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REVIEW

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External eye symptoms in indoor environments

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Abstract

Eye irritation, for example dry or irritated eyes, is generally among top three reported symptoms in office-like environments, in particular among workplaces with cognitive demanding visual display unit (VDU) work. The symptoms are especially among middle and advanced ages and particularly among women more than men. The symptoms are also among the most commonly reported complaints in the eye clinic. To be in a position to interpret the high prevalence of eye symptoms, a multidisciplinary and integrated approach is necessary that involves the external eye physiology (separate from internal eye effects), eye diseases (evaporative dry eye (DE), aqueous-deficient DE, and gland dysfunctions), and risk factors that aggravate the stability of precorneal tear film (PTF) resulting in hyperosmolarity and initiation of inflammatory reactions. Indoor environmental, occupational and personal risk factors may aggravate the PTF stability; factors such as age, contact lenses, cosmetics, diet, draft, gender, low humidity and high temperature, medication, outdoor and combustion pollutants, and VDU work. Psychological stressors may further influence the reporting behavior of eye symptoms. The impact of the risk factors may occur in a combined and exacerbating manner.

KEYWORDS

environmental and climatic factors, eye symptoms, indoor air pollution, office workers, personal risk factors, relative humidity

1 | INTRODUCTION

Reported eye irritation, for example burning and dry or red eyes, is among top two to three reported symptoms in indoor environments as shown in several epidemiological studies in offices,[1–5] and aircraft.[6,7] The symptoms are also among the most commonly reported complaints in the eye clinic,[8] and dry eye disease (DED) is the most common cause of chronic eye irritation in patients over age of 50.[9,10] These external symptoms, as opposed to internal symptoms such as tired or strained eyes (asthenopia) as already described by Dante in 1304–1307,[11] are categorized as dry eye (DE)-like symptoms.[12] The symptoms are especially among middle and advanced ages throughout the world and expected to increase due to visually highly demanding workplaces increase continuously and so does the average age of the workforce.

Indoor air pollution and low relative humidity (RH) have been proposed to explain the external DE symptoms; furthermore, a number of occupational and personal risk factors have been suggested to exacerbate the symptom reporting.[13] For instance, high ozone concentrations, especially in aircraft, have been proposed to initiate both gas (homogeneous) and surface (heterogeneous) reactions with reactive substances to produce a complex host of gas- and particle-phase products, for example formaldehyde.[14–16] The key question in search of causality for DE symptoms in office workers is how important indoor air pollution is in comparison with occupational, environmental, and personal risk factors. For instance, reported DE symptoms among young and middle-aged Japanese office workers were significantly higher among those with clinically diagnosed DED (12%) than in those with probable (54%) or undiagnosed DED (34%);[17] a similar prevalence of DED was reported among the Singapore population by Tan et al.[18] This implies that immanent DED on the ocular surface,[19,20] affecting 20% of the population, in general,[4,21] may contribute to the overall reported prevalence; in

addition, environmental and occupational exposures, and personal factors may further contribute. Thus, the ophthalmic clinical picture is hampered by the temporality of office-related eye symptoms vs DED.

The prevalence of DE symptoms is between 20% and 40% in offices depending on the recall period; for instance, 1 week,[22] 4 weeks,[1,5] and 3 months for aircraft.[7] The shorter the recall period the lower is the prevalence. For instance, the average prevalence of DE symptom dropped from 39% to 26% going from last 4 weeks to right now.[23] Another study asking for any kind of eye symptom showed a prevalence of 29% (average number being 1.5 symptoms) adjusted for contact lens use, medication, and external stimuli, but only 12% of the respondents reported to experience symptoms often and constantly.[24] Although the recall periods may differ, it is striking that the self-reported prevalence of DE symptoms in offices roughly has remained the same during the last three decades, despite the continuous development of low-emitting building materials and consumer products, and the advancement of ventilation strategies. The high prevalence of DE symptoms results in substantial productivity work loss or disruption in the order of some percentage;[25–28] furthermore, DE symptoms deteriorate quality of life.[29,30]

From an indoor air science and indoor air quality point of view, there is a need for an updated analysis and identification of attributed causalities and their possible synergism, other than DED, for preventive and interventive measures of external eye symptoms. State-of-the-science knowledge about indoor air quality, ophthalmologic, and physiologic risk factors that influence the external eye (precorneal tear film [PTF]) has been integrated and assessed. Environmental, thermal climate (temperature, RH), personal risk factors (e.g., age, medication, affectivity), and occupational (e.g., visual display unit work [VDU]) will also be assessed for exacerbation of DE symptoms.

2 | METHOD—LITERATURE APPROACH

Recent literature from 2012 up to June 2016 has been updated in the context of DE symptom reporting in office-like environments by searches in the databases PubMed and Google Scholar, and with backup from previous reviews.[13,31–34] Exclusions are ergonomics, lighting (glare, reflection, etc.); other exclusions are microbiological exposure and associated inflammatory reactions and associated eye diseases, for example, allergic and bacterial conjunctivitis. This overview is focused on symptoms in the external eye like "dry eyes" as opposed to internal symptoms like "visual strain or eye strain" (asthenopia), inter alia caused by refractive disorders; other commonly reported symptoms related to "dry eyes" are "irritated", "burning", and "itching", while "ocular discomfort", in general, is a mixture of internal and external symptoms with potential overlap, and different and or combined causalities.[35] For example, internal symptoms ("tired and strained eyes") amounted to total 45% and external symptoms ("dry itching, burning, or irritated eyes") amounted to 31% among 7637 respondents in 12 office buildings.[5]

Practical Implications

Dry eyelike symptoms are common in office-like environments. A multidisciplinary approach to understand the multifactorial causalities shows two key indoor parameters, visually demanding tasks combined with low relative humidity. A substantial fraction of office workers may have unrecognized dry eye diseases, which may further be exacerbated by environmental, occupational, and personal risk factors. Dry eye-like-related symptoms in office-like environments may be considered a subgroup of "dry eye" disease.

3 | RESULTS

A number of environmental, occupational, and personal factors were identified as relevant for obtaining an integrated picture of potential causalities of reporting DE symptoms that may occur among office workers, such as use of cosmetics and contact lenses, RH and temperature, office (VDU) work, and certain pollutants, and further personal factors, for example age, medication, and psychosocial factors. Selected studies about potential risk factors and relevant phenomena associated with the external eye will be discussed below.

3.1 | Precorneal tear film

The PTF provides the cornea with a continuous smooth surface with a refraction index greater than air and maintains integrity by retardation of tear (aqueous) evaporation (TE) from the ocular surface (i.e., keeping the external eye moist). The PTF contains antioxidants, proteins of antibacterial activity, nutrients, lubricants, vitamins, and other substances protecting the ocular surface against damage that are caused by, for example, oxidative stress.[36]

A common model of the PTF contains three compartments (Fig. 1). An anterior two-phase lipid layer (LL) secreted mostly from the meibomian glands in the eyelids (meibum) with the outermost layer comprising a non-polar (oily) LL; this interfaces the air and an inner amphiphilic LL interfacing the intermediate and major aqueous-mucin layer secreted from the lacrimal glands. The aqueous-mucin layer interfaces the innermost mucin layer that covers the corneal epithelial cells with adsorbed mostly glycoproteins (mucin) secreted from the conjunctival goblet cells between the epithelium cells. The LL oil is constantly secreted, but is also aided by the blink action, and is almost jetted into the PTF immediately following a blink. An intact LL layer should retard TE efficiently, provide good spreading capability (low surface tension), be sufficiently fluid (unaltered melting point) to prevent blockage of the meibomian gland orifices at the eyelid, and strong enough to resist forces that may disrupt it.[37] Recently, the degree of the anti-evaporative properties of the LL has been debated by Millar and Schuett.[38]

Blinking is essential for maintenance of an intact and moist PTF. However, the blink pattern, activity, and the completeness of blinking depend on a number of different internal and external conditions;

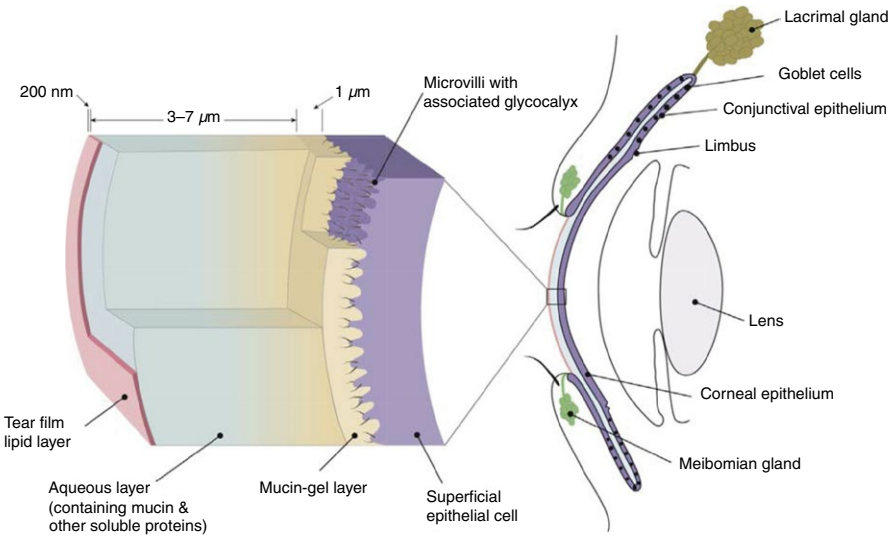

FIGURE 1 Classical three-layer model of the precorneal tear film. A lipid (oily) layer secreted from the meibomian glands interfacing the air and the major aqueous-mucin layer from the lacrimal glands. The aqueous-mucin layer interfaces the inner-most mucin layer that covers the corneal epithelial cells with adsorbed mostly glycoproteins (mucin) secreted from the conjunctival goblet cells between the epithelium cells. For further details, see text. Taken from Yañez-Soto et al.,[20] with kind permission from Elsevier

especially, the blink frequency (BF; blinks/minute) is substantially reduced by cognitive, mentally, or visually demanding work, for example VDU work,[39,40] reading,[41] and personal conditions, for example speech.[42] Further, electronic reading (tablets and personal computers) increases the number of incomplete blinks[39,43,44] that may be associated with ocular discomfort by decrease in the PTF stability[45–48] rather than lower BF itself. It appears, however, that the BF is governed, in part, by stimulation of the cold (transient receptor potential cation channel subfamily M member 8) TRPM8 thermoreceptors as a result of sensing local hyperosmolarity that is caused by increased TE from local dry spots,[49,50] and thus, the local tear film break-up.[51]

The composition and structure of the LL are important for an intact and moist PTF and perhaps less so its thickness, but rather its spatial variation.[49,52,53] The composition of LL is mainly non-polar longer chained lipids such as wax- and cholesteryl esters and glycerides and to a minor extent amphiphilic lipids such as *o*-acyl-omega-hydroxy fatty acids (OFA) and phospholipids.[37,54–57] A substantial fraction of the esters in LL is unsaturated fatty acids (both mono-diene, and trienes).[58,59] However, not the unsaturated, but essential hydrocarbon squalene; although this compound has been found in eyelid lipids, it is speculated that squalene is secreted from sebaceous glands and not from the meibomian glands.[60]

It is unclear how the mixed composition of these lipids may retard the TE.[38] It is speculated that branched and hydroxylated wax esters form a more uniform LL that more efficiently retards the TE;[53] alternatively, compositional changes of the lipids may alter the interfacial viscosity and elasticity of LL forming two separate interfaces, air/lipid and water/lipid.[20,61,62] For instance, bacterial lipases may break down the various esters[49] or they may be broken down by ambient pollutants. All in all, the anti-evaporative capacity appears to depend strongly on the composition and molecular structure of the LL.

3.1.1 | Osmolarity

Clinically, elevated tear osmolarity is considered the best single metric for diagnosing DED and with a proportionality that correlates with the severity.[21] Deficient tear secretion and excessive TE result in hyperosmolarity, as observed in mild-to-moderate patients with DED.[63] Hyperosmolarity depends upon draft, RH, sustained reading (cognitive demanding tasks),[64] and outdoor air pollutants, and coexist with PTF instability,[21] and break-up time (BUT; seconds) of the PTF.[65]

A slow increase in the PTF hyperosmolarity may cause gradual increase in DE symptoms during the thinning process, while a sharp increase in discomfort during break-up may reflect more complex stimulus of the corneal nerves.[66] Patients with DED tend to have higher plasma osmolarity than controls, thus indicating that whole-body hydration is not optimal and may be important to consider regarding preventive measures.[67]

Benzalkonium chloride, a common preservative and disinfectant, used in various eyedrops products and cleaning products, may destabilize the PTF, thus increasing TE that results in hyperosmolarity, and potentially enhancing the cytotoxic effect of the preservative.[68] Note that other medications also aggravate the PTF.[69,70]

A number of studies have indicated associations between hyperosmolarity and morphological (composition and molecular structure) changes of the PTF and symptoms.[21,64,71] For instance, in vitro studies of cells of conjunctiva and cornea resulted in apoptosis, thus increasing PTF instability, which is associated with inflammatory processes and loss of goblet cells, ultimately resulting in damage of the corneal epithelial barrier and fluorescein permeation (dry spots).[71] Furthermore, formation of dry spots enhances direct exposure of the epithelium to environmental pollutants; thus, the eyes may possibly become more susceptible without a barrier and react faster with sensory irritants or oxidants.

Hyperosmolarity may also be negatively associated with BUT and positively with the DE diagnostic questionnaire by McMonnies[72] in mild-to-moderate patients with DED;[73] other studies, however, have only found weak, but significant association between high hyperosmolarity and lower LL thickness,[74] changes in symptoms and dry spot formation (fluorescein staining).[75] One study was unable to find associations between hyperosmolarity and reported DE symptoms and frequency among mild-to-moderate patients with DED (mean

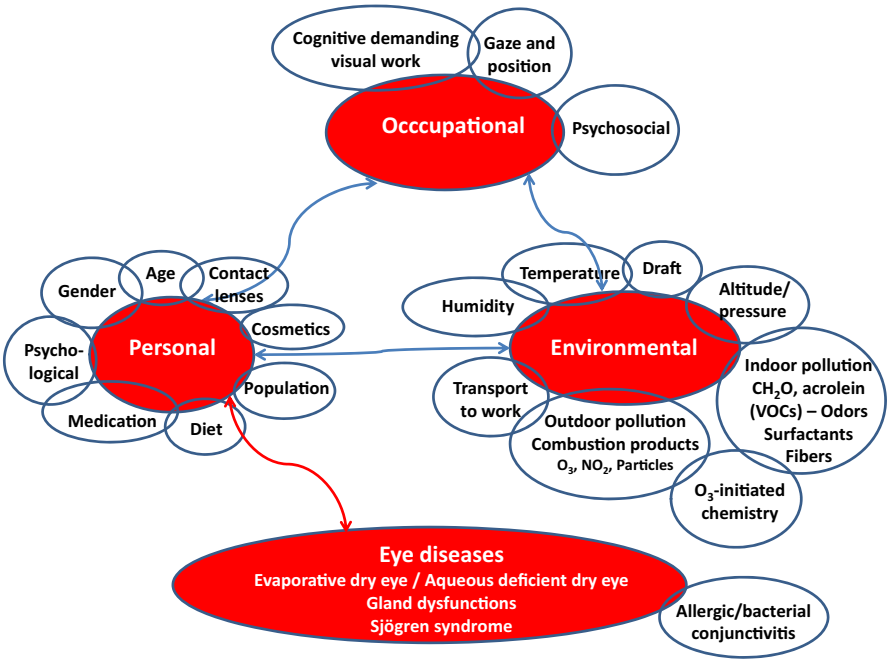

FIGURE 2 Factors associated with risk of exacerbation of eye symptoms in office-like environments, in addition to diseases of the external eye. Blue lines represent factors that may interact. Red line shows the connection to external eye diseases

age = 28 years);[63] however, the study, apart from relatively young subjects, is hampered by a number of factors as discussed by the authors.

3.1.2 | Signs and symptoms

The absence of clear associations between clinical signs and perceived symptoms among patients with DED is well known;[76–81] thus, a substantial fraction of early/mild DE patients remain undiagnosed at the clinic,[21] if the combination of non-invasive assessments is not applied.[82] Alternatively, signs in borderline patients, which are exposed to environmental and occupational risk factors, reverse in the absence of exposures, for example low RH or modified behavior. This has prompted search for new biomarkers and definition of DED.[21,83,84] Field studies in offices, however, have shown associations between reported DE symptoms and changes of the PTF. For instance, a less stabilized PTF reflected by thinner LL during the working day, lower BUT, and more dry spot formation were found among office workers and associated with a higher prevalence of DE symptoms than in the general population.[85–87] This agrees with the present understanding that perceived DE symptoms (or discomfort) increase "when break-up occurs with presumed local spikes in the PTF osmolarity and possible desiccation and deformation".[88] It is common that the symptoms, for example, burning, appear later in the day, which would be consistent with a slowly increasing hyperosmolarity within local areas of the PTF break-up that stimulates nociceptors or cold receptors.[88–90]

The lack of a clear association between symptoms and signs may in part be the borderline between having DE symptoms in a mild-to-moderate form and further exacerbated by office work-related conditions, for example, low RH, high-demanding VDU work, and possibly strong sensory irritants, but absent at the time of the clinic investigation. Thus, perceived DE symptoms during office (VDU) work could be considered a subtype of DED, but temporary in nature.

Correction for the eyelid opening (cm) appears to be an important parameter in correlations of PTF characteristics (BUT and Schirmer's test [production of tears]) and the ocular surface disease index;[91] this agrees with the observation that the position of gaze influences the outcome of the Schirmer's test.[92]

In the following, risk factors that either aggravate the PTF stability or in a combined manner have exacerbated properties with other risk factors, as shown in Fig. 2, will be presented and discussed.

3.2 | Personal factors

3.2.1 | Population

Aging is relevant, not only in view of an older working force, but also in view that many experimental studies have been carried out with young subjects which not necessarily reflect the impact and susceptibility in the older population.[9,93,94] Meibum, essential for the PTF, has a higher protein level and less CH_3 and carbon–carbon double bonds (C=C) with more ordered and tighter lipid–lipid interactions in children than in adults.[95] Malondialdehyde, a proxy of lipid oxidation, has been found to be higher in adult human tears than in younger ones;[96] this agrees with the elevated protein level and C=C bonds in elderly people, that is more susceptible to oxidative attack. In general, the PTF stability decreases with age due to compositional and structural changes of the PTF.[95,97] For instance, tears of children are more stable than those of adults.[95] This is reflected in an increasing BF at increasing age[42,98] and a decrease in the BUT from about 35 seconds in children to about 10 seconds in adults.[99,100] Thus, in general, a short BUT is associated with a destabilized PTF and increase in DE symptoms.[35,101] Recently, however, corneal sensitivity for pain by mechanical stimuli has been suggested to be an additional condition that contributes to DE symptoms.[102]

Non-invasive BUT is greater in children than in adults,[103] indicating a disrupted tear production from the lachrymal and meibomian glands, essential for a stable homeostasis and healthy ocular surface.[104] This agrees with less tear production (Shirmer's test) and lower BF among 60 (±4) years than in younger women (46 ± 6 years),[105] and, in general, a less stable PTF that results in elevated TE from elderly women.[13] Eyelid malposition and malfunctioning, apart from incomplete blinks, is an additional risk factor of DE symptoms.[104]

It was found that the ocular surface and incomplete blinks were greater in an Asian population compared with a Caucasian population, in addition to meibum dropout, thus indicating that Asians may be more predisposed to a less stable PTF.[106]

3.2.2 | Contact lenses

The adverse effects of using contact lenses are well known,[107,108] for example altering the surface distribution of the PTF. The PTF stability decreases and BF increases,[109] while end-of-day dryness is more common among contact lens users with a high sensitivity to mechanical stimulation.[110] Contact lens users are more likely to complain about DE symptoms than non-contact lens wearers after 6 hours of VDU work.[111] Wearing contact lenses substantially increases TE compared to non-contact lens wearers,[112] and this would increase the osmolarity in agreement with contact lens wearers experience worse discomfort than not wearing them at conditions of low RH.[113]

3.2.3 | Cosmetics

The use of cosmetic products may be associated with increased DE symptoms and reflected by increased ocular surface disease index scores,[114] as also inferred in epidemiologic studies.[115–117]

Studies have indicated alteration of meibum, which could adversely affect the PTF stability, by use of cosmetics.[118–120] One important determinant is the polarity and lipophilicity of the chemicals and their capability to alter the anterior LLs (non-polar [LL] and amphiphilic) of the PTF and migration across and further through the intermediary aqueous-mucin layer.[119] The common preservative, benzalkonium chloride, alters the PTF structure leading to a less stable anterior LL, which decreases BUT.[121]

Particles in a facial scrub have been reported to interfere with the PTF resulting in foreign body sensation that was resolved by removal of the particles.[122] Another study showed solvent-based mascaras to be more irritating than oil–water emulsions resulting in contact dermatitis; this was attributed to the use of unidentified irritating substances.[123] Eyelid tattooing has also been shown to induce meibum loss.[124]

3.2.4 | Diet

Deficiency in omega-3- and 6-fatty acids results in an altered PTF structure.[54,125] Their ratio is elevated in DE patients and proportional to PTF dysfunctions; the authors conclude that the metabolic deficiency of omega-3-fatty acids may trigger ocular surface inflammation.[126] Thus, diet appears to be essential to maintain an intact LL by balance of the OFA which are an essential fraction of the meibum;[54,127,128] however, large consumption of a OFA supplement may be necessary to result in increased PTF stability.[129,130] Topical application with unsaturated fatty acids has been shown to be beneficial against inflammation and decreased fluorescein staining[131] including DE symptoms among elderly women carrying out VDU work.[105] A double-masked study with 138 mild-to-moderate patients with DED taking oral supplementation of OFA did not show significant changes in signs and DE symptoms; only, a non-significant trend was observed for reduced biomarker expression of epithelium inflammation and improvement of DE symptoms.[132] However, positive findings were seen in a double-blind randomized study with daily intake twice of 1200 mg eicosapentaenoic/docosahexaenoic acids in a 3/2 ratio for 45 days and compared with a control group taking a placebo of olive oil.[129] The examination of 518 eyes in the OFA-3 group showed significant improvements in DE symptoms and BUT, but not in Schirmer's test; changes were not significant in the placebo group.

Vitamin C is also an important antioxidant protecting against UV light-induced mediated damage of the PTF, for example, by reactive oxygen species.[133,134] Intake of bilberry extracts has shown in a double-blind study with patients with DED to mitigate eye fatigue and discomfort in comparison with a control group, although the underlying mechanism is unknown;[135] BUT was unchanged in the groups after two hours of VDU work.

Ethanol intake among 10 healthy subjects and 10 controls showed significantly shorter BUT, higher fluorescein staining and secretion of ethanol in the tears; tear hyperosmolarity was also observed indication of a less stable PTF.[136] Religious fasting and a minor body weight loss (<2%), however, did not affect tear secretion and BUT among young subjects.[137]

3.2.5 | Gender

A large number of women suffer from eye symptoms,[138–140] and generally with complaint rates 50%–100% higher than reported by men in offices.[33,141] Several risk factors may contribute to this difference, such as age and associated hormonal changes that alter the PTF composition (i.e., less stable PTF) especially among women after 40 years of age, use of cosmetics, psychological and psychosocial factors, and differences in type of work.

3.2.6 | Medication

The use of systemic and topical medications increases over the 60-population and may aggravate or cause DE symptoms.[70] Several types of systemic medications alter the tear production; some of the more prominent are anti-androgens, antidepressants, antihistamines, and diuretics leading to tear-deficient DE or exacerbation thereof.[18,69,104,142] Topical use of eyedrops with preservatives, for example, benzalkonium chloride, is also known to alter the PTF resulting in hyperosmolarity. It was found that the preservative may penetrate in deep ocular surface structures, for example, cornea, conjunctiva, but also sclera, in rabbit eyes.[143]

Lacrimal production is regulated by androgens; thus, age-regulated production of androgens and estrogen in women impacts ocular surface homeostasis and the PTF stability. Diseases, in general, may also influence the PTF stability, for example, diabetes.[144]

3.2.7 | Psychological and psychosocial factors

Psychosocial factors and personal vulnerability (e.g., depression, stress) may be associated with subjects reporting more DE symptoms. For example, it was indicated in a controlled human exposure study that occupational stress lowers the threshold for eye irritation.[145]

Studies have suggested that low coping (e.g., low sense of coherence) of psychosocial challenges may change the threshold for reporting symptoms[146] and enhancing the reporting of DE symptoms, as shown for women;[147,148] this also includes increase in work demand and limited control of the environment in aircraft.[6] Furthermore, a number of studies suggest that depression has a negative influence on DE reporting,[149–151] PTF characteristics,[149,152] and blurred vision has been associated with depression in patients with DED.[153] In contrast, perceived happiness at work has been shown to decrease the reporting of DE symptoms, but without correlation with PTF signs.[154]

3.3 | Environmental factors

3.3.1 | Altitude

The effect of air pressure (altitude) and RH was studied in 14 young healthy subjects that were exposed for six hours to 10% and 60% RH at different air pressures (sea level and 2000 m altitude), independently. Low pressure increased body fluid loss, which was exacerbated by low RH.[155] Thus, it is fair to conclude that low pressure enhances TE and causes hyperosmolarity and reduced BUT as demonstrated by Willmann et al.[156] This is supported by studies at high altitudes in Tibetans and veterans,[157,158] and see references in Wolkoff et al.[13] The impact of high altitude, for example, in aircraft, may further be exacerbated by factors that aggravate PTF stability, thus facilitating an increase in TE.

3.3.2 | Indoor pollution (organic volatiles)

Building materials and products, cleaning and consumer products emit a large number of both chemically non-reactive volatile organic compounds (VOCs) and biologically reactive compounds such as formaldehyde and acrolein; these latter compounds are also formed in ozone-initiated reactions with C=C containing VOCs, for example, terpenes.

Recent measurements in public buildings generally show concentration levels one to three orders of magnitude below thresholds for sensory irritation in the eyes and upper airways as shown in Wolkoff;[159] thus, the concentrations are too low to cause DE irritation-related symptoms, even if the potencies of the compounds are added together by assuming normal addition.[160] Events may occur where the concentration of formaldehyde, either emitted from materials or produced from ozone-initiated reactions with alkenes (e.g., terpenes) or debris, reaches above the threshold for reported sensory irritation of 0.3–0.44 mg/m^3, and with a no observed adverse effect level value of about 0.8–1 mg/m^3 for objective changes of the eye.[161] It is uncertain whether the events are sufficiently long, in view of recent field studies,[162,163] to cause sensory irritation. For instance, weak sensory irritation, less than 13 on a continuous intensity scale from 0 to 100 (20 = slight irritation), was perceived by young subjects with or without mild asthma, when exposed to a steady-state reaction mixture of ozone (max 37 ppb) and limonene (36 ppb) for 3 hours.[164]

Although the threshold for sensory irritation in the upper airways by formaldehyde is unaltered at low RH in mice,[165] it may be speculated that a desiccated PTF with dry spots would facilitate direct exposure contact to the corneal epithelium and thus become more susceptible to sensory irritants or reactive oxygen species. For instance, patients with DED perceived a rapid increase and higher intensity of irritation after the last blink during forced blinking, while the intensity among controls remained unaltered the first 10 seconds and then increased.[166]

Several of the VOCs, in particular the aldehydes, have low odor thresholds.[167] This impacts the perceived indoor air quality and possibly the overall perception of sensory symptoms.[159] Thus, personality factors, as expectations about the odor, anxiety, or attitudes toward health risks, may lead subjects to increase reporting of symptoms.[168]

3.3.3 | Indoor particles

A Nordic consensus group concluded that office particles are generally not associated with the reported health symptoms in offices.[169] So far, controlled human exposure studies with indoor particles have not been convincing, see assessment in Wolkoff.[159] Settled man-made vitreous fibers, however, have been suggested to be associated with reported symptoms[170] in agreement with the finding that levels of airborne particles (>0.5 μm diameter) were significantly higher in offices with work-related eye and upper airway symptoms than in offices with no symptoms.[171] This is further supported by two intervention studies. One showed substantial reduction in eye, nasal and facial complaints after the replacement of partially coated glass wool ceiling boards, emitting vitreous fibers, with fully coated ceiling boards.[172] In the other study, particle release from a ceiling material was shown to be associated with eye problems;[173] however, caution should be taken, as no follow-up was carried out.[174]

Intensified high-efficiency particulate-air filtering of the vacuum exhaust air over several weeks in an office building did not reduce the particle concentration,[175] and no clear effects were found regarding sensory symptoms.[176] In a double-blind intervention study, comprehensive cleaning of all surfaces was carried out, that included all walls, ceiling, desks, bookshelves, and windows, and high-efficiency vacuuming of carpets with a microfilter; the total mean dust concentration was reduced 25 μg/m^3 opposed to only 10 μg/m^3 in the control group. A significant reduction in both sensory irritation symptoms (three week recall period) was observed among the intervention group, but only among employees that spent a majority of their time inside their office

during the workday.[177] A significant reduction in sensory irritation was also reported in another blinded intervention study of intensive cleaning by high-performance vacuum and cleaning practices at different floors.[178]

It is difficult, however, to draw an unambiguous conclusion about the indoor particles being causative, inter alia because other type of pollutants was reduced at the same time.[169] In contrast, in a double-blind crossover study in public buildings a 94% reduction in respirable particles (<3 μm) at low particle levels was not associated with a reduction in DE symptoms.[179] For combustion particles, see below.

3.3.4 | Outdoor air pollution and combustion products

Exposure to traffic pollution and combustion products has been associated with adverse effects on the PTF, for example, in the form of discomfort and reduced BUT,[180–182] as found for exposure to environmental tobacco smoke,[183–186] although the causalities remain unclear.[187]

In the Building Assessment and Survey Evaluation (BASE) study of 97 office buildings, adjusted odd ratios for "irritated or itching eyes" increased to about 1.5 for air intakes below 60 m down to −3 m; the authors speculate that this "striking and consistent" finding may be associated with outdoor pollutants that are related to vehicle emission.[188] These findings are compatible with a number of studies in which alteration of the PTF have been associated with combustion-related pollutants of which some are considered proxies of traffic pollution.

Alteration of the PTF has been associated with traffic proxies such as nitrogen dioxide,[189–191] particulate matter (PM),[192,193] and smoke from wood fires.[194] This is further corroborated by three recent studies. Increase in emergency department visits for conjunctivitis that is associated with ambient ozone, nitrogen dioxide, and $PM_{2.5}$.[195,196] It was found in a population-based cross-sectional study (16 824 participants) that (mean annually) higher outdoor ozone levels and lower RH levels were significantly associated with perceived DE symptoms and diagnosed DED, but not with PM_{10}.[197] Similarly, in the above BASE study a non-significant trend was also found for DE symptoms to be associated with late-afternoon outdoor ozone and the authors speculated this to be associated with ozone-initiated reaction products;[198] however, this appeared to be less probable in a study of European offices.[163] Taken together, the combined effects of ozone exposure and low RH appear to be a plausible route of exacerbation of DE symptoms; however, the ozone may be a proxy of potent irritants or reactive oxygen species. Peroxyacetyl nitrate, a photochemical oxidant in smog, has been considered causative of eye symptoms; however, its threshold for sensory irritation is high,[159] but very low concentrations in indoor modeling studies.[199]

Unstable reactants, such as reactive oxygen species and radicals, are also present on the PM [200] and in environmental tobacco smoke. These and other combustion particulates, as in traffic air, cause constantly oxidative stress on the site of deposition and render the PTF vulnerable to oxidative damage. Reactive oxygen species are generally scavenged by an antioxidant system (e.g., ascorbate, glutathione, and squalene) in the PTF.[133,201,202]. The LL may act as the first antioxidative barrier, while the aqueous-mucin layers of the PTF act as a biochemical barrier by scavenging. At the air–LL interface ozone may react with C=C bonds in the OFAs and wax esters, however, strongly retarded by antioxidants in the aqueous layer.[203] Thus, overloading of the antioxidative defense system in the PTF compartments leads to inflammatory reactions and conjunctival goblet cell damage, as demonstrated for mucin-secreting cells in a mouse model at very high (1 and 4 mg/m^3) ozone concentrations.[204] DE symptoms, however, would not be expected to develop at ozone concentrations below 0.6 mg/m^3 in healthy subjects based on a climate study with nine healthy subjects exposed for 3 hours at 45% RH[205]; furthermore, combined exposure with additional 75 $\mu g/m^3$ suspended office dust (size: 1–7 μm) did increase the general irritation in eyes, nose, and throat. It is noted that both the ozone and the dust concentrations are substantially higher than generally found indoors; it may be speculated, however, that low RH or PTF instability would cause significant eye effects according to Hwang et al.[197]

The OFAs are important for the PTF stability by interconnecting the aqueous-mucin layer with the LL[54] and the polar lipids in building up the PTF after a blink.[206] Loss of the mono-unsaturated OFAs, like oleic acid, in LL has been associated with chronic blepharitis and viscous meibum in patients with DED.[207] The PTF structure could also be altered by isomerization of the C=C bonds in the OFAs, like in oleic acid, by the action of nitrogen dioxide.[208] Such isomerization[54] may alter the structure of the LL aggravating the PTF stability.[125] This aggravation could be amplified by climatic conditions that further alter the PTF stability and increases TE, for example, low RH and high temperature. Furthermore, supply of fresh tear secretion is reduced by less blinking during visual and cognitive demanding tasks, for example, VDU work.[40] Diet (OFAs and other unsaturated compounds in the LL) and the antioxidant status are also important for the PTF maintenance.

3.3.5 | Draft

The stagnant (boundary) layer around the ocular surface region disappears by high horizontal or downward air velocity along the head region[209] and may substantially enhance the TE rate;[210] this accelerates a temperature decrease, especially in cornea. High air velocity (>1.4 m/s) for 30 minute may slightly increase BF during resting conditions in DED patients with low subjective BUT, but not in normal subjects.[211,212] The tear meniscus height and area decreased among the patients with DED, while an increase in the lower meniscus area was observed among the normal subjects; the authors speculate that patients with DED have an altered PTF favoring TE.[211]

The physiologic need for normal or increased BF may, however, be overruled by cognitive and visual workloads, for example, game playing or VDU work.[45,213,214] Thus, elevated air velocity on the PTF and high temperature caused discomfort.[215,216] This probably would increase at extended duration in agreement with elevation of DE complaints in patients with DED was associated with air conditioning and windy environments.[41]

3.3.6 | Relative humidity

Recent epidemiological studies have shown strong associations between low RH and the prevalence of DE symptoms,[22,31] in agreement with controlled studies.

The stability of the PTF in patients with DED was inversely correlated with RH by an increase in TE rate.[217] Thus, controlled studies with both moderate DE patients and healthy subjects in low RH conditions (desiccating stress) for a couple of hours have demonstrated adverse effects on the PTF such as increased TE, reduced tear production and stability, and increased ocular discomfort.[13,218–221] For instance, one-hour exposure of healthy subjects to 5% RH adversely affected PTF characteristics as similarly found in patients with DED;[218] also, BF and fluorescein staining increased in patients with DED.[219] Conversely, the exposure to controlled humidified air increases the PTF stability in DE patients by reduction in the mean break-up area.[222] Healthy students (n=39), that were exposed to different types of ventilation and draft in a climate chamber with controlled temperature and RH, reported significantly less DE symptoms by elevation of RH from 57% to 74%;[223] however, the air velocity was substantially higher in the high RH condition, the finding should be considered cautiously.

Noteworthy is the observation that different outdoor RHs may adversely affect BUT and fluorescein staining;[197,224,225] this hampers comparison of PTF characteristics across different climatic regions. Furthermore, animal models have shown a decrease in meibum and lacrimal gland functions at low RH conditions. For instance, exposure of mice to dry air showed less tear production and elevated dry spot formation,[226–230] and epithelial damage.[230] Desiccation increases the osmolarity of the PTF, which results in a cascade of inflammatory reactions including epithelial damage.[230,231]

Although humidification by moist cool air devices has been shown to be beneficial for office workers resulting in lower DE prevalence and a more stable PTF compared to sham workers,[232] a number of studies have demonstrated the opposite; for instance, the use of portable humidifiers was associated with an increase in DE symptoms[233] and references therein. Clearly, inadequate maintenance or excessive use of disinfectants in the water may be causative by the emission and exposure to microbiological contaminants or surface active compounds.

3.3.7 | Room temperature/corneal temperature

The TRPM8-dependent cold thermoreceptors of the cornea regulate the basal tear flow (i.e., ocular surface wetness) without interferences from other stimuli-mediated tearing, for example irritative. This indicates that the flow of basal tear secretion is reduced by warming of the cornea;[234] thus, elevated room temperature may potentially cause a decrease in the PTF quality as found by Nygaard et al.[216] This agrees with 19% decrease in DE symptoms in a double-blind crossover study in public buildings by lowering the room temperature 1°C in the 22–26°C interval.[179]

The BF is partly triggered by a lower corneal temperature. For instance, higher temperature lowers BF, in accord with stimulation of the thermo-sensitive TRPM8 cold fibers in cornea that initiates reflex blinking by cooling.[235,236] A threefold increase in the TE rate was measured as ambient temperature increased to 25°C[237] and from 25°C to 34°C.[210] Low temperature has also an adverse effect by lower non-invasive BUT (5 second less) and LL thickness (halved) at 5°C than at 25°C.[237] Overall, both low RH and low/high temperature have detrimental effects on the PTF characteristics; this agrees with a more impaired performance of the meibum lipid film resulting in structural changes by reduced viscoelasticity[61] or compositional changes.[49]

Ocular surface temperature is an additional important PTF characteristic shown to correlate with increased discomfort in comparison to controls.[238] A higher initial ocular surface temperature may be associated with a thicker LL in normal subjects, but not a more stable PTF;[239] however, longer BUT (more stable PTF) has been found at lower initial ocular surface temperature.[240]

Meibum production is essential for maintaining an intact PTF and assumed to retard TE; thus, meibomian dysfunction is considered the most important cause of DED by reduction in the lipid content of LL.[241,242] There are several causes of dysfunction. Some of these are compositional changes of the LL, either chemically or microbiologically, that increases the melting point of LL causing gland blockage at the meibomian orifices. Second, desiccating stress by low RH exposure of the ocular surface epithelium results in keratinization (cornification) of the goblet cell orifices which may cause further gland blockage of the delivery of mucin.[243]

3.4 | Occupational conditions

3.4.1 | VDU work

It is well established that BF is substantially reduced during visual and cognitive demanding tasks such as VDU work,[39,40,48] in comparison with conditions of, for example easy speaking.[244] An accelerated BF was observed immediately after cessation of demanding VDU work indicating the need for restoration of the PTF.[40] Furthermore, the interblink interval during cognitive demanding VDU work is lower and with an increase in incomplete blinks,[39,43,48,109] which may be associated with visual fatigue.[39,43,48] In general, extended VDU work is associated with DE symptoms, the more the more cognitive demanding tasks.[245,246] For draft, humidity, temperature, environmental exposures, and psychological factors, see above.

Frequent short breaks (0.5–1 minute) should be encouraged to minimize DE symptoms[246,247] and at the same time maintain or even improve work productivity.[248–250]

4 | DISCUSSION AND CONCLUSION

In the EU OFFICAIR study, 34% of the workers in 167 European offices reported DE symptoms “during the last 4 weeks” and 91% reported relief of the DE symptoms on days away from the office.[233] The building mean prevalence was 30.5% ranging from 21.5% in Greece to 39% in the Netherlands. It may be speculated, disregarding

age, gender, and climate differences, that the Mediterranean diet is more beneficial for the PTF stability than a north European diet.

The OFFICAIR study has identified a number of associations with building characteristics that in part are compatible with identified risk factors in this overview. Thus, adjustment for covariates of individual and building characteristics showed the following items to be positively associated with DE symptoms: "proximity (<100 m) to potential sources of outdoor air pollution that might influence the indoor environment", "non-openable windows", and "portable humidifiers." The identified risk of combustion products, proxies of both fire and traffic pollutants, agrees with the "proximity" to outdoor pollutants assumed to origin from vehicle emissions. It is a well-established fact that non-openable windows, which limit the degree of freedom to control the near microenvironment, are associated with elevated complaints, for example Aries et al.[251]; Leder et al.[252]; Kamaruzzaman et al.,[253] as also stated by the authors. The association with portable humidifiers is incompatible with the general finding of the positive influence of elevated RH in the office; inadequate maintenance may have elevated the risk of exposure to microbiological contaminants or surface active biocides and aggravated the PTF stability. Particle release from construction materials, for example ceiling materials, has been reported to be associated with DE symptoms and the surface cleaning studies of intervention agree with the OFFICAIR findings[233] and the conclusions by Azuma et al.[22] The association between "crowded office spaces" and DE symptoms found in both the OFFICAIR and Japanese studies is compatible with the general finding that open-planar offices with >6 workers have significantly more sickness days of absence than workers in cellular offices,[254] although the mechanism(s) is not clear; furthermore, psychosocial work stressors are important regarding the health of the workers[252] as also pointed out by Azuma et al.[22]

A fraction of office workers may already have unrecognized DED that increases with age;[21] this may be further exacerbated by the environmental and occupational conditions. Reporting of DE symptoms among healthy (non-DED) office workers is caused by several risk factors that elevate the TE during working conditions, thus mimicking the evaporative DED (caused by meibomian dysfunction in patients with DED). A distinction of internal symptoms comprising ache, pain, muscle stress, and headache and external that comprise burning, irritation, and dryness is necessary for understanding the complex phenomena of eye symptoms.[12]

The two most common and important occupational conditions that elevate DE symptoms are tasks that require visual and cognitive demands, for example, VDU work, and low RH. The VDU work causes substantial lower BF and incomplete blinks, thus increasing the desiccation by TE and followed by break-up, dry spot formation, hyperosmolarity, and symptom development. For instance, this is shown by the burst of eye blinks immediately after the cessation of demanding VDU work.[40] The second important factor, low RH around the ocular surface region accelerates the TE, greatest among patients with DED, and to be exacerbated by high altitude (e.g., in aircraft) and draft. A secondary effect is reduced lacrimal secretion at elevated temperature, while elevated ocular surface temperature may alter the LL structure increasing its melting point causing blockage of the meibomian orifices, as an alternative hypothesis to hyperkeratinization of the epithelium sealing the orifices;[255] the issue has further been discussed by Millar and Schuett[38] that question the TE retardation capacity of LL; it is clear, however, that the composition and molecular structure of the PTF are critical factors.

A number of other risk factors in the office environment have been identified to be associated with reported DE symptoms, such as age, contact lenses, cosmetics, diet, draft, gender, low RH and high temperature, medication, and personal psychological factors; the latter may influence the frequency and intensity of the symptom reporting. Use of cosmetics should be discouraged especially in users of eyedrops medication.[119] Low RH around the ocular area should be avoided.

Lukcso et al.[5] conclude that "an identifiable population of occupants with high prevalence of asthma and allergy disease who disproportionately report discomfort and lost productivity due to symptoms" despite the indoor environment in "normal" buildings is within "acceptable air quality standards". It is very likely that part of this population suffers from unrecognized DED according to Yokoi et al.[17]

Except for special combined events indoor VOCs, formaldehyde and acrolein are not expected to be a direct cause of sensory-related symptoms in offices without combination with other exacerbating risk factors that aggravate the PTF, thus becoming more susceptible, and facilitate access to the corneal epithelium. Many risk factors may occur in a concerted and multifactorial manner; for instance, outdoor pollutants such as ozone and low RH together show an amplifying effect, not seen for the single exposure alone. Similarly, exposure to combustion products and low RH would have an exacerbating effect. So far, indoor particles have not been convincingly associated with eye symptomatology; however, combustion-related particles do adversely affect the PTF stability.

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