	–	**High**	**Not associated with symptoms**
			Signs	1	43	Low	N/A	Precise	Direct	Sparse	Very low	None
		$PM_{2.5}$	Diagnosis	4	136,486	Moderate	Inconsistent	Precise	Direct	–	Very low	None (inconsistent results)
			Symptoms	4	670	Moderate	Inconsistent	Precise	Direct	–	Very low	None (inconsistent results)
			Signs	4	670	Moderate	Inconsistent	Precise	Direct	–	Very low	None (inconsistent results)
	Incinerated waste	Incinerated waste	Diagnosis	0	0	–	–	–	–	–	–	None
			Symptoms	1	115	Moderate	N/A	Precise	Direct	Sparse	Very low	None
			Signs	1	519	Moderate	N/A	Precise	Direct	Sparse	Very low	None
	Unspecified	Air pollution, unspecified	Diagnosis	1	500	Moderate	N/A	Imprecise	Direct	Sparse	Very low	None
			Symptoms	0	0	–	–	–	–	–	–	None
			Signs	0	0	–	–	–	–	–	–	None
Soil	Metal pollutants	Cd	Diagnosis	1	11,220	Low	N/A	Precise	Direct	Sparse	Very low	None
			Symptoms	0	0	–	–	–	–	–	–	None
			Signs	0	0	–	–	–	–	–	–	None
		Cr	Diagnosis	2	Unclear	Low	Consistent	Precise	Indirect	Sparse	**Low**	**Associated with DED and Sjogren's diagnoses**
			Symptoms	0	0	–	–	–	–	–	–	None

(*continued on next page*)

Table 9 (*continued*)

Type	Subtype	Specific Pollutant	Outcome	N Studies	N Participants	Risk of Bias	Consistency	Precision	Directness	Other	Certainty of Evidence	Conclusions
			Signs	0	0	–	–	–	–	–	–	None
		Cu	Diagnosis	1	11,220	Low	N/A	Precise	Direct	Sparse	Very low	None
			Symptoms	0	0	–	–	–	–	–	–	None
			Signs	0	0	–	–	–	–	–	–	None
		Hg	Diagnosis	1	11,220	Low	N/A	Precise	Direct	Sparse	Very low	None
			Symptoms	0	0	–	–	–	–	–	–	None
			Signs	0	0	–	–	–	–	–	–	None
		Ni	Diagnosis	2	Unclear	Low	Inconsistent	Precise	Direct	Sparse	Very low	None (inconsistent results)
			Symptoms	0	0	–	–	–	–	–	–	None
			Signs	0	0	–	–	–	–	–	–	None
		Pb	Diagnosis	1	11,220	Low	N/A	Precise	Direct	Sparse	Very low	None
			Symptoms	0	0	–	–	–	–	–	–	None
			Signs	0	0	–	–	–	–	–	–	None
		Zn	Diagnosis	1	11,220	Low	N/A	Precise	Direct	Sparse	Very low	None
			Symptoms	0	0	–	–	–	–	–	–	None
			Signs	0	0	–	–	–	–	–	–	None
Water	Water pollutants	PCE	Diagnosis	1	1,303	Moderate	N/A	Precise	Direct	Sparse	Very low	None
			Symptoms	0	0	–	–	–	–	–	–	None
			Signs	0	0	–	–	–	–	–	–	None

Abbreviations: Cd = cadmium, CO = carbon monoxide, Cr = chromium, Cu = copper, DED = dry eye disease, Hg = mercury, Ni = nickel, O_3 = ozone, Pb = lead, PCE = tetrachloroethylene, PM_{10} = particulate matter <10 μm in diameter, $PM_{2.5}$=particulate matter <2.5 μm in diameter, NO_2 = nitrogen dioxide, NO_x = reactive nitrogen oxides, No_y reactive nitrogen compounds, SO_2 = sulfur dioxide, TBUT = tear film break-up time, Zn = zinc.

be diagnosed with dry eye disease than those exposed to those levels <124 days a year (adjOR 2.01, 95% CI 1.79 to 2.26) [517].

- Four studies reported on dry eye disease symptoms (using the ocular surface disease index) [21,27,34,166]. Although three studies reported that incremental increases in exposure were not associated with symptoms, one reported that a 1 ppb increment in exposure in South Korea was associated with higher ocular surface disease index scores at 1 day (adjMD 0.38, 95% CI 0.06 to 0.70) and at 1 week (adjMD 0.40, 95% CI 0.09 to 0.070) but not at 1 month [27].
- The same four studies also reported on dry eye disease signs [21,27,34,166]. Incremental increases in exposure led to inconsistent results across signs. Specific signs evaluated included corneal staining, conjunctival staining, tear break-up time, Schirmer test, tear film osmolarity, tarsal conjunctival goblet cell density, and mucin 5AC mRNA levels.

5.4.6.1.8. Air pollution from incinerated waste. One cross-sectional study [515] and one single-group study [518] reported on air pollution from incinerated waste (Appendix Table C-8). The single-group study reported on two dry eye signs (non-invasive tear break-up time and self-reported break-up time, (assessed by recording the time the participant could keep eyes open without blinking when looking at a fixed point) separately for males and females in the aftermath of an explosion accident in Norway [515]. High exposure to the explosion waste was associated only with reduced self-reported break-up time, specifically among males (adjOR 2.0, 95% CI 1.1 to 3.8). Symptoms of ocular dryness and discomfort were associated with high exposure to incinerated organic waste and noxious gases when US war veterans were in Iraq (adjOR 3.17, 95% CI 1.30 to 7.77), but this association was not observed immediately after their return to the US or at their next clinic visit [518].

5.4.6.1.9. Air pollution, unspecified. One cross-sectional study in the Indian state of Rajasthan reported on air pollution without naming specific pollutants (Appendix Table C-9). High exposure to air pollution was not associated with dry eye disease diagnosis (adjOR 1.38, 95% CI 0.39 to 2.33) [516].

5.4.6.2. Pollution measured by satellite-based measurements. No studies addressing these pollutants were found.

5.4.6.3. Soil pollution. Two single-group studies in Taiwan (Lee 2019 and Lian 2018) reported on soil pollution from various metals (Appendix Table C-10) [189,190]. In Lee 2019, among the seven metals evaluated, only chromium was found to be associated with diagnosis of Sjögren syndrome (regression coefficient 6.1, standard error (SE) 2.8; ₱ 0.03) [190]. Lian 2018 reported that participants in counties with exposure to a combination of high chromium and nickel in the soil had greater risks of dry eye disease diagnosis (GiZscores [using ArcGIS] ranging from 2.1 to 2.9; $p < 0.05$ for each) [189].

5.4.6.4. Water pollution. One retrospective cohort study in Cape Cod, Massachusetts, USA reported on water pollution from tetrachloroethylene (Appendix Table C-11). High exposure to tetrachloroethylene was not associated with diagnosis of dry eye disease (adjPR 1.2, 95% CI 0.8 to 1.8) [520].

5.5. Discussion

5.5.1. Summary of findings

This systematic review evaluated evidence for the association between various air, soil, and water pollutants and dry eye disease. Air pollution from NO_2 is probably associated with increased ocular irritation (but no other dry eye symptoms) and lower tear break-up time (but no other dry eye signs). CO is probably associated with increased dry eye symptoms. Particulate matter <10 μm is not associated with dry eye disease diagnosis or symptoms. Soil pollution from chromium may be associated with dry eye disease and Sjögren syndrome diagnoses. The evidence for other air, soil, and water pollutants is very low and therefore does not meet the criteria for drawing conclusions. No eligible studies addressing pollutants measured by satellite-based measurements were found.

5.5.2. Limitations of the evidence

High-certainty conclusions were possible only for particulate matter <10 μm; certainty of the remaining conclusions was at best moderate. Fifteen of the 19 studies were single-group studies, which predominantly reported results analyzed using correlation coefficients between levels of exposures and outcomes. Moreover, it is worth noting that 25% of the studies excluded during full-text screening were comparative studies that did not adjust for differences between study groups.

Other than sparsity of the evidence, the main limitations that contributed to downgraded certainty of the evidence were moderate risk of bias and inconsistency in results across studies. Some of this inconsistency likely stemmed from heterogeneity in how exposures were assessed and/or categorized or how outcomes (e.g., dry eye disease) were defined. Differences in study populations by age, sex, amount of exposure, and geography (nine countries were represented) also likely contributed to the heterogeneity. Taken together, these contributors to heterogeneity precluded any meta-analyses. The sparsity of the evidence also precluded exploration of differences in associations of exposures with outcomes by subgroups of participants (for example by age and sex).

5.5.3. *Limitations of the systematic review process*

Although contemporary best practice methods for searching, screening, extracting data, assessing risk of bias, and assessing certainty of evidence were employed in this systematic review, a number of limitations are worth noting. First, it is possible that some studies published in journals not indexed in Medline or Embase were missed. The systematic review investigators are not aware of, and therefore did not search, any topic-specific databases of studies addressing environmental pollutants or dry eye disease. Second, as conference abstracts (20% of excluded records during full-text screening) were excluded, it is possible that some studies were missed. However, due to their brevity and often-preliminary nature, conference abstracts suffer from inadequate detail and results that cannot be confirmed to be reliable, and therefore their exclusion from systematic reviews is justified and common [521,522].

5.5.4. *Implications for clinical practice*

Given the generally low-quality evidence identified on the topic of this systematic review, it is not possible to make recommendations for clinical practice. However, it would be reasonable to suggest that eye care practitioners evaluating the ocular surface of patients exposed to high levels of pollutants should consider that short-term symptoms might be due to dry eye disease or a range of other ocular surface abnormalities that need to be appropriately assessed and managed.

5.5.5. *Implications for research*

Future studies evaluating associations between environmental pollutants and dry eye disease should adequately account for important confounders, such as age and sex. In addition, when studies are longitudinal (i.e., follow participants over time), the period of participant follow-up should be sufficiently long for dry eye disease diagnoses to develop. As many of the symptoms of dry eye disease (e.g., redness, itching) are indistinguishable from other related diagnoses, such as conjunctivitis, future studies should report on diagnoses of dry eye disease or, at the least, on both symptoms and signs as well as diagnoses of dry eye disease.

5.6. *Conclusions*

Although this systematic review included 19 studies from 10 different countries, it was possible to draw only limited specific conclusions. These conclusions confirm increased dry eye disease with air pollution (from NO_2) and soil pollution (from chromium), but no increased in dry eye disease with air pollution from CO or particulate matter <10 μm. Future research should adequately account for confounders, follow up participants over time, and might helpfully report results separately for diagnosis, symptoms, and signs of dry eye disease.

Evidence of at least low certainty and corresponding conclusions are bolded.

6. Conclusions and recommendations

Environmental conditions are a broad and diverse set of factors which can interact closely with the ocular surface. Multiple risk factors can play a pivotal role in the mechanisms of a specific ocular surface disease, (for example, pterygium and exposure to ultraviolet radiation, exposure to allergens and allergic conjunctivitis), but also can increase risk and/or aggravate clinical presentation and outcomes in many others such as dry eye disease.

One of the major challenges for the evaluation of the studies addressing links between the ocular surface and environment is the lack of clear definitions and classification systems for environmental hazards. Throughout the narrative review, many published studies were included and reviewed but there were only a limited number of population-based and well-designed studies. Mostly, studies were of case-control or cross-sectional designs, with small sample sizes. Unfortunately, there is a lack of robust data and consistent studies focusing on the potential associations between environmental exposure and ocular surface diseases. Some risk factors have been more thoroughly investigated than others, such as pollution and allergens, but challenges remain as the methods for measurements and evaluation differ substantially across the studies. Further research about ocular surface disease and its associations with water (pipe water, swimming areas, rivers, lakes, sea beaches) and soil pollution is needed.

Indoor exposures are very common throughout the world, in the general population, affecting children and adults, workers and non-workers, and individuals in office and domestic environments. There are several national-wide studies addressing this topic, since it affects the workforce leading to reduced productivity and absenteeism. Symptoms are often non-specific and there is no consistent symptom pattern reported in published studies. Most studies are surveys and collectively suggest that the relationships between indoor environmental conditions and human well-being are complex and not easy to unravel.

Evidence for specific ocular surface diseases and their relationship to environmental conditions was considered. Most patients with dry eye disease frequently experience aggravation of symptoms, in association with environmental stresses, and many risk factors are considered triggers. Outdoor and indoor environmental factors may further induce epigenetic changes, and alterations in the ocular surface microbiome, immune tolerance, and response. Variations in the prevalence of ocular allergy arise from some climate-related factors such as high environmental temperature, low humidity and exposure to mold/dampness dust particles and smoke. Pterygium and ocular surface neoplastic disease are strongly associated with long-term exposure to ultraviolet radiation and outdoor occupations. However, a critical limitation in human studies of environmental exposure is the difficulty in properly measuring and standardizing climate factors and pollutants.

The systematic review was performed using standard rigorous methodology and addressed the research question: “What are the associations between outdoor environmental pollution and dry eye disease, symptoms, and signs in humans?“. It was, however, possible to only make a limited number of specific conclusions that pointed to an increased risk of dry eye disease in response to a number of air-borne and soil-based pollution hazards.

Future research should include well-designed adequately designed population-based studies that incorporate rigorous measurements and study designs, minimize the impact of confounders, follow up participants over extended periods of time, and to evaluate and report results in standardized ways to advance knowledge and awareness of the impact of environmental changes on the incidence and progression of ocular surface diseases.

Declaration of competing interest

Monica Alves: FAPESP (G), FAEPEX (G), Alcon (L,C), Allergan (L,C), Latinofarma (L,C), Uniaoquimica (L); Penny Asbell: Regeron (F), Sylentis (F), Recordati (F), Senju (C), Olia (C); Murat Dogru: Kobayeshi Pharmaceuticals (F), Otsuka (F), Icorn GMBH (F), Twenty/Twenty Therapeutics (C); Giuseppe Giannaccare: Théa (C), Bausch + Lomb (R); Arturo Grau: None; Darren Gregory: None; Dong Hyun Kim: Santen (C),

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Appendix A. Search Syntaxes for searches in Medline and EMBASE

Medline (via PubMed)

("Outdoor Pollut*" OR "Environmental Pollution" [36] OR "gases" OR "Air Pollut*" OR "Carbon monoxide" OR "Carbon monoxide" [36] OR "Nitrogen Oxide" OR "Nitrogen dioxide" OR "Nitric Oxide" OR "Nitrogen Oxides" [36] OR "Sulfur dioxide" OR "Sulfur dioxide" OR "Sulfur dioxide" [36] OR "Ozone" OR "Ozone" [36] OR "Particulate Matter*" OR "Particulate Matter" [36] OR "Volcan*" OR "Volcanic Eruptions" [36] OR "Asian dust*" OR "Yellow Sand*" OR (("wind" OR "dust") AND "storm*") OR "forest fire*" OR "Wildfires" [36] OR "salt spray*" OR "rock debris*" OR "gaseous emission*" OR "soil ero*" OR "Soil Erosion" [36] OR (("fuel" OR "coal") AND "combust*") OR "smoke*" OR "Smoke" [36] OR "haze*" OR "petroleum" OR "oil spill" OR "Petroleum Pollution" [36] OR (("cement" OR "glass" OR "steel") AND "manufactur*") OR "smelt*" OR "mines" OR "mining" OR "Mining" [36] OR ("power plant" AND "emiss*") OR "Soil Pollut*" OR "Agricultural Pollut*" OR "Aerosol*" OR "Aerosols" [36] OR "Satellite*" OR "Satellite Imagery" [36] OR "Moderate Resolution Imaging Spectroradiomet*" OR "MODIS" OR "Multi-angle Imaging Spectroradiomet*" OR "MISR" OR "Water Pollut*" OR "Water Pollution" [36])
AND
("dry eye*" OR "eye dry*" OR "ocular dry*" OR "ocular surface dry*" OR "xerophthal*" OR "sicca*" OR "red eye*" OR "eye red*" OR "ocular red*" OR "ocular surface red*"
OR "itchy eye*" OR "eye itch*" OR "ocular itch*" OR "ocular surface itch*"
OR "foreign body sensation" OR "conjunctival hyperemia" OR "conjunctival hyperemia"
OR "Sjogren*" OR "dry eye syndromes" [36] OR "tear osmolarity" OR "hyperosmolarity" OR "hyper-osmolarity" OR "TBUT" OR "tear break*" OR "tear film*" OR "tear instabilit*" OR "NITBUT" OR "corneal stain*" OR "conjunctival stain*" OR "fluorescein stain*" OR "tear menisc*" OR "Ocular Surface Disease Index" OR "OSDI" OR "Schirmer*" OR "impression cytology")

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Number of Hits = 1,397

Embase

#1. 'pollutant'/exp OR 'pollution'/exp
#2. 'gases'
#3. 'air pollutant'/exp OR 'air pollution'/exp OR 'air pollut*'
#4. 'carbon monoxide'/exp OR 'carbon monoxide'
#5. 'nitrogen oxide'/exp OR 'nitrogen oxide' OR 'nitric oxide*' OR 'nitrogen dioxides'
#6. 'sulfur dioxide'/exp OR 'sulfur dioxide' OR 'sulfur dioxide'
#7. 'ozone'/exp OR 'ozone'
#8. 'particulate matter'/exp OR 'particulate matter'
#9. 'volcano'/exp OR 'volcan*'
#10. 'asian dust'/exp OR 'asian dust' OR 'yellow sand'
#11. 'dust storm'/exp OR 'dust storm' OR 'duststorm' OR 'wind storm' OR 'windstorm'
#12. 'forest fire'/exp OR 'wildfire'/exp OR 'forest fire*' OR 'wild fire*' OR 'wildfire*'
#13. 'salt spray*' OR 'rock debris'
#14. 'gaseous emission*'
#15. 'soil erosion' OR 'soil erosion*'
#16. 'coal combustion'/exp OR 'coal combust*' OR 'fuel combust*'
#17. 'smoke'/exp OR 'smoke'
#18. 'haze'/exp OR 'haze'
#19. 'oil spill'/exp OR 'oil spill*' OR 'petroleum pollution*'
#20. 'cement manufact*' OR 'glass manufact*' OR 'steel manufact*'
#21. 'smelting'/exp OR 'smelt*'
#22. 'mining'/exp OR 'mines' OR 'mining*'

#23. 'power plant emiss*' OR 'powerplant emiss*'
#24. 'soil pollution'/exp OR 'soil pollutant'/exp OR 'soil pollut*' OR 'agricultural pollut*'
#25. 'aerosol'/exp OR 'aerosol*'
#26. 'satellite imagery'/exp OR 'satellite*' OR 'moderate resolution imaging spectroradiometer'/exp OR 'moderate resolution imaging spectroradiomet*' OR 'modis' OR 'multi-angle imaging spectroradiomet*' OR 'multiangle imaging spectroradiomet*' OR 'misr'
#27. 'water pollutant'/exp OR 'water pollution'/exp OR 'water pollut*'
#28. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27
#29. 'dry eye syndrome'/exp OR 'dry eye*' OR 'sicca*' OR 'sjoegren*' OR 'sjogren*' OR 'xeropthalmi*' OR 'red eye*' OR 'eye red*' OR 'ocular red*' OR 'ocular surface red*' OR 'itchy eye*' OR 'eye itch*' OR 'ocular itch*' OR 'ocular surface itch*' OR 'foreign body sensation' OR 'conjunctival hyperemia' OR 'conjunctival hyperemia'
#30. 'tear osmolarity'/exp OR 'tear osmolarity' OR 'hyperosmolarity'/exp OR 'hyperosmolarity' OR 'hyper-osmolarity'
#31. 'tear break-up time'/exp OR 'tear break*' OR 'tear film'/exp OR 'tear film*' OR 'tear instabilit*' OR 'NITBUT'
#32. 'corneal staining'/exp OR 'corneal stain*' OR 'conjunctival staining'/exp OR 'conjunctival stain*' OR 'fluorescein staining'/exp OR 'fluorescein stain*'
#33. 'tear meniscus height'/exp OR 'tear meniscus area'/exp OR 'tear meniscus depth'/exp OR 'tear menisc*'
#34. 'Ocular Surface Disease Index'/exp OR 'Ocular Surface Disease Ind*' OR 'OSDI'
#35. #29 OR #30 OR #31 OR #32 OR #33 OR #34
#36. #28 AND #35

Date: January 4, 2022
Number of Hits = 1,696

Appendix B. Risk of bias tables

Appendix Table B1
Risk of bias assessment for the retrospective cohort study.

Study, Year, Reference	Was the exposed group representative?	How was the non-exposed group selected?	How was the exposure ascertained?	Was outcome not present at start of study?	How was the outcome assessed?	Was follow-up long enough for outcomes to occur?	Was the follow-up adequate?	Did the analysis account for age and sex?	Overall risk of bias
Aschengrau 2015 [520]	Somewhat	Same community as the exposed group	Secure record	Yes	Self-report of symptoms	Yes	No, 45.5% lost	Yes	Moderate

Appendix Table B2
Risk of bias assessment for the case-control study.

Study, Year	Was the case definition adequate?	Were the cases representative?	How were controls defined?	How were controls selected?	How was exposure ascertained?	Was exposure ascertained the same way for cases and controls?	Was the non-response rate the same for cases and controls?	Did the analysis account for age and sex?	Overall risk of bias
Chung 2021 [22]	Yes, self-report of symptoms	Yes	No history of disease	NR	Secure record	Yes	Yes	Yes	Low

Abbreviations: NR = not reported.

Appendix Table B3
Risk of bias assessment for the cross-sectional studies.

Study, Year	Was the exposed group representative?	How was the non-exposed group selected?	How was the exposure ascertained?	How was the outcome assessed?	Did the analysis account for age and sex?	Overall risk of bias
Moen 2011 [515]	Somewhat	Same community as the exposed group	Structured interview	Clinical examination during study	Age only	**Moderate**
Sahai 2005 [516]	Truly	Same community as the exposed group	Self-report	Independent blind assessment	NR	**Moderate**

Abbreviations: NR = not reported.

Appendix Table B4
Quality and risk of bias assessment for the single group studies.

Author, Year, Reference	Were eligibility criteria clearly described?	How was the exposure ascertained?	Was the follow-up adequate?	How was the outcome assessed?	Overall risk of bias
Berg 2020 [34]	Yes	Secure record	Complete	Self-report of symptoms and clinical assessment	**Low**
Hwang 2016 [160]	Yes	Secure record	<10% loss to follow up	Self-report of symptoms	**Low**
Kim 2019 [170]	Yes	Secure record	Complete	Independent blind assessment	**Low**
Kim 2020 [27]	Yes	Secure record	Complete	Record linkage	**Low**
Lee 2019 [318]	Yes	Secure record	Complete	Record linkage	**Low**
Lian 2018 [189]	Yes	Secure record	Complete	Record linkage	**Low**
Modi 2014 [518]	Yes	Self-report	Complete	Self-report of symptoms	**Moderate**
Novaes 2010 [18]	Yes	Secure record	Complete	Record linkage	**Low**
Torricelli 2013 [21]	Yes	Secure record	Complete	Independent blind assessment	**Low**
Torricelli 2014 [166]	Yes	Secure record	Complete	Independent blind assessment	**Low**
Um 2014 [39]	Yes	Secure record	<10% loss to follow up	Self-report of symptoms	**Low**
Vehof 2021 [150]	Yes	Secure record	Complete	Self-report of symptoms	**Low**
Wiwatanadate 2014 [519]	Yes	Secure record	Complete	Self-report of symptoms	**Low**
Yu 2019 [517]	Yes	Secure record	Complete	Record linkage	**Low**
Zhong 2018 [169]	Yes	Secure record	<10% loss to follow up	Record linkage	**Low**

Appendix C. Evidence Tables

Appendix Table C1

Association between air pollution from sulfur dioxide (SO_2) and dry eye

Author, Year, Reference	Design	Overall risk of bias	Outcome	Outcome measurement	Exposure	Measure	Effect Size (95% CI)	P Value
Chung 2021 [22]	Case-control	Moderate	DED diagnosis	Patient self-report	per 1 ppb increment	adjOR	1.01 (0.91, 1.11)	NS
					≥4.61 ppb vs. <4.61 ppb		1.20 (0.98, 1.48)	NS
Berg 2020 [34]	Single-group	Moderate	Dry eye signs	Conjunctival staining score	Higher SO_2	Correlation coefficient	0.02	NS
				Corneal staining score			0.01	NS
				TBUT			—0.02	NS
				Schirmer's test score			—0.02	NS
			Dry eye symptoms	OSDI	Higher SO_2	Correlation coefficient	—0.01	NS
Hwang 2016 [160]	Single-group	Low	DED diagnosis	Ever diagnosed	per 0.003 ppm increment	adjOR	1.16 (0.87, 1.54)	0.31
			Dry eye symptoms	Dryness/irritation	per 0.003 ppm increment	adjOR	1.27 (0.94, 1.73)	0.13
Um 2014 [39]	Single-group	Low	DED diagnosis	Ever diagnosed	per 1 SD increment	adjOR	**1.09 (1.01, 1.18)**	**NR**
			Dry eye symptoms	Any dry eye symptoms	per 1 SD increment	adjOR	**1.09 (1.01, 1.19)**	**NR**
Wiwatanadate 2014 [519]	Single-group	Low	Dry eye symptoms	Ocular irritation	per 1 ppb increment	adjOR	**1.26 (1.09, 1.47)**	**NR**
				Ocular redness	per 1 ppb increment	adjOR	**2.95 (1.46, 5.94)**	**NR**
				Blurred vision	per 1 ppb increment	adjOR	**1.21 (1.00, 1.46)**	**NR**
Yu 2019 [517]	Single-group	Low	DED diagnosis	Ever diagnosed	≥ vs. <124 days when levels exceed "extreme value"	adjOR	**1.64 (1.50, 1.79)**	**<0.0001**
Zhong 2018 [169]	Single-group	Low	DED diagnosis	Ever diagnosed	per 1 ppb increment	adjOR	1.00 (0.99, 1.01)	0.923

Abbreviations: adj = adjusted, DED = dry eye disease, N/A = not applicable, TBUT = tear film break-up time, NR = not reported, NS = not statistically significant, OR = odds ratio, OSDI = Ocular Surface Disease Index, ppb = parts per billion, SD = standard deviation.
Statistically significant results are **bolded**.

Appendix Table C2

Association between air pollution from nitrogen dioxide (NO_2) and dry eye

Author, Year, Reference	Design	Overall risk of bias	Outcome	Outcome measurement	Exposure	Measure	Effect Size (95% CI)	P Value
Chung 2021 [22]	Case-control	Moderate	DED diagnosis	Patient self-report	Per 1 ppb increment	adjOR	1.05 (0.93, 1.19)	NS
					≥28.89 ppb vs. <28.89 ppb		**1.43 (1.15, 1.78)**	**<0.01**
Berg 2020 [34]	Single-group	Moderate	Dry eye signs	Conjunctival staining score	Higher NO_2	Correlation coefficient	—0.01	NS
				Corneal staining score			—0.06	NS
				TBUT			**¡0.14**	**<0.0038**
				Schirmer's test score			0.03	NS
			Dry eye symptoms	OSDI	Higher NO_2	Correlation coefficient	—0.02	NS
Hwang 2016 [160]	Single-group	Low	DED diagnosis	Ever diagnosed	per 0.003 ppm increment	adjOR	**1.12 (1.02, 1.23)**	**0.02**
			Dry eye symptoms	Dryness	per 0.003 ppm increment	adjOR	1.04 (0.96, 1.15)	0.26
Novaes 2010 [18]	Single-group	Low	Dry eye signs	Corneal Rose Bengal staining score	Higher NO_2	Correlation coefficient	NR	NS (for trend)
				Corneal fluorescein staining score	Higher NO_2	Correlation coefficient	NR	NS (for trend)
				TBUT	Higher NO_2	Correlation coefficient	**¡0.316**	**0.019**
				Schirmer's test score	Higher NO_2	Correlation coefficient	NR	NS (for trend)
				Meibomitis	<20 vs. 20–26, 30–35, and >35 $\mu g/m^3$	adjOR	NR	NS (for trend)
			Dry eye symptoms	OSDI	<20 vs. 20–26, 30–35, and >35 $\mu g/m^3$	adjMD	**NR**	**0.01 (for trend)**
				Ocular irritation		adjOR	**NR**	**<0.05 (for trend)**

Appendix Table C2 (*continued*)

Author, Year, Reference	Design	Overall risk of bias	Outcome	Outcome measurement	Exposure	Measure	Effect Size (95% CI)	P Value
				Ocular dryness		adjOR	NR	NS (for trend)
				Ocular heaviness/ fatigue		adjOR	NR	NS (for trend)
				Ocular itching		adjOR	NR	NS (for trend)
Torricelli 2013 [21]	Single-group	Low	Dry eye signs	Corneal fluorescein staining score	per 10 mg/m^3 increment	adjMD	NR	NS
				Corneal Lissamine staining score			NR	NS
				Schirmer's test score			NR	NS
				Tear film osmolarity			NR	NS
			Dry eye symptoms	OSDI	per 10 mg/m^3 increment	adjMD	NR	NS
Torricelli 2014 [166]	Single-group	Low	Dry eye signs	Tarsal goblet cell density	Higher NO_2	Correlation coefficient	NR	NS
				Mucin 5AC mRNA levels			NR	NS
			Dry eye symptoms	OSDI	Higher NO_2	Correlation coefficient	NR	NS
Um 2014 [39]	Single-group	Low	DED diagnosis	Ever diagnosed	per 1 SD increment	adjOR	1.01 (1.00, 1.02)	NS
			Dry eye symptoms	Any dry eye symptoms	per 1 SD increment	adjOR	1.00 (1.00, 1.02)	NS
Vehof 2021 [150]	Single-group	Low	DED diagnosis	Ever diagnosed	NR	adjOR	1.01 (1.00, 1.02)	NS
Wiwatanadate 2014 [519]	Single-group	Low	Dry eye symptoms	Ocular irritation	per 1 ppb increment	adjOR	**1.05 (1.03, 1.07)**	**NR**
				Ocular redness	per 1 ppb increment	adjOR	NR	NS
				Blurred vision	per 1 ppb increment	adjOR	NR	NS
Yu 2019 [517]	Single-group	Low	DED diagnosis	Ever diagnosed	≥ vs. <124 days when levels exceed "extreme value"	adjOR	**0.90 (0.83, 0.98)**	**0.014**
Zhong 2018 [169]	Single-group	Low	DED diagnosis	Ever diagnosed	per 10 ppb increment	adjOR	**1.08 (1.04, 1.11)**	**<0.001**

Abbreviations: adj = adjusted, DED = dry eye disease, MD = mean difference, N/A = not applicable, NIBUT = non-invasive break-up time, NR = not reported, NS = not statistically significant, OR = odds ratio, OSDI = Ocular Surface Disease Index, ppb = parts per billion, SBUT = self-reported break-up time, SD = standard deviation.
Statistically significant results are **bolded**.

Appendix Table C3
Association between air pollution from NO_x and NO_y and dry eye

Author, Year	Design	Overall risk of bias	Outcome	Outcome measurement	Exposure	Measure	Effect Size	P Value
Berg 2020 [34]	Single-group	Moderate	Dry eye signs	Conjunctival staining score	Higher NO_x	Correlation coefficient	−0.02	NS
				Corneal staining score			**−0.08**	**<0.0038**
				TBUT			−0.06	NS
				Schirmer's test score			0.03	NS
			Dry eye symptoms	OSDI	Higher NO_x	Correlation coefficient	−0.01	NS
			Dry eye signs	Conjunctival staining score	Higher NO_y	Correlation coefficient	**−0.06**	**<0.0038**
				Corneal staining score			−0.03	NS
				TBUT			−0.03	NS
				Schirmer's test score			0.04	NS
			Dry eye symptoms	OSDI	Higher NO_y	Correlation coefficient	−0.03	NS

Abbreviations: DED = dry eye disease, N/A = not applicable, NIBUT = non-invasive break-up time, NR = not reported, NS = not statistically significant, OR = odds ratio, ppb = parts per billion, SBUT = self-reported break-up time.
Statistically significant results are **bolded**.

Appendix Table C4
Association between air pollution from ozone (O_3) and dry eye

Author, Year, Reference	Design	Overall risk of bias	Outcome	Outcome measurement	Subgroup	Time-Point	Exposure	Measure	Effect Size (95% CI) or Effect Size (SE)	P Value
Chung 2021 [22]	Case-control	Moderate	DED diagnosis	Patient self-report	All participants	N/A	Per 1 ppb increment	adjOR	1.01 (0.89, 1.15)	NS
							≥21.81 ppb vs. <21.81 ppb		0.98 (0.79, 1.21)	NS
Berg 2020 [34]	Single-group	Moderate	Dry eye signs	Conjunctival staining score	All participants	N/A	Higher O_3	Correlation coefficient	0.03	NS

Appendix Table C4 (*continued*)

Author, Year, Reference	Design	Overall risk of bias	Outcome	Outcome measurement	Subgroup	Time-Point	Exposure	Measure	Effect Size (95% CI) or Effect Size (SE)	P Value
				Corneal staining score					—0.02	NS
				TBUT					**0.07**	**<0.0038**
				Schirmer's test score					0.02	NS
			Dry eye symptoms	OSDI score	All participants	N/A	Higher O_3	Correlation coefficient	—0.01	NS
Hwang 2016 [160]	Single-group	Low	DED diagnosis	Ever diagnosed	All participants	N/A	per 0.003 ppm increment	adjOR	**1.27 (1.09, 1.48)**	**0.002**
			Dry eye symptoms	Dryness/ irritation	All participants	N/A	per 0.003 ppm increment	adjOR	**1.17 (1.02, 1.34)**	**0.03**
Kim 2019 [170]	Single-group	Low	Dry eye signs	Schirmer's test score	All participants	N/A	per 0.01 ppm increment	adjMD	**↓ 1.43 (0.49)**	**0.015**
					Males	N/A			—0.35 (0.99)	0.749
			Dry eye symptoms	OSDI score	Females	N/A	per 0.01 ppm increment	adjMD	**↓ 2.01 (0.66)**	**0.008**
					All participants	N/A			**3.43 (9.92)**	**0.002**
					Males	N/A			6.84 (4.00)	0.105
					Females	N/A			**3.43 (1.03)**	**0.004**
Kim 2020 [27]	Single-group	Low	Dry eye signs	Corneal staining score	All participants	1 day	per 1 ppb increment	adjMD	0.00 (—0.01, 0.00)	NS
						1 week			—0.01 (—0.02, 0.00)	NS
						1 month			0.00 (—0.02, 0.01)	NS
				TBUT	All participants	1 day	per 1 ppb increment	adjMD	0.00 (—0.01, 0.01)	NS
						1 week			0.01 (—0.01, 0.02)	NS
						1 month			0.00 (—0.02, 0.02)	NS
				Schirmer's test score	All participants	1 day	per 1 ppb increment	adjMD	**↓ 0.08 (-0.12, -0.01)**	**0.036**
						1 week			**↓ 0.14 (-0.26, -0.05)**	**0.003**
						1 month			**↓ 0.16 (-0.30, -0.03)**	**0.017**
			Dry eye symptoms	OSDI	All participants	1 day	per 1 ppb increment	adjMD	**0.33 (0.16, 0.49)**	**<0.001**
						1 week			**0.49 (0.29, 0.70)**	**<0.001**
						1 month			**0.48 (0.18, 0.78)**	**0.002**
Um 2014 [39]	Single-group	Low	DED diagnosis	Ever diagnosed	All participants	N/A	per 1 SD increment	adjOR	0.99 (0.97, 1.01)	NS
			Dry eye symptoms	Any dry eye symptoms	All participants	N/A	per 1 SD increment	adjOR	1.00 (0.97, 1.02)	NS
Wiwatanadate 2014 [519]	Single-group	Low	Dry eye symptoms	Ocular irritation	All participants	N/A	per 1 ppb increment	adjOR	NR	NS
				Ocular redness	All participants	N/A	per 1 ppb increment	adjOR	0.89 (0.85, 0.94)	NR
				Blurred vision	All participants	N/A	per 1 ppb increment	adjOR	0.96 (0.95, 0.98)	NR
Yu 2019 [517]	Single-group	Low	DED diagnosis	Ever diagnosed	All participants	N/A	≥ vs. <124 days when levels exceed "extreme value"	adjOR	**3.97 (3.67, 4.29)**	**<0.0001**
Zhong 2018 [169]	Single-group	Low	DED diagnosis	Ever diagnosed	All participants	N/A	per 10 ppb increment	adjOR	1.00 (0.99, 1.01)	0.616

Abbreviations: adj = adjusted, DED = dry eye disease, MD = mean difference, N/A = not applicable, NIBUT = non-invasive break-up time, NR = not reported, NS = not statistically significant, OR = odds ratio, OSDI = Ocular Surface Disease Index, ppb = parts per billion, ppm = parts per million, SBUT = self-reported break-up time. SD = standard deviation, SE = standard error.

Statistically significant results are **bolded**.

Appendix Table C5

Association between air pollution from carbon monoxide (CO) and dry eye

Author, Year, Reference	Design	Overall risk of bias	Outcome	Outcome measurement	Exposure	Measure	Effect Size (95% CI)	P Value
Berg 2020 [34]	Single-group	Moderate	Dry eye signs	Conjunctival staining score	Higher CO	Correlation coefficient	—0.04	NS
				Corneal staining score			—0.04	NS
				TBUT			—0.06	NS
				Schirmer's test score			0.02	NS
			Dry eye symptoms	OSDI	Higher CO	Correlation coefficient	—0.05	NS
Um 2014 [39]	Single-group	Low	DED diagnosis	Ever diagnosed	Per 1 SD increment	adjOR	1.00 (1.00, 1.00)	NS
			Dry eye symptoms	Any dry eye symptoms	Per 1 SD increment	adjOR	1.00 (1.00, 1.00)	NS
Yu 2019 [517]	Single-group	Low	DED diagnosis	Ever diagnosed	≥ vs. <124 days when levels exceed "extreme value"	adjOR	**0.49 (0.42, 0.56)**	**<0.0001**
Zhong 2018 [169]	Single-group	Low	DED diagnosis	Ever diagnosed	Per 1 ppm increment	adjOR	**1.11 (1.00, 1.22)**	**0.042**

Abbreviations: adj = adjusted, DED = dry eye disease, N/A = not applicable, NIBUT = non-invasive break-up time, NR = not reported, NS = not statistically significant, OR = odds ratio, ppb = parts per billion, ppm = parts per million, SBUT = self-reported break-up time.
Statistically significant results are **bolded**.

Appendix Table C6

Association between air pollution from particulate matter less than 10 μm in diameter (PM_{10}) and dry eye

Author, Year, Reference	Design	Overall risk of bias	Outcome	Outcome measurement	Time-Point	Exposure	Measure	Effect Size (95% CI)	P Value
Hwang 2016 [160]	Single-group	Low	DED diagnosis	Ever diagnosed	N/A	per 5 μg/m^3 increment	adjOR	1.01 (0.92, 1.12)	0.81
			Dry eye symptoms	Dryness/irritation	N/A	per 5 μg/m^3 increment	adjOR	0.99 (0.89, 1.10)	0.81
Kim 2020 [27]	Single-group	Low	Dry eye signs	Corneal staining score	1 day	per 1 ppb increment	adjMD	0.00 (—0.01, 0.01)	0.676
					1 week			0.00 (—0.01. 0.01)	0.526
					1 month			0.00 (—0.01, 0.01)	0.751
				TBUT	1 day	per 1 ppb increment	adjMD	**ɨ 0.03 (-0.05, -0.01)**	**0.001**
					1 week			**ɨ 0.03 (-0.05, -0.01)**	**0.001**
					1 month			**ɨ 0.02 (-0.03, -0.01**	**0.018**
				Schirmer's test score	1 day	per 1 ppb increment	adjMD	—0.11 (—0.23, 0.01)	0.076
					1 week			—0.09 (—0.19, 0.02)	0.113
					1 month			0.01 (—0.11, 0.13)	0.871
			Dry eye symptoms	OSDI	1 day	per 1 ppb increment	adjMD	—0.24 (—0.48, 0.01)	0.060
					1 week			—0.20 (—0.43, 0.04)	0.113
					1 month			—0.17 (—0.45, 0.11)	0.236
Um 2014 [39]	Single-group	Low	DED diagnosis	Ever diagnosed	N/A	per 1 SD increment	adjOR	1.01 (1.00, 1.03)	NS
			Dry eye symptoms	Any dry eye symptoms	N/A	per 1 SD increment	adjOR	1.01 (0.99, 1.03)	NS
Vehof 2021 [150]	Single-group	Low	DED diagnosis	Ever diagnosed	N/A	NR	adjOR	1.04 (0.99, 1.09)	0.13
Wiwatanadate 2014 [519]	Single-group	Low	Dry eye symptoms	Ocular irritation	N/A	per 1 ppb increment	adjOR	NR	NS
				Ocular redness	N/A	per 1 ppb increment	adjOR	NR	NS
				Blurred vision	N/A	per 1 ppb increment	adjOR	1.01 (1.00, 1.01)	NR
Zhong 2018 [169]	Single-group	Low	DED diagnosis	Ever diagnosed	N/A	per 10 μg/m^3 increment	adjOR	1.00 (0.99, 1.01)	0.92

Abbreviations: adj = adjusted, DED = dry eye disease, N/A = not applicable, NIBUT = non-invasive break-up time, NR = not reported, NS = not statistically significant, OR = odds ratio, ppb = parts per billion, SBUT = self-reported break-up time, SD = standard deviation.
Statistically significant results are **bolded**.

Appendix Table C7

Association between air pollution from particulate matter less than 2.5 μm in diameter ($PM_{2.5}$) and dry eye

Author, Year, Reference	Design	Overall risk of bias	Outcome	Outcome measurement	Time-Point	Exposure	Measure	Effect Size (95% CI, if applicable)	P Value
Chung 2021 [22]	Case-control	Moderate	DED diagnosis	Patient self-report	N/A	per 1 ppb increment	adjOR	1.04 (0.94, 1.15)	NS
					N/A	≥28.13 ppb vs. <28.13 ppb		1.09 (0.88, 1.36)	NS
Berg 2020 [34]	Single-group	Moderate	Dry eye signs	Conjunctival staining score	N/A	Higher $PM_{2.5}$	Correlation coefficient	0.03	NS
				Corneal staining score				**¡0.08**	**<0.0038**
				TBUT				**0.06**	**<0.0038**
				Schirmer's test score				0.05	NS
			Dry eye symptoms	OSDI	N/A	Higher $PM_{2.5}$	Correlation coefficient	—0.04	NS
Kim 2020 [27]	Single-group	Low	Dry eye signs	Corneal staining score	1 day	per 1 ppb increment	adjMD	0.01 (—0.01, 0.02)	0.401
					1 week			0.00 (—0.01, 0.01)	0.727
					1 month			0.01 (0.00, 0.03)	0.116
				TBUT	1 day	per 1 ppb increment	adjMD	0.02 (—0.01, 0.04)	0.174
					1 week			0.01 (—0.02, 0.03)	0.630
					1 month			—0.01 (—0.03, 0.02)	0.715
				Schirmer's test score	1 day	per 1 ppb increment	adjMD	0.23 (0.08, 0.37)	0.002
					1 week			**0.21 (0.07, 0.34)**	**0.003**
					1 month			**0.19 (0.02, 0.36)**	**0.029**
			Dry eye symptoms	OSDI	1 day	per 1 ppb increment	adjMD	**0.38 (0.06, 0.70)**	**0.022**
					1 week			**0.40 (0.09, 0.70)**	**0.011**
					1 month			0.22 (—0.16, 0.61)	0.256
Torricelli 2013 [21]	Single-group	Low	Dry eye signs	Corneal fluorescein staining score	1 day	per 10 mg/m^3 increment	adjMD	NR	NS
				Corneal Lissamine staining score	1 day			NR	NS
				TBUT	1 day			NR	NS
				Schirmer's test score	1 day			NR	NS
				Tear film osmolarity	1 day			**¡10.9**	**<0.05**
			Dry eye symptoms	OSDI	1 day	per 10 mg/m^3 increment	adjMD	NR	NS
Torricelli 2014 [166]	Single-group	Low	Dry eye signs	Tarsal goblet cell density	1 day	Higher $PM_{2.5}$	Correlation coefficient	**0.67**	**0.005**
				Mucin 5AC mRNA levels	1 day			NR	NS
			Dry eye symptoms	OSDI	1 day	Higher $PM_{2.5}$	Correlation coefficient	NR	NS
Vehof 2021 [150]	Single-group	Low	DED diagnosis	Ever diagnosed	N/A	NR	adjOR	1.01 (0.92, 1.10)	0.91
Yu 2019 [517]	Single-group	Low	DED diagnosis	Ever diagnosed	N/A	≥ vs. <124 days when levels exceed "extreme value"	adjOR	**2.01 (1.79, 2.26)**	**<0.0001**
Zhong 2018 [169]	Single-group	Low	DED diagnosis	Ever diagnosed	N/A	per 10 $μg/m^3$ increment	adjOR	1.00 (0.99, 1.02)	0.90

Abbreviations: adj = adjusted, DED = dry eye disease, N/A = not applicable, NIBUT = non-invasive break-up time, NR = not reported, NS = not statistically significant, OR = odds ratio, OSDI = Ocular Surface Disease Index, ppb = parts per billion, SBUT = self-reported break-up time.
Statistically significant results are **bolded**.

Appendix Table C8

Association between air pollution from incinerated waste and dry eye

Author, Year	Design	Overall risk of bias	Outcome	Outcome measurement	Time-Point	Subgroup	Exposure	n/N (%)	Measure	Effect Size (SE)	P Value
Moen 2011 [515]	Cross-sectional	Moderate	Dry eye signs	NIBUT ≤20 s	N/A	Males	High exposure to explosion waste	NR	adjOR	1.6 (0.7, 3.5)	NS
							Low exposure to explosion waste	NR		Ref	–
						Females	High exposure to explosion waste	NR		0.9 (0.4, 2.1)	NS
							Low exposure to explosion waste	NR		Ref	–
				SBUT ≤30 s		Males	High exposure to explosion waste	NR		**2.0 (1.1, 3.8)**	**NR**

(*continued on next page*)

Appendix Table C8 (*continued*)

Author, Year	Design	Overall risk of bias	Outcome	Outcome measurement	Time-Point	Subgroup	Exposure	n/N (%)	Measure	Effect Size (SE)	P Value
							Low exposure to explosion waste	NR		Ref	–
						Females	High exposure to explosion waste	NR		0.9 (0.4, 1.9)	NS
							Low exposure to explosion waste	NR		Ref	–
Modi 2014 [518]	Single-group	Moderate	Dry eye symptoms	Dryness/ discomfort	When overseas	All participants	High exposure to incinerated organic waste and noxious gases	NR	adjOR	**3.17 (1.30, 7.77)**	**0.01**
					After return to the USA	All participants		NR		NR	NS
					During clinic visit	All participants		NR		0.90 (0.37, 2.20)	0.82

Abbreviations: adj = adjusted, DED = dry eye disease, N/A = not applicable, NIBUT = non-invasive break-up time, NR = not reported, NS = not statistically significant, OR = odds ratio, SBUT = self-reported break-up time.
Statistically significant results are **bolded**.

Appendix Table C9
Association between unspecified air pollution and dry eye

Author, Year	Design	Overall risk of bias	Outcome	Outcome measurement	Time-Point	Exposure	n/N (%)	Measure	Effect Size (SE)	P Value
Sahai 2005 [516]	Cross-sectional	Moderate	DED diagnosis	Based on reported signs and symptoms	N/A	High exposure to air pollution	16/70 (22.9)	adjOR	1.38 (0.39, 2.33)	NS
						Low exposure to air pollution	76/430 (17.7)		Ref	–

Abbreviations: adj = adjusted, N/A = not applicable, NS = not statistically significant, OR = odds ratio.

Appendix Table C10
Association between soil pollution and dry eye

Author, Year	Design	Overall risk of bias	Outcome	Outcome measurement	Time-Point	Exposure	Measure	Effect Size (SE, if relevant)	P Value
Lee 2019 [190]	Single-group	Low	Sjogren's diagnosis	AECG definition of Sjogren's	N/A	High exposure to cadmium	Regression coefficient	—8.4 (10.2)	0.41
						High exposure to chromium		**6.1 (2.8)**	**0.03**
						High exposure to copper		—0.5 (0.2)	0.06
						High exposure to mercury		4.5 (6.9)	0.51
						High exposure to nickel		0.5 (0.7)	0.49
						High exposure to lead		—0.1 (0.2)	0.58
						High exposure to zinc		—0.1 (0.2)	0.51
Lian 2018 [189]	Single-group	Low	DED diagnosis	Medical records (ICD-9)	1 year	Chromium: 5.98 mg/kg; Nickel: 8.64 mg/kg	GiZScore (using ArcGIS)	**2.9**	**<0.05**
						Chromium: 5.14 mg/kg; Nickel: 6.82 mg/kg		**2.1**	**<0.05**
						Chromium: 7.79 mg/kg; Nickel: 4.46 mg/kg		**2.8**	**<0.05**

Abbreviations: AECG = American-European Consensus Group, ICD-9 = International Classification of Diseases-9, N/A = not applicable, NS = not statistically significant.
Statistically significant results are **bolded**.

Appendix Table C11
Association between water pollution and dry eye

Author, Year	Design	Overall risk of bias	Outcome	Outcome measurement	Time-Point	Pollutant	n/N (%)	Measure	Effect Size (95% CI)	P Value
Aschengrau 2015 [520]	Retrospective cohort	Moderate	DED diagnosis	Self-report by questionnaire	N/A	High exposure to tetrachloroethylene (PCE)	65/775 (8.4)	adjPR	1.2 (0.8, 1.8)	NS
						Low exposure to tetrachloroethylene (PCE)	37/528 (7.0)		Ref	–

Abbreviations: adj = adjusted, DED = dry eye disease, N/A = not applicable, NS = not statistically significant, PR = prevalence ratio, Ref = reference group

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