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The relationship between sedentary behavior and dry eye disease

Long Nguyen [a,1], Morten Schjerven Magno [a,b,c,d,1], Tor P. Utheim [b,c,e,j],
Christopher J. Hammond [c,f,g], Jelle Vehof [h,i,j,*]

[a] Department of Plastic and Reconstructive Surgery, Oslo University Hospital, Oslo, Norway
[b] Department of Ophthalmology, Sørlandet Hospital Arendal, Arendal, Norway
[c] Department of Medical Biochemistry, Oslo University Hospital, Oslo, Norway
[d] Department of Ophthalmology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands
[e] Department of Ophthalmology, Oslo University Hospital, Oslo, Norway
[f] Department of Twin Research & Genetic Epidemiology, King's College London, St Thomas' Hospital, London, United Kingdom
[g] Department of Ophthalmology, King's College London, St Thomas' Hospital, London, London, United Kingdom
[h] Dutch Dry Eye Clinic, Velp, the Netherlands
[i] Departments of Ophthalmology and Epidemiology, University of Groningen, University Medical Center Groningen, Hanzeplein 1, Postbus 30.001, Groningen, the Netherlands
[j] Department of Ophthalmology, Vestfold Hospital Trust, Tønsberg, Norway

ABSTRACT

Purpose: Sedentary behavior (SB) has been linked with low-grade systemic inflammation, which could play a role in the development of dry eye disease (DED). This cross-sectional study aims to investigate the association between SB and DED.
Methods: We assessed 48,418 participants from the population-based Lifelines cohort (58% female, 18–96 years). Women's Health Study (WHS)-defined DED was the primary outcome. SB was assessed using the Marshall Sitting Questionnaire. The relationship between DED and SB was analyzed using logistic regressions, corrected for age, sex, BMI, smoking status, demographics, and 48 comorbidities. Any potential modifying effect of physical activity (PA) was also assessed, and the analyses were repeated excluding the most computer-intensive domains, investigating SB independent from screen exposure.
Results: WHS-defined DED was present in 9.1% of participants. Greater SB was associated with an increased risk of DED (odds ratio (OR) 1.015 per hour/day, 95%CI 1.005–1.024, P = 0.004). The association between SB and DED was only significant for those with less than WHO-recommended PA (OR 1.022, 95%CI 1.002–1.042, P = 0.027), and not in participants meeting WHO's recommendation (OR 1.011, 95%CI 0.999–1.023, P = 0.076). Lastly, when excluding computer-related sitting, the relationship between SB and DED was attenuated, and no longer significant (OR 1.009, 95%CI 0.996–1.023, P = 0.19).
Conclusions: Greater sedentary time was tied to an increased risk of DED, especially for those with lower PA levels than WHO recommendations. However, as there was no significant association when computer-intensive sitting time was excluded, screen use could explain the observed relationship and should be noted as a possible key confounder.

1. Introduction

Dry eye disease (DED) is a common multifactorial disease of the tears and ocular surface characterized by tear film instability and/or deficiency and ocular inflammation, causing discomfort and visual disturbances [1]. Depending on instruments used, the prevalence of DED ranges from 5% to 50% and is more common in females and those of older age [2,3]. DED often decreases quality of life [4–8] and interferes with activities of daily life, such as reading, watching television, work-related tasks, and quality of sleep [6,9]. In the US alone, the economic burden of DED is estimated to an annual cost of USD 3.84 billion [10]. Symptoms are generally difficult to treat, and there is

currently no cure for DED [2,11,12]. It is therefore important to discover modifiable risk factors and interventions that may combat the development of DED.

Sedentary behavior (SB) is a key modifiable lifestyle factor that increases the risk of several negative health outcomes, such as cardiovascular disease and mortality [13–15]. This could partially stem from SB-induced chronic inflammation [16,17], a process which can also disrupt the ocular surface [18,19]. Three past studies assessing the association between SB and DED [20–22] revealed varying results; with a positive association in two studies [20,21], but negative association in one [22]. Ultimately, the link between SB and DED remains unclear.

Thus, this cross-sectional study from the Netherlands seeks to further

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Table 1
Demographics of the study population.

	All (N = 48,418)	Males (N = 20,257)	Females (N = 28,161)
Age, years, mean (standard deviation [sd])	51.4 (12.6)	52.7 (12.7)	50.5 (12.5)
Ethnicity – White, European, %	98.8	99.0	98.6
Income			
<2000 Euro per month, %	27.4	20.4	32.5
2000-3000 Euro per month, %	30.0	34.3	26.9
>3000 Euro per month, %	35.8	40.3	32.5
Chose not to answer, %	6.8	5.0	8.1
Smoker			
Current, %	14.2	15.4	13.4
Former, %	34.4	37.5	32.1
Never, %	51.4	47.1	54.5
Dry Eye			
Women's Health Study definition, %	9.1	5.0	12.1
Highly symptomatic dry eye, %	1.9	0.8	2.6
Clinical diagnosis, %	8.5	4.7	11.3
Comorbidities[a]			
Number of comorbidities, mean (sd)	2.9 (2.1)	2.4 (1.8)	3.2 (2.2)
Presence of ≥1 comorbidity, %	89.0	85.3	91.6
Sedentary Behavior			
Total sitting time, h/day, mean (sd)	8.98 (3.64)	9.19 (3.60)	8.83 (3.66)
Transport, h/day, mean (sd)	1.14 (1.36)	1.35 (1.48)	1.00 (1.24)
Television watching, h/day, mean (sd)	2.57 (1.47)	2.55 (1.43)	2.59 (1.49)
At-work, h/day, mean (sd)	2.67 (2.36)	2.90 (2.39)	2.51 (2.33)
At-home computer use, h/day, mean (sd)	1.41 (1.33)	1.42 (1.35)	1.41 (1.31)
Other leisure, h/day, mean (sd)	1.24 (1.32)	1.05 (1.23)	1.37 (1.37)
Physical Activity			
MVPA, min/week, mean (sd)	483 (619)	562 (735)	427 (515)
Under WHO-recommended levels (150 min of moderate or 75 min of vigorous activity/week), %	26.7	25.4	27.6

MVPA: moderate-to-vigorous intensity physical activity.

[a] Contact lens wear, hypertension (measured), macular degeneration, glaucoma/ocular hypertension, eye surgery (any), allergic conjunctivitis, Bell's palsy, keratoconus, laser refractive surgery, irritable bowel syndrome, fibromyalgia, osteoarthritis, spinal disc herniation, repetitive strain injury, rheumatoid arthritis, systemic lupus erythematosus, Sjogren's disease, atherosclerosis, cardiac arrhythmia, liver cirrhosis, chronic cystitis, urinary incontinence, spasticity, migraine, chronic fatigue syndrome, depression, burnout, autism, gastric ulcer, Crohn's disease, asthma, acne, psoriasis, eczema, rosacea, hay fever, allergy (any), anemia, diabetes mellitus, osteoporosis, thyroid disease (any), Graves' disease, carpal tunnel syndrome, obstructive sleep apnea, lichen planus, sarcoidosis, chronic back pain, sinusitis.

clarify the link between SB and DED in the general population. Our study is the first to assess this relationship in a European population. There are notable differences in patterns of SB between cultures and cohorts [23–25]. It is, therefore, important to analyze this in a diverse range of populations. We assessed the relationship in several ways. Importantly,

we corrected for a large number of medical comorbidities associated with DED. We are also the first to test if physical activity (PA) is an effect modifier of this association, as it has been shown to be with other health outcomes like cardiovascular disease and mortality [15,26].

2. Methods

2.1. Lifelines cohort and participants

Lifelines is a multi-disciplinary, prospective, population-based cohort study examining the health and health-related behaviors of 167,729 persons living in the north of the Netherlands. It employs a broad range of investigative procedures in assessing the biomedical, socio-demographic, behavioral, physical, and psychological factors which contribute to the health and disease of the general population, with a special focus on multi-morbidity and complex genetics [27]. Participants, almost exclusively of European ancestry, were included via general practitioners or self-enrolment between 2006 and 2013 and will be followed for at least 30 years. The cohort is described in detail elsewhere [28]. The study protocol was approved by the medical ethics committee of the University Medical Center Groningen and carried out in accordance with the Declaration of Helsinki, and all participants provided written informed consent.

The first (baseline) general assessment (1A) was conducted between 2007 and 2013, followed by two subsequent questionnaires. The second general assessment (2A) was between 2014 and 2017, with a follow-up questionnaire given between 2015 and 2019 (2B).

2.2. Assessment of DED

DED status was assessed at 2A with the Women's Health Study (WHS) dry eye questionnaire [29], the most common DED assessment tool in large population-based studies [2]. The questionnaire has been validated against a standardized clinical exam, showing a similar sensitivity and specificity as a 16-item survey [29]. It contains three questions [1]: "How often do your eyes feel dry (not wet enough)?" [2] "How often do your eyes feel irritated?" and [3] "Have you ever received a diagnosis of dry eye?" Items 1 and 2 have the answers: "Never," "Sometimes," "Often," and "Constantly." Item 3 has the answers: "Yes," "No," and "I don't know." The main outcome measure of this study was WHS-defined DED. WHS-defined DED is defined as either a self-reported clinical diagnosis of DED or 'highly symptomatic dry eye' (both dryness and irritation "often" or "always"), or both [29,30]. The two secondary dry eye outcomes, described in further details elsewhere [31], were: (i) 'clinical diagnosis of DED' and (ii) 'highly symptomatic dry eye.' Among the 89,830 participants from the Lifelines cohort attending the second baseline assessment 2A, 89,397 participants had available DED data.

2.3. Assessment of sedentary behavior and physical activity

Participants reported their SB in total daily sitting time using the Marshall Sitting Questionnaire (MSQ) [32]. This validated questionnaire

Table 2
Relationship between total sitting time and dry eye phenotypes.

Dry Eye Phenotypes	All (N = 48,418)					
	OR (95% CI), Model 1[a]	P-value	OR (95% CI), Model 2[b]	P-value	OR (95% CI), Model 3[c]	P-value
WHS-Defined DED	1.023 (1.014–1.031)	<0.001	1.025 (1.015–1.034)	<0.001	1.015 (1.005–1.024)	0.004
- Highly Symptomatic Dry Eye	1.053 (1.035–1.072)	<0.001	1.054 (1–034–1.074)	<0.001	1.045 (1.024–1.066)	<0.001
- Clinical Diagnosis	1.019 (1.010–1.028)	<0.001	1.021 (1.011–1.031)	<0.001	1.010 (1.000–1.021)	0.041

OR: odds ratio of having dry eye per hour of total sitting time; CI: confidence interval; WHS: Women's Health Survey; DED: dry eye disease.

[a] Model 1: Corrected for age and sex only.

[b] Model 2: Corrected for age, sex, body mass index, smoking status, education level, and net monthly household income, full data available for 42,639 participants.

[c] Model 3: corrected for age, sex, body mass index, smoking status, education level, net monthly household income, and 48 comorbidities associated with dry eye, full data available for 42,201 participants.

Table 3
Relationship between total sitting time and dry eye phenotypes, stratified by sex.

Dry Eye Phenotypes	Males (N = 20,257)						Females (N = 28,161)					
	OR (95% CI), Model 1[a]	P-value	OR (95% CI), Model 2[b]	P-value	OR (95% CI), Model 3[c]	P-value	OR (95% CI), Model 1[a]	P-value	OR (95% CI), Model 2[b]	P-value	OR (95% CI), Model 3[c]	P-value
WHS-Defined DED	1.015 (0.997–1.033)	0.10	1.016 (0.997–1.036)	0.11	1.006 (0.987–1.027)	0.53	1.025 (1.015–1.035)	<0.001	1.028 (1.017–1.039)	<0.001	1.017 (1.006–1.028)	0.003
- Highly Symptomatic Dry Eye	1.067 (1.022–1.113)	0.003	1.058 (1.010–1.107)	0.017	1.049 (1.001–1.100)	0.043	1.050 (1.030–1.071)	<0.001	1.052 (1.030–1.075)	<0.001	1.043 (1.020–1.066)	<0.001
- Clinical Diagnosis	1.009 (0.991–1.028)	0.32	1.010 (0.990–1.031)	0.31	1.000 (0.980–1.021)	0.97	1.021 (1.011–1.031)	<0.001	1.024 (1.013–1.036)	<0.001	1.014 (1.002–1.025)	0.022

OR: odds ratio of having dry eye per hour of total sitting time; CI: confidence interval; WHS: Women's Health Survey; DED: dry eye disease.
[a] Model 1: Corrected for age and sex only.
[b] Model 2: Corrected for age, sex, body mass index, smoking status, education level, and net monthly household income, full data available for 42,639 participants.
[c] Model 3: corrected for age, sex, body mass index, smoking status, education level, net monthly household income, and 48 comorbidities associated with dry eye, full data available for 42,201 participants.

[32,33] assesses sitting time in hours and minutes on weekdays and weekend days across five domains [1]: transportation [2], work [3], television watching [4], at-home computer use, and [5] leisure not specified in other domains. SB, in daily sitting hours, was calculated by summing the sitting time for each domain. In line with past studies, SB time per day was truncated at 18 h if it exceeded 18 h [34,35]. The MSQ was administered at 2B, on average 20.5 (SD 3.9) months after the DED assessment at 2A. Around sixty-four thousand participants completed the 2B follow-up questionnaires. Of them, 56,939 participants had also attended 2A and had valid data for DED. Participants with partly answered MSQs were included if they had reported sitting time in at least the two biggest domains; "sitting-time at work" and "television watching". Sitting time in the missing domains for these participants were imputed by the mean.

PA was assessed at 2A with the 'Short Questionnaire to Assess Health-Enhancing Physical Activity' (SQUASH), developed by the Dutch National Institute of Public Health and the Environment [36]. The questionnaire explores PA in "an average week in the past months" across four categories [1]: commuting [2], leisure time and sports [3], household work, and [4] employment and school. Frequency (days/week), duration (hours/day), and intensity (light, moderate, or vigorous) of each activity is noted. According to WHO, adults should perform ≥150 min of moderate or ≥75 min of vigorous PA per week, or an equivalent combination of the two [37]. We used this cut off to classify participants as either sufficiently or insufficiently active.

2.4. Assessment of possible confounding factors

At 1A, baseline, participants would indicate: "… which of the following disorders you have or have had?" for several cardiovascular, chronic pain, gastrointestinal, kidney and urinary, neurological, hematological, autoimmune, skin, and mental conditions. Participants reported other disorders that they had been diagnosed with in free text. At subsequent visits, the participants provided information related to new occurrence of disease since previous survey. An ocular questionnaire was separately administered at 2A, which included the DED assessment and questions about several other ocular conditions. Dichotomous variables for the presences of numerous diagnoses and conditions were created using these answers, as described in greater detail in past works [38]. Forty-eight of these comorbidities were associated with WHS-defined DED [38], and are listed in Supplemental Table 1.

2.5. Statistics

Population characteristics were assessed by descriptive statistics. Multivariable logistic regression models were used to investigate the relationship between the dry eye phenotypes (dependent variables) and SB (independent variable, base unit hour/day). Three main regression models were used. Model 1 corrected for age and sex only. Model 2 corrected for age, sex, education level [low, middle, high], net household income [< 2000, 2000–3000, >3000 euros/month], body mass index (BMI), and smoking status (never, current, past smoking). Model 3 included all factors in Model 2 along with 48 medical comorbidities associated with WHS-defined DED [38]. As pathophysiology and risk factors of DED have been found to be highly sex-specific [39,40], sex-stratified analyses were also conducted. The interaction term [sex*SB] tested the statistical significance of potential differences between males and females in associations, and the interaction term [sufficient PA*SB] was tested to assess the potential interaction effect of being sufficiently active.

Furthermore, greater computer use has been linked to increased prevalence of DED [41,42]. Thus, to ascertain the impact of SB independent of computer use, the analyses were repeated for sitting time excluding the two most computer-intensive domains; "computer use at home" and "sitting time at work". Lastly, stratification by sufficient/insufficient PA based on WHO's cut-off was conducted in

Table 4
Relationship between sitting time without computer-related sitting and dry eye phenotypes.

Dry Eye Phenotypes	All (N = 48,418)					
	OR (95% CI), Model 1[a]	P-value	OR (95% CI), Model 2[b]	P-value	OR (95% CI), Model 3[c]	P-value
WHS-Defined DED	1.011 (0.998–1.024)	0.091	**1.019 (1.005–1.033)**	**0.007**	1.007 (0.993–1.022)	0.31
- *Highly Symptomatic Dry Eye*	**1.061 (1.035–1.088)**	**<0.001**	**1.064 (1.035–1.093)**	**<0.001**	**1.050 (1.020–1.080)**	**0.001**
- *Clinical Diagnosis*	1.005 (0.992–1.018)	0.44	**1.015 (1.000–1.029)**	**0.045**	1.003 (0.988–1.018)	0.71

OR: odds ratio of having dry eye per hour of total sitting time; CI: confidence interval; WHS: Women's Health Survey; DED: dry eye disease.

[a] Model 1: Corrected for age and sex only.

[b] Model 2: Corrected for age, sex, body mass index, smoking status, education level, and net monthly household income, full data available for 42,639 participants.

[c] Model 3: corrected for age, sex, body mass index, smoking status, education level, net monthly household income, and 48 comorbidities associated with dry eye, full data available for 42,201 participants.

secondary analyses.

The participants' age at dry eye assessment (2A) was used in the statistical analyses. A P-value of <0.05 was regarded as statistically significant for all analyses. All analyses were conducted using SPSS software, version 25.0 (SPSS Inc.).

3. Results

Table 1 gives an overview of the population characteristics. The prevalence of WHS-defined DED was 9.1% in the total population of 48,418 participants, with females being more than twice as likely to have DED as males (12.1% vs 5.0%). On average, the participants in our sample were 2.6 years older than the total Lifelines-cohort. The average total sitting time per day was 9.2 and 8.8 hrs in males and females, respectively. Television watching and at-work sitting time were the greatest contributors to SB.

Table 2 shows the relationship between SB and the dry eye phenotypes. Greater SB was linked to a higher risk of the main outcome, WHS-defined DED, in all analyses. After correcting for 48 medical comorbidities associated with DED, each hour of daily SB time increased the odds of having WHS-defined DED by 1.5% (odds ratio (OR) 1.015 per hour of sitting/day, 95% CI 1.005–1.024, P = 0.004, Model 3). Interestingly, SB conferred a higher risk increase for highly symptomatic dry eye (OR 1.045, 95% CI 1.024–1.066, P < 0.001, Model 3) than for clinical diagnosis (OR 1.010, 95% CI 1.000–1.021, P = 0.041, Model 3).

Table 3 presents the sex-stratified analyses. SB was tied to a significantly increased risk of WHS-defined DED in females (OR 1.017 per hour of sitting/day, 95% CI 1.006–1.028, P = 0.003, Model 3), but the association was not significant in males (OR 1.006, 95% CI 0.987–1.027, P = 0.53, Model 3). Nevertheless, the interaction term [sex*SB] was not significant (P = 0.60, Model 3).

After excluding sitting time from computer use-intensive domains, which made up 45% of total sitting time, the association between SB and WHS-defined DED was no longer significant (OR 1.007 per hour of sitting/day, 95% CI 0.993–1.022, P = 0.31, Model 3). Table 4 shows the results of these analyses. Of the secondary outcomes, SB without computer use was significantly linked to highly symptomatic dry eye in all models (OR 1.050, 95% CI 1.020–1.080, P = 0.001, Model 3), but not with having a clinical diagnosis after adjusting for comorbidities (OR 1.003, 95% CI 0.988–1.018, P = 0.71, Model 3). Under the same conditions, similar results were observed in those with PA levels below WHO recommendations: the association remained significant between SB and highly symptomatic dry eye (OR 1.075, 95% CI 1.016–1.137, P = 0.012), but not between SB and clinical diagnoses (OR 0.994, 95% CI 0.964–1.024, P = 0.69) or WHS-defined DED (OR 0.997, 95% CI 0.968–1.027, P = 0.85).

Table 5 shows the results of the PA-stratified analyses. For those below WHO's recommendations, each hour of SB significantly increased the risk of WHS-defined DED by 2.2% (OR 1.022 per hour of sitting/day, 95% CI 1.002–1.042, P = 0.027, Model 3). For those meeting WHO's recommendations, the increased risk with greater SB was approximately half of that seen for participants not meeting recommended PA levels

and was not significant after correcting for comorbidities (OR 1.011, 95% CI 0.999–1.023, P = 0.076, Model 3). Still, no significant interaction effect was observed in either model using the interaction term [sufficient PA*SB] (P = 0.40, Model 3).

4. Discussion

As hypothesized, greater SB was tied to a higher risk of having WHS-defined DED in this large, Dutch population of 48,418 participants. When excluding sitting time related to computer use, the risk increase of SB time was diminished, and only significant for the highly symptomatic dry eye phenotype when simultaneously correcting for comorbidities. This indicates that computer use may be an important confounding factor of the relationship. Our results also showed that the relationship was only significant in those with PA levels below WHO recommendations, despite not finding a significant interaction effect of PA.

Three previous studies have assessed the link between DED and SB or a sedentary lifestyle [20–22]. In line with our study, Hanyuda et al. found that greater sitting time was linked to a greater risk of DED in a general Japanese population of 102,582 adults [20]. They assessed DED status using the WHS dry eye questionnaire, and SB by simply asking about the duration and frequency of at-work and at-home sitting time [20]. A smaller study found increased PA, based on the International Physical Activity Questionnaire, to be linked to a lower risk of DED in office workers from the Japanese Osaka study (n = 672) [21]. The authors further reported higher SB times in those with a short tear film break-up time (≤5 s). Despite this, they observed no significant relationship between SB and DED diagnosis, based on clinical signs and a symptom questionnaire, in their population. Intriguingly, in the American Beaver Dam Study cohort, participants with a sedentary lifestyle had a reduced risk of DED compared to more active counterparts (n = 2, 414) [22]. Physical inactivity, regular physical activity <3 times per week, was used to define participants as having a sedentary lifestyle. SB and physical inactivity may not be directly comparable, and the terms should not be used synonymously [43,44], as a person could meet PA recommendation with short durations of vigorous exercise, but still spending most of their time sitting, thus being both physically active and highly sedentary.

No previous study looking at the relationship between SB and DED has adjusted for medical comorbidities associated with DED. Our results showed that SB remained significantly associated with higher risk of all DED phenotypes even when correcting for 48 comorbidities, despite the increased risk being considerably lower after this adjustment across all the analyses. Several disorders associated with DED have also been linked to greater SB, such as type 2 diabetes [45,46], depression [47] and connective tissue disease [48,49], likely explaining the lower increase in risk per SB hour after comorbidity adjustment.

Computer use, an established risk factor for DED [42,50,51], likely explains part of the link between SB and DED in this study. Prolonged computer use reduces blink frequency, increases incomplete blinking [52–55], and lowers mucin concentrations in tears [56]. These factors subsequently shorten tear film break-up times and accelerate tear

Table 5
Relationship between total sitting time and dry eye phenotypes, stratified by activity level.

Dry Eye Phenotypes	Under WHO's recommendation of physical activity (<150 min/week, N = 11,783)						Meeting WHO's recommendation (≥150 min/week, N = 32,353)					
	OR (95% CI), Model 1[a]	P-value	OR (95% CI), Model 2[b]	P-value	OR (95% CI), Model 3[c]	P-value	OR (95% CI), Model 1[a]	P-value	OR (95% CI), Model 2[b]	P-value	OR (95% CI), Model 3[c]	P-value
WHS-Defined DED	1.035 (1.017–1.053)	<0.001	1.035 (1.016–1.054)	<0.001	1.022 (1.002–1.042)	0.027	1.017 (1.006–1.028)	0.002	1.020 (1.009–1.032)	<0.001	1.011 (0.999–1.023)	0.076
- Highly Symptomatic Dry Eye	1.090 (1.053–1.128)	<0.001	1.085 (1.045–1.126)	<0.001	1.072 (1.031–1.116)	0.001	1.035 (1.013–1.058)	0.002	1.040 (1.016–1.065)	0.001	1.032 (1.007–1.057)	0.13
- Clinical Diagnosis	1.029 (1.011–1.048)	0.001	1.032 (1.013–1.052)	0.001	1.018 (0.998–1.039)	0.073	1.014 (1.003–1.025)	0.012	1.017 (1.005–1.029)	0.005	1.007 (0.995–1.020)	0.24

OR: odds ratio of having dry eye per hour of total sitting time; CI: confidence interval; WHS: Women's Health Survey; DED: dry eye disease.

[a] Model 1: Corrected for age and sex only.

[b] Model 2: Corrected for age, sex, body mass index, smoking status, education level, and net monthly household income, full data available for 40,013 participants.

[c] Model 3: corrected for age, sex, body mass index, smoking status, education level, net monthly household income, and 48 comorbidities associated with dry eye, full data available for 39,613 participants.

evaporation [53,54,57,58]. Hanyuda et al. found a significant relationship between sitting time and WHS-defined DED despite correcting for computer use and demographics in their regression models [20]. This aligns with our findings when excluding computer-related sitting, where in Model 2, after correcting for age, sex, education, income, BMI, and smoking status, each hour of SB without computer-related sitting time still significantly increased the risk of DED. The risk increase, however, was lower than in the main analyses that included computer-related sitting time. Furthermore, the association lost significance after comorbidity adjustment. It, therefore, appears that both medical comorbidities and greater computer use are important confounders of the positive link between SB and DED. Interestingly, the only study not finding more sedentary lifestyles related to a greater risk of dry eye [22], was conducted in an older population assessed between 1993 and 1995, a time when computers use was much less common [59], especially in older age groups [60]. However, it should be noted that when excluding computer use-related sitting time, the relationship between highly symptomatic dry eye and sitting time remained significant even after adjusting for comorbidities.

SB-induced systemic low-grade inflammation could be another mechanism underlying the relationship between SB and DED. SB and physical inactivity are linked with systemic low-grade inflammation and elevated serum levels of pro-inflammatory cytokines such as C-reactive protein, IL-6, and TNF-a [61–63]. Constant low-grade activation of the immune system over time damages tissues and organs [17]. As a consequence, chronic inflammation increases the risk of cardiovascular disease [64,65], kidney disease [66], liver disease [67], and cancer [68]. Several autoimmune and systemic inflammatory diseases, such as Sjögren syndrome [69], rheumatoid arthritis [70], and systemic lupus erythematosus [71], are long-established risk factors of DED development. Non-Sjögren dry eye has also been directly linked to a higher serum neutrophil-to-lymphocyte ratio [72], a marker of systemic inflammation [73]. In addition, the increased production of reactive oxygen species seen with systemic inflammation [74,75], could, in turn, promote age-related damage to the lacrimal gland [76]. In murine models, sedentary mice showed higher levels of reactive oxygen species than more active counterparts [77,78], possibly speeding up age-related DED development. Ultimately, SB-induced systemic low-grade inflammation, and consequently oxidative stress, could promote DED development and may explain parts of the association between SB and DED in this study.

We found that more SB presented a substantially greater increased risk for highly symptomatic dry eye than for clinical diagnosis of DED in all analyses. Previous interventional studies have observed that exercise positively affects dry eye symptoms [79,80] but did not change signs of dry eye [79]. Although high SB does not necessarily equate to low PA levels, the results of our study and the mentioned exercise-intervention studies may still indicate that lifestyle patterns are more closely tied to symptoms than signs of DED. Interestingly, Hanyuda et al. found SB to be more strongly associated with clinical diagnosis of DED [20]. In their study population, there was a considerably higher prevalence of highly symptomatic dry eye than clinical diagnoses;19.8% had highly symptomatic and 11.8% had a clinical diagnosis, and in total 24.6% had WHS-defined DED. In contrast, the prevalence of WHS-defined DED prevalence in our study was 9.1%, made up of 1.9% highly symptomatic dry eye and 8.5% clinical diagnosis. These differences in population characteristics likely contribute to the variations between the studies.

PA appeared to attenuate the relationship between SB and DED. Past studies have observed a similar modulating effect of PA with associations between SB and cardiovascular disease and mortality [15,26]. In our analyses corrected for medical comorbidities, SB was only significantly associated with an increased risk of DED in participants with PA levels under WHO's recommendations. Our study is the first to report a modifying effect of PA for this association and could indicate PA as a potential preventive measure against DED, although causation cannot be assumed from this cross-sectional study.

There are several strengths to our study. First, the large sample size and detailed information available on the participants from the Lifelines cohort allowed us to analyze the association of SB with DED in multiple ways. For instance, we were able to stratify for PA, discovering a possible effect modification, as well as correct for medical comorbidities of DED which is important as many of these comorbidities are known to increase SB. Second, this study assessed SB and DED using validated questionnaires. Third, to investigate the impact of SB independent of computer use, we were able to include analyses of sitting time without computer-intensive time spent sitting.

This study also has some limitations. First, participants retrospectively self-reported SB with the MSQ, and recall error is possible. Second, the assessments of SB and DED were collected at different visits. SB in adults, however, has been shown to be stable over time in a general population [81], and in a past study with repeated interventions aimed at reducing SB, it was still unchanged after three years in individuals at high risk of type 2 diabetes [82]. Third, the inherent limitations of the cross-sectional natural of this study prevents determination of the causality of the observed relationship. Fourth, although we corrected for many confounding factors, including 48 comorbidities of DED, residual confounding could remain. Fifth, our study did not include objective measurements of DED as it was not feasible with this large population-wide study design. Sixth, clinical diagnoses of DED were self-reported, and could be a source of bias as the responsible entity and diagnostic criteria used were not recorded. Last, the attrition of participants from the baseline assessment to the second assessment, in which DED and SB status was assessed, has been reported to be selective [83], which could possibly bias our results and affect the representativity of our study population. Withdrawn participants were more often female, overweight, and smokers, and had lower educational levels, no paid job and worse perceived health [83].

5. Conclusions

In conclusion, greater sedentary time was associated with a higher risk of Women's Health Study-defined dry eye disease in this large cross-sectional study, even after correcting for medical comorbidities. If computer use-intensive sitting time was excluded from total sitting time, the association remained significant between sedentary behavior and highly symptomatic dry eye, but no significant association between sitting time and clinical diagnosis of DED or WHS-defined DED. Additionally, sufficient physical activity attenuated the increased risk of dry eye from greater sedentary time, when also adjusting for medical comorbidities of dry eye disease. Screen use, medical comorbidities, and sufficient physical activity should, therefore, be considered as key confounding factors in the relationship between sedentary behavior and dry eye disease.

Declaration of competing interest

None.

Acknowledgements

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jtos.2023.01.002.

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