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ABSTRACT

Purpose: To assess the association between dry eye disease (DED) and alcohol consumption using a large population-based cohort.
Methods: 77,145 participants (19–94 years, 59% female) from the Dutch Lifelines cohort were cross-sectionally assessed for DED using the Women's Health Study (WHS) dry eye questionnaire. Alcohol intake was assessed using self-reported food frequency questionnaires. The relationship between DED and alcohol use was analyzed using logistic regression, corrected for age, sex, BMI, smoking status, education, income, and 55 potentially confounding comorbidities.
Results: Overall, 30.0% of participants had symptomatic dry eye. Alcohol use significantly increased the risk of symptomatic dry eye in females (odds ratio [OR] 1.095, 95%CI 1.045–1.148), but not in males (OR 0.988, 95%CI 0.900–1.084). Contrarily, in male drinkers, increasing alcohol intake (in 10 g/day) had a protective effect on symptomatic dry eye (OR 0.962, 95%CI 0.934–0.992), which was not seen in females (OR 0.986, 95%CI 0.950–1.023). Alcohol use and intake had a sex-specific effect on all outcomes of DED assessed: symptomatic dry eye, highly symptomatic dry eye, clinical diagnosis, and WHS definition dry eye.
Conclusions: This large population-based study found alcohol use to have a clear sex-specific effect on DED, presenting as a risk-factor only in females. This adds to the evidence of sex-specific pathophysiological mechanisms of dry eye and illustrates the importance of sex stratification in studies investigating DED. The mild protective effect of increased alcohol intake in male drinkers is advised to be interpreted with caution, as alcohol's other health effects might be of greater clinical significance.

Introduction

Dry eye disease (DED) is a multifactorial disorder of the ocular surface characterized by tear film instability, hyperosmolarity, inflammation, and neurosensory abnormalities [1]. DED is a highly prevalent disorder with prevalence estimates ranging from 5 to 50%, depending on the population investigated and the exact definition of dry eye used [2]. Dry eye severely reduces the quality of life [3–6] and

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comes with substantial direct and indirect costs [3,7,8]. In the US alone, the estimated societal loss from DED has been estimated to be around 55 billion US dollars [7]. Despite numerous available treatment options [9–12], complete remission of symptoms is rare, and the disease is often chronic. Therefore, illuminating modifiable risk factors is essential to prevent the development of DED or curb the disease at an early stage.

Alcohol consumption has been proposed as a possible modifiable risk factor of DED, warranting further research [2,13]. Past studies investigating the association between dry eye and alcohol consumption have reported conflicting results. In one experimental study, alcohol was found to be secreted into the tears, increasing tear film osmolarity and shortening tear film breakup-time with high consumption [14]. A recent meta-analysis, including eight observational studies, concluded with a borderline significant positive association between dry eye and alcohol use [13]. However, it should be noted that this increased risk mainly stemmed from a single large study that only assessed the effect of diagnosed alcohol dependency on dry eye [15], weakening the conclusions drawn [13]. The need for studies specifically designed to evaluate the role of alcohol in the development of dry eye was also stressed in the Tear Film and Ocular Surface Society Dry Eye Workshop II (TFOS DEWS II) Epidemiology Report due to the inconclusive findings in past studies [2].

The current study has several aims. First, we assessed the association between the current use of alcohol and several measures of dry eye disease in a large Northern-European population, the Lifelines cohort, taking into account a large number of potentially confounding variables. Second, we evaluated the impact of increased alcohol intake in standard units (10 g) per day [16] and stratified into quartiles of intake on the risk of having symptomatic dry eye, in those consuming alcohol. Third, we assessed the effect of sex on this relationship and stratified by sex to investigate males and females separately. Finally, to explore the effect of age on the association between symptomatic dry eye and alcohol use, we stratified the participants into three age groups, 20–39, 40–59, and 60+ years. As DED has both sex- and age-specific mechanisms and risk factors [2,17], and alcohol use has been shown to affect males and females differently [18–20], we hypothesized these stratifications are necessary to shed light on this association.

Methods

LifeLines cohort and participants

Lifelines is a multi-disciplinary prospective population-based cohort study examining the health and health-related behaviours 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, behavioural, 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 [21]. 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 [22]. 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. For the current study, we have data available for 77,145 participants. With this number, we would be able to detect an odds ratio of 1.10 of symptomatic dry eye, with a power as high as 97.5%, given an alpha of 0.05, and an estimated overall prevalence of symptomatic dry eye of 30% [23] and an estimated ratio of alcohol users to non-users of 7:1 [24].

Assessment of dry eye

There is no gold standard for a diagnosis of dry eye disease available for large-scale epidemiological studies. The most widely used dry eye questionnaire in population-based studies is the Women's Health Study (WHS) dry eye questionnaire [2]. This short questionnaire has three questions and has been validated against a standardized clinical exam and showed similar sensitivity and specificity as a 16-item instrument [25,26]. The study participants completed this questionnaire during the period 2014 to 2018. For this study, we used two questions of the WHS questionnaire about current symptoms of dry eye: "How often do your eyes feel dry (not wet enough)?" and "How often do your eyes feel irritated?" (both with possible answers: 0 = never, 1 = sometimes, 2 = often, or 3 = constantly). As a primary outcome variable, we defined 'symptomatic dry eye' as a total score of 2 or higher on these two questions (i.e., either both dryness and irritation symptoms "sometimes" or at least "often" symptoms of dryness and/or irritation) [23]. As secondary outcome variables, we used the WHS outcome variables (i) 'highly symptomatic dry eye' which is both dryness and irritation symptoms either "often" or "constantly," and (ii) a past clinical diagnosis of dry eye, and (iii) the WHS definition, which is the presence of either one of these two outcomes [25].

Assessment of alcohol consumption

To assess dietary intake, a 110-item semi-quantitative food frequency questionnaire (FFQ) was developed for the Lifelines cohort study and administered between 2009 and 2013. Alcohol intake in grams per day was calculated based on responses to specific questions regarding both frequency of alcohol intake (number of drinking days per week) and intake quantity (average number of alcoholic units per drinking day). These questions were split up for different alcoholic groups (beer, alcohol-free beer, red wine/rose, white wine, sherry, distilled wine, other alcoholic beverages). Individuals who reported consuming alcohol during the past month were considered drinkers. The Dutch dietary guidelines (2015) were used to estimate the average amount of alcohol per individual drink (varying from 0.10 g for a glass of alcohol-free beer to 10 g per glass of red wine or rosé) and the total amount (grams) of alcohol per day was subsequently calculated. Next, participants reporting alcohol use were stratified by sex and divided into four sex-specific quartiles based on the total amount of alcohol intake.

Assessment of possible confounding factors

All participants repeatedly completed questionnaires from baseline to 2018 that included questions about the presence of a broad range of disorders using the question: 'Could you indicate which of the following disorders you have or have had?' In addition, subjects were asked to report, using free text, any other disorders that they have or have had. Using this information, dichotomous variables were created for the occurrence of a broad range of diagnoses contemporaneous with the WHS dry eye questionnaire, see Vehof et al. [27]. Of these 119 disorders and traits, 99 were associated with WHS definition dry eye at $p < 0.20$ when corrected for age and sex only. These 99 disorders and traits were then tested for an association with grams per day of alcohol intake ($P < 0.20$) in a linear regression model, adjusted for age and sex. In that way, a total of 55 disorders and traits were associated with both WHS definition dry eye and alcohol use. These conditions were: contact lens use, eye surgery (any), laser refractive surgery, glaucoma/ocular hypertension, macular degeneration, Bell's palsy, heart valve disease, thrombosis, pulmonary embolism, myocardial infarction, heart failure, blood clot disorders, carotid stenosis, stroke, cardiac arrhythmia, hypertension (measured), hypertension (diagnosis), hypercholesterolemia, anemia, vitamin B12 deficiency, allergy (any), hay fever, eczema, psoriasis, asthma, chronic obstructive pulmonary disease (COPD), sarcoidosis, Sjogren's disease, rheumatoid arthritis, osteoarthritis, thyroid disease, diabetes mellitus, urine incontinence, kidney stones, renal failure, diverticulitis, gallstones, gastric reflux, irritable bowel syndrome (IBS), endometriosis, pelvic pain syndrome, fibromyalgia, whiplash, borderline personality disorder, panic disorder, burnout, chronic fatigue

syndrome, depression, Meniere's disease, epilepsy, spasticity, migraine, autism specter disorder, attention deficit hyperactivity disorder (ADHD), and addiction disorder.

Other variables also corrected for in this study were age, sex, BMI, smoking status (now, ever, never), income level (below 2000 euro per month, between 2000 and 3000 euro per month, above 3000 euro per month), and education level (low, middle, higher).

Statistics

Descriptive statistics were used to describe the characteristics of the study population. Logistic regression models were used to assess whether alcohol users were more likely to have symptomatic dry eye than non-users. Additionally, in alcohol users, the relationship between symptomatic dry eye (dependent variable) and the amount of alcohol intake (sex-specific quartiles and standard units (10 g/day), independent variable) was investigated. Results were corrected for (i) age and sex only, and (ii) age, sex, BMI, smoking status, education and income level, and 55 comorbidities associated with both WHS definition dry eye and alcohol use. Next, to test whether any risk of dry eye for alcohol consumers was significantly different in males versus females, we included the interaction terms [sex*alcohol intake(quartiles)] and [sex*alcohol use] in the multivariable model including all participants. In addition, similar analyses were performed in different age groups (20–39, 40–59, and 60+ years old), and the interaction terms [age*alcohol intake(quartiles)] and [age*alcohol use] were tested for significance to determine the role of age on the risk of symptomatic dry eye with alcohol use. As a sensitivity and secondary analysis, we investigated the more severe outcomes highly symptomatic dry eye (both dryness and irritation symptoms either "often" or "constantly"), a self-reported clinical diagnosis of dry eye (the third question of the WHS questionnaire), and the WHS definition of dry eye (either of the previous two outcomes positive). A P-value lower than 0.05 was regarded as statistically significant in all analyses.

Results

The characteristics of the study population are presented in Table 1. In total, 77,119 participants were included in this study, of which 59% were female, 98.4% of participants were of European ancestry. A total of 30.0% of participants were classified as having symptomatic dry eye; 1.9% had highly symptomatic dry eye, and 8.5% reported having a clinical diagnosis of dry eye, leading to 9.0% of participants fulfilling the WHS definition of dry eye. All dry eye outcomes were more prevalent in female participants; 35.3% of females and 22.2% of males had symptomatic dry eye. Alcohol use was less frequent in females than in males (72.3% vs. 89.7%).

Table 2 shows the association between the presence of alcohol use and several dry eye outcome variables after correction for age, sex, BMI, smoking status, relationship status, income, and education level, and 55 comorbidities associated with both alcohol use and WHS definition dry eye. Compared to non-users, alcohol users were more likely to have symptomatic dry eye (OR 1.078, 95% CI 1.033–1.124, P < 0.0001). This effect was driven by the effect in females (OR 1.095, 95% CI 1.045–1.148, P < 0.0001), while no effect was observed in males (OR 0.988, 95% CI 0.900–1.084, P = 0.79). This sex-specific effect of alcohol use on symptomatic dry eye was significant (interaction term [sex*-alcohol use], P = 0.02). Interestingly, highly symptomatic dry eye was not found to be significantly more prevalent in alcohol users than in non-users (OR 0.905, 95% CI 0.797–1.028, P = 0.13). Moreover, in males, there was a significantly decreased risk of highly symptomatic dry eye in alcohol users (OR 0.658, 95% CI 0.469–0.924, P = 0.02). In females, no significantly decreased risk was observed (OR 0.944, 95% CI 0.823–1.082, P = 0.41). For highly symptomatic dry eye there was a significant effect of sex on the effects of alcohol (interaction term [sex*alcohol use], P = 0.03). The sex-specific effect of alcohol on dry eye was also seen in the self-reported clinical diagnosis of dry eye (interaction term [sex*alcohol use], P = 0.02) and WHS definition of dry eye (interaction term [sex*alcohol use], P = 0.01). Both a clinical diagnosis and WHS definition of dry eye showed a non-significant increased risk with alcohol use in the combined population, driven by the effect in females, with a non-significant decreased risk in males.

Table 1
Characteristics of the study population.

	All (n = 77,145)	Males (n = 31,571)	Females (n = 45,574)
Age (yr), mean (sd)	50.6 (12.2)	51.3 (12.3)	50.0 (12.1)
Ethnicity – White, European, %	98.4%	98.6%	98.2%
Income			
- <2000 Euro per month	27.0%	21.3%	30.9%
- 2000–3000 Euro per month	29.9%	33.2%	27.6%
>3000 Euro per month	33.6%	38.2%	30.5%
-Not answered	9.5%	7.3%	11.0%
Smoking			
-Active	14.9%	16.3%	13.9%
-Ex	32.9%	35.5%	31.2%
-Never	52.2%	48.2%	54.9%
Dry Eye			
- Symptomatic dry eye, %	30.0%	22.2%	35.3%
- Highly symptomatic dry eye, %	1.9%	0.8%	2.6%
- Clinical diagnosis	8.4%	4.6%	11.1%
- WHS definition, %	9.0%	4.9%	11.8%
Alcohol Consumption			
- Current alcohol use, %	79.4%	89.7%	72.3%
- Alcohol intake (g/day), mean (sd)	6.7 (8.5)	9.8 (10.2)	4.6 (6.4)
Comorbidities			
- Presence of ≥1 comorbidity	90.8%	87.3%	93.2%
- Mean number of comorbidities	3.3	2.8	3.6

Table 3 shows the relationship between symptomatic dry eye and continuous alcohol intake, after correcting for all relevant comorbidities and excluding non-drinkers. Each standard unit (10 g of alcohol) increase of alcohol intake per day showed a protective effect on symptomatic dry eye in the overall population (OR 0.976, 95% CI 0.954–0.999, P = 0.04) and in males (OR 0.962, 95% CI 0.934–0.992, P = 0.01), but not in females (OR 0.986, 95% CI 0.950–1.023, P = 0.45). When the drinkers were divided into sex-specific quartiles of alcohol intake, increasing alcohol intake showed no clear effect in the combined population or in females. However, in males, decreased risk of symptomatic dry eye was found in the third (OR 0.919, 95% CI 0.846–0.999, P = 0.047), and fourth (OR 0.895, 95% CI 0.822–0.974, P = 0.01) quartiles of alcohol intake, compared to the lowest quartile. This sex-specific effect of increasing alcohol intake was significant (interaction term [sex*alcohol intake(quartiles)], P = 0.007).

Table 4 shows the association between alcohol use, alcohol intake in standard units, 10 g of alcohol, per day, and symptomatic dry eye, stratified by age groups (20–39 yrs, 40–59 yrs, and 60+ yrs), corrected for all included confounders. The effect of alcohol use on symptomatic dry eye was similar between age groups, with no significant effect of age in neither the combined population nor either sex separately (interaction term [age*alcohol use] in combined population, P = 0.11). However; in alcohol users, the interaction term [age*alcohol intake (quartiles)] was statistically significant in the combined population (P = 0.006) and in females (P = 0.012), indicating that increasing age has a protective effect on the relationship between alcohol intake and symptomatic dry eye.

Supplemental Tables 1–3 present the results of the analyses only corrected for age and sex, so not corrected for comorbidities and other demographic factors. Interestingly, before correction for comorbidities, alcohol use appeared protective against highly symptomatic dry eye (OR

Table 2
Relationship between the presence of alcohol use and different dry eye phenotypes, stratified by sex.

Definition dry eye	All (n = 77,145)			Males (n = 31,571)			Females (n = 45,574)			P-value interaction term [alcohol use[a] sex]
	Prevalence in drinkers (%)	OR (95% CI), corrected for all[a]	P-value	Prevalence in drinkers (%)	OR (95% CI), corrected for all[a]	P-value	Prevalence in drinkers (%)	OR (95% CI), corrected for all[a]	P-value	
Symptomatic dry eye	29.6	1.078 (1.033–1.124)	<0.0001	22.2	0.988 (0.900–1.084)	0.793	35.9	1.095 (1.045–1.148)	<0.0001	0.022
Highly symptomatic dry eye	1.7	0.905 (0.797–1.028)	0.126	0.8	0.658 (0.469–0.924)	0.016	2.5	0.944 (0.823–1.082)	0.405	0.033
Clinical diagnosis	8.1	1.008 (0.944–1.076)	0.811	4.5	0.870 (0.736–1.030)	0.107	11.1	1.026 (0.956–1.101)	0.483	0.017
WHS definition of dry eye	8.6	1.001 (0.940–1.067)	0.969	4.8	0.864 (0.734–1.017)	0.078	11.9	1.020 (0.952–1.092)	0.570	0.021

[a] Non-users are reference group. Corrected for age, sex, BMI, smoking status, income and education level, and 55 comorbidities associated with alcohol use and dry eye.

0.584, 95% CI 0.420–0.812, P = 0.001), a clinical diagnosis of dry eye (OR 0.804, 95% CI 0.684–0.944, P = 0.008), and WHS definition dry eye (OR 0.794, 95% CI 0.680–0.928, P = 0.004) in males, as well as highly symptomatic dry eye (OR 0.872, 95% CI 0.769–0.990, P = 0.035) in females (Supplemental Table 1). This effect was lost with correction for the relevant comorbidities in all but highly symptomatic dry eye in males, as alcohol intake was negatively associated with 39 of the comorbidities positively associated with WHS definition dry eye.

The ORs of having symptomatic dry eye, corrected for all possible confounding factors, with increasing alcohol intake in drinkers are presented in Fig. 1. It shows the risks of symptomatic dry eye of sex-specific alcohol intake quartiles in drinkers, with the lowest quartile as the reference group. As can be seen, the two highest quartiles of alcohol intake were significantly linked with decreased risk of symptomatic dry eye in males.

Discussion

This large population-based study found a highly significant association between alcohol use and symptomatic dry eye. This association was driven by females, whereas no increased risk was seen in males. The increased risk in females who consumed alcohol was also present after correction for demographic variables and systemic comorbidities. For all outcome measures of dry eye, there was a significant sex-specific effect of alcohol use, with female sex being associated with a higher risk of dry eye with alcohol use. In males, alcohol use was associated with decreased risk of highly symptomatic dry eye. Furthermore, increasing intake of alcohol in drinkers was tied to a small reduced risk of symptomatic dry eye in the combined populations, driven by a significant effect in males.

Only two interventional studies have assessed the short-term effects of orally administered alcohol on the ocular surface [14,28]. Both studies evaluated the intake of a relatively large quantity of alcohol (0.75 g/kg ethanol or 200 ml 25% vodka) at one time and evaluated the effects on symptoms and tear film parameters. Both studies followed the participants over 12 h, finding alcohol to increase tear film osmolarity, shorten tear film breakup-time (TBUT), and induce more ocular pain [14,28]. Interestingly, alcohol was detectable in the tear film 8 h after intake and found in the tear film at concentrations near half the participants' blood alcohol [14]. These studies highlight the effect of a single intake of alcohol on the ocular surface and may provide some clues to parts of the mechanisms behind the increased risk of dry eye with alcohol use observed in this study.

This epidemiological study is the first to assess the relationship between alcohol consumption and symptomatic dry eye, taking into account a large number of medical comorbidities, smoking status, and several demographic variables and stratifying by age and sex. Past epidemiological studies that investigated the link with alcohol have been hypothesis-free, general prevalence and risk factor studies, that included alcohol consumption as one of the many variables tested. A meta-analysis from 2016 summarizing eight general risk and prevalence studies found that intake of alcohol was borderline significantly associated with DED [13]. However, the study found no increased risk of dry eye in heavy drinkers compared to non-drinkers, which they partly attributed to alcoholic neuropathy in heavy drinkers. This was supported by the fact that alcohol use was only associated with dry eye as assessed by both clinical signs and symptoms, and not with dry eye defined by symptoms alone. However, none of the included articles focused specifically on the relationship between alcohol and dry eye. A register study using the National United States Veterans Affairs' database to assess the influence of psychiatric disorders on the risk of dry eye [15] accounted for nearly one-third of the weighted average in the meta-analysis [13]. This study on veterans only corrected for age and sex, but found that having a diagnosis of alcohol dependence was associated with an increased risk of dry eye [15].

Other epidemiological studies, beyond those included in the 2016 meta-analysis, have not found an association between alcohol use and dry eye. In one Chinese study, consumption of one or more alcoholic beverages per day was found not to be associated with dry eye [29]. However, only 549 of the 4141 subjects reported drinking any alcohol at all, limiting the study's power. Apart from a slit-lamp examination, no further description of how DED was assessed was mentioned in this paper. A Japanese population-based study in 2645 subjects (44.0% drinkers) by Uchino et al. examined general risk factors of dry eye, using the WHS definition [30]. They did not identify current use of alcohol as a risk factor in neither men nor women [30]. The Beaver Dam Offspring Study found no association between the previous year's reported alcohol consumption in grams per week and several self-reported variables of DED. Of the 3275 participants in that study, 2907 drank at least some alcohol the previous year [31]. In our current study of 77,119 participants, 61,412 of whom consumed alcohol in the last month, we found continuous alcohol intake to be associated with less symptomatic dry eye in male drinkers. Surprisingly, with each unit of alcohol (10 g) per day, the risk of dry eye fell by 4% in males, while no significant effect was seen in females.

The influence of sex on the association between alcohol use and all outcome measures of dry eye found in this study is particularly intriguing. Past studies have not investigated this relationship. Stratification by sex is crucial as alcohol has been found to have different physiological and pathological effects on males and females [18,19,32].

Table 3
Relationship between the amount of alcohol intake and symptomatic dry eye, in alcohol drinkers only.

Alcohol intake quartiles	All (n = 61,412)				Males (n = 28,361)				Females (n = 33,051)			
	Prevalence of symptomatic dry eye (%)	Mean alcohol intake (g/day)	OR (95% CI), corrected for all[a]	P-value	Prevalence of symptomatic dry eye (%)	Mean alcohol intake (g/day)	OR (95% CI), corrected for all[a]	P-value	Prevalence of symptomatic dry eye (%)	Mean alcohol intake (g/day)	OR (95% CI), corrected for all[a]	P-value
First quartile	29.9%	1.3	Ref	n/a	23.3	1.8	ref	n/a	35.4	0.9	ref	n/a
Second quartile	29.4%	4.1	0.987 (0.937–1.040)	0.62	22.1	5.7	0.934 (0.860–1.014)	0.11	35.8	2.7	1.024 (0.957–1.096)	0.49
Third quartile	29.9%	8.6	0.991 (0.941–1.044)	0.74	22.1	11.3	0.919 (0.846–0.999)	0.047	36.4	6.4	1.034 (0.966–1.106)	0.34
Fourth quartile	29.2%	19.9	0.974 (0.923–1.028)	0.34	21.2	24.7	0.895 (0.822–0.974)	0.010	36.0	15.7	1.016 (0.948–1.089)	0.65
Alcohol intake (10 g/day)	n/a		0.976 (0.954–0.999)	0.041	n/a		0.962 (0.934–0.992)	0.013	n/a		0.986 (0.950–1.023)	0.45

[a] Corrected for age, sex, BMI, smoking status, income and education level, and 55 comorbidities associated with alcohol use and dry eye.

In addition, the prevalence, clinical characteristics, pathophysiology, and treatment response of dry eye are all well-known to be substantially different in females and males [17,33]. The TFOS DEWS II Sex, Gender and Hormone Report stressed the importance of understanding these sex-related differences in dry eye for the development of new approaches to diagnosis, treatment, and prevention of disease [33].

There are several proposed mechanisms that could explain why females might be more prone to dry eye than males. Differences in sex hormones are the most widely accepted, with decreased androgens being particularly important, as they are believed to play a major role in maintaining healthy ocular surface and adnexa [33,34]. Studies have suggested that androgen deficiency can cause an auto-immune process leading to tear deficiency, corneal and conjunctival damage, lacrimal gland inflammation, and meibomian gland dysfunction [33]. This is supported by recent findings showing that the anti-androgen finasteride disrupts the ocular homeostasis and induces dry eye [35]. While estrogen is reported to stimulate immune responses, the effects of estrogen on the ocular surface in human and animal studies remain inconclusive [33].

Chronic alcohol use has been linked to various changes in sex hormone levels in women [36]. Alcohol consumption has been associated with higher plasma estrogen levels [18] and decreased progesterone [37], and an altered function of the hypothalamus and gonads, resulting in increased conversion of androgen to estrogen [38]. A prospective study measuring estradiol in the luteal phase in premenopausal women found levels of estradiol to be positively associated with both presence of alcohol consumption and increased alcohol intake [39]. Alcohol intake over one drink per day has also been linked to higher blood estradiol levels in postmenopausal women [40,41], and both moderate alcohol consumption and chronic alcoholism were associated with low testosterone and high estrogen levels in postmenopausal women [42]. This was thought to stem from an increased aromatization of testosterone to estrogens [42]. In a prospective cross-over study, 34 premenopausal women were randomly assigned to either consume 30 g of alcohol per day for three menstrual cycles and then abstain from alcohol entirely the following three cycles, or the other way round [43]. Urinary and plasma hormone measurements were collected at the end of each three-cycle period. The authors found total estrogen levels to increase with alcohol consumption [43]. This increase in estrogen and decrease in androgens may account for the sex and age-specific effects of alcohol observed in our current study. The TFOS DEWS II Sex, Gender and Hormone report noted that the sex-specific effects on dry eye appeared to diminish with age, likely due to falling androgens in both sexes [33]. This could explain the results observed in this study, where increasing age reduced alcohol intake's negative effect on symptomatic dry eye in females.

This study found alcohol use to be protective for highly symptomatic dry eye, especially in male participants. Furthermore, there was a mild protective effect of alcohol intake in all males and in females in the older age category. One possible mechanism for this finding might be that alcohol-induced peripheral neuropathy leads to a decreased corneal sensitivity and, thus, fewer symptoms [13,44]. This could particularly be present for older age groups where cumulative exposure to alcohol is higher. Of note, longer history of heavy drinking in men has been associated with worse Schirmer I, TBUT, and conjunctival impression cytology scores [45]. Dry eye symptoms were not investigated in the same study [45], but in the Beaver Dam-cohort, a past or current history of heavy drinking was not associated with dry eye symptoms after correcting for relevant comorbidities [46]. It is therefore possible that chronic alcohol consumption masks the symptoms of dry eye while still deteriorating the ocular surface and that the association is best uncovered by assessing objective dry eye parameters in addition to symptoms. Assessment of both signs and symptoms is important in all studies investigating dry eye; however, objective exposure and outcome measures appear to be particularly important in the setting of alcohol consumption and dry eye. Future studies assessing this link might also

Table 4
Relationship between the presence of alcohol consumption and symptomatic dry eye across age groups, stratified by sex.

	Prevalence of symptomatic dry eye (%)			Mean alcohol intake (g/day)			Alcohol use						Alcohol intake (10 g/day)[b]					
							All			Males			All			Males		
Age group	All	Males	Females	All	Males	Females	OR (95% CI), corrected for all[a]	P-value	OR (95% CI), corrected for all[a]	P-value	OR (95% CI), corrected for all[a]	P-value	OR (95% CI), corrected for all[a]	P-value	OR (95% CI), corrected for all[a]	P-value	OR (95% CI), corrected for all[a]	P-value
20–39 years old (n = 15,181)	30.9	24.9	34.7	6.2	10.0	3.8	1.086 (0.978–1.205)	0.12	0.936 (0.736–1.190)	0.59	1.114 (0.992–1.252)	0.07	0.962 (0.905–1.022)	0.21	0.923 (0.855–0.996)	0.038	1.046 (0.940–1.165)	0.41
40–59 years old (n = 46,960)	29.9	22.2	35.0	6.4	9.3	4.5	1.068 (1.013–1.126)	0.015	1.009 (0.894–1.138)	0.89	1.076 (1.014–1.141)	0.016	1.003 (0.974–1.034)	0.84	0.997 (0.958–1.037)	0.87	1.007 (0.960–1.056)	0.78
60 years and older (n = 17,877)	29.7	21.0	36.8	7.9	10.6	5.8	1.079 (0.982–1.186)	0.12	0.986 (0.816–1.193)	0.88	1.098 (0.985–1.225)	0.09	0.926 (0.883–0.971)	0.001	0.931 (0.874–0.991)	0.025	0.912 (0.847–0.981)	0.014

[a] Corrected for age, sex, BMI, smoking status, income and education level, and 55 comorbidities associated with alcohol use and dry eye.
[b] Non-users were excluded from this analysis. The analysis included 61,141 participants, n = 12,215, n = 35,521, and n = 13,675, in the respective age groups.

Fig. 1. Comparison of odds ratio (OR) for having symptomatic dry eye across quartiles of alcohol intake in drinkers, for both sexes: OR for *symptomatic dry eye* (either both dryness and irritation symptoms "sometimes" or either dryness or irritation at least "often") in each quartile of alcohol intake, in both males and females, corrected for BMI, smoking status, income and education level, and 55 comorbidities associated with alcohol intake and dry eye. The first quartile, the 25% of participants with the lowest intake of alcohol, serves as reference. Non-drinkers were excluded from the analysis. The error bars represent the 95% confidence intervals. The interaction term [sex*alcohol intake(quartiles)] was significant, P = 0.007, indicating a sex-specific response to increasing alcohol intake.

benefit from evaluating corneal nerve status using either Cochet-Bonnet esthesiometer, non-contact Belmonte esthesiometer, or *in-vivo* confocal microscopy [47,48].

Furthermore, in addition to affecting the peripheral nerves, alcohol also alters levels of, and responsiveness to, many neurotransmitters, including GABA [49], dopamine [50–52], serotonin [53], endorphins [54,55], and glutamate [56,57]. Neural processing of corneal pain is complex, involving both peripheral and central sites of processing and several of these neurotransmitters [58,59]. Although not much is known about how alcohol-induced changes in central nervous system (CNS) processing could affect pain arising from the ocular surface, several of these neurotransmitters have been tied to dry eye in the past. GABA has been shown to be important in modulating the corneal pain signals transmitted through the trigeminal nerve stemming from the cornea [60]. Acute intake of alcohol activates GABA receptors inhibiting excitatory signals [49], while the opposite is seen in chronic alcohol use [61]. Similarly, acute intake of alcohol increases dopamine levels [50,51], while chronic use decreases dopamine response [52]. Low dopamine levels decrease blink rates, leaving the ocular surface exposed for longer durations of time [62–64]. The intake of alcohol also delays the clearance of serotonin in the CNS [53]. Higher serotonin levels in the tear film have been correlated with more dry eye signs and symptoms [65], and the use of selective serotonin reuptake inhibitors (SSRI) was shown to aggravate dry eye in patients with depression [66]. Acute alcohol intake has been shown to increase beta-endorphin [54] and other endogenous opioid peptides [55], while chronic use of alcohol depresses the same systems [67]. Endorphins are important in all types of pain modulation, and injection of morphine in the basal ganglia was shown to reduce corneal pain stimulus in rats [68]. The inverse is seen in glutamate signaling, where acute intake of alcohol reduces glutamate signaling, and chronic use increases the number and activity of the glutamate receptors and enhances signaling in withdrawal [56]. Disturbances in glutamate signaling in the dorsal spinal cord have also been implicated in sensitization of corneal pain signaling and altered pain perception of peripheral input, such as hyperalgesia and allodynia [47].

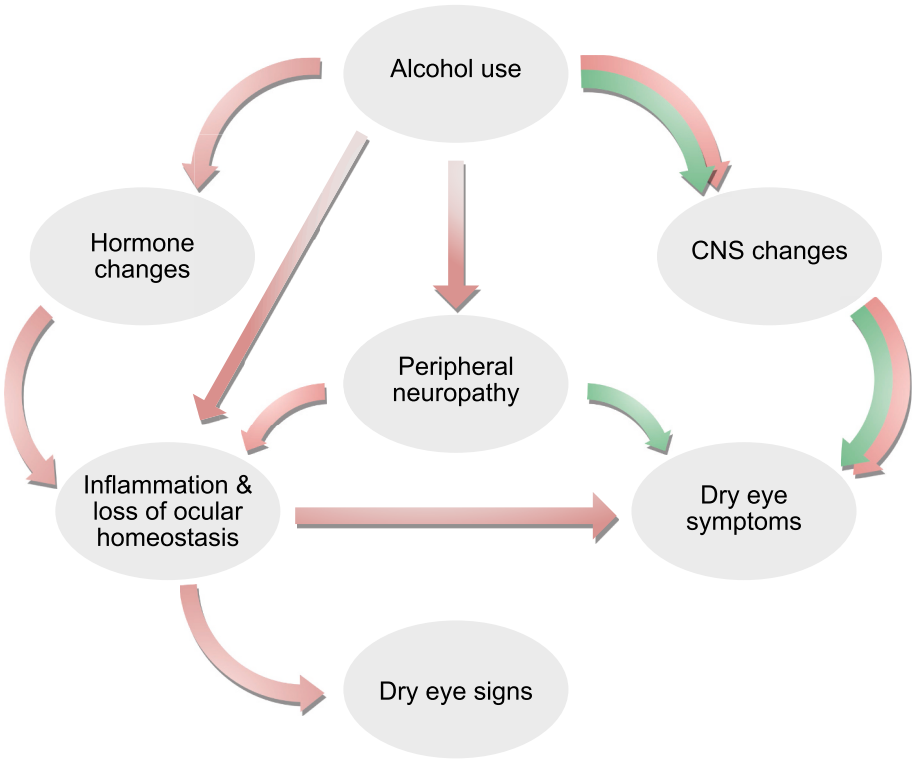

Fig. 2. Proposed model of action for alcohol's impact on dry eye. The red arrows indicate changes that negatively influence dry eye signs and symptoms. The green arrows show the potentially beneficial effects of alcohol use on dry eye. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Overall, it is thus plausible that acute and chronic intake of alcohol induces different CNS changes that could affect dry eye symptoms and ocular pain stimuli differently. However, the chemical effects of alcohol on the tear film and ocular surface might be more pronounced than CNS changes with the acute intake of alcohol [14,28].

Fig. 2 illustrates a proposed model for how alcohol use could lead to changes in both signs and symptoms of dry eye. Alcohol is likely to contribute both directly and indirectly to the loss of ocular homeostasis through chemical properties and hormonal changes. It also highlights the possible neurological effects of alcohol use on signs and symptoms through both peripheral neuropathy and CNS changes.

Non-drinkers were used as the reference group in several of the analyses performed; however, it should be noted that non-drinkers represent a highly heterogeneous group [69]. Non-drinkers abstain from drinking alcohol for many different reasons, including health issues, past problems with control of intake, and cultural, social, and familial reasons [69]. When assessing the effect of confounders in the present study, we found continuous alcohol intake to be protective against a majority of the comorbidities associated with more WHS definition dry eye, including Sjogren's disease, rheumatoid arthritis, and Bell's palsy. This could indicate that non-drinkers more frequently have chronic conditions than drinkers, that could confound the relationship. This might be due to a survivor bias, where people with chronic diseases stop drinking due to their underlaying condition. It is thus important to take this into account and correct for all relevant comorbidities. Similarly, it is possible that some with severe dry eye might abstain from drinking alcohol, possibly explaining part of the protective effect of alcohol use on highly symptomatic dry eye in males. Furthermore, this study used the intake of alcohol in the last month to distinguish drinkers and non-drinkers. Past results have found that a 12-month timeframe for alcohol assessment may provide a more complete image of true intake than 30-day measurements [70].

This study has several strengths. First, the large sample size allowed for stratification for both sex and age groups, which is essential when assessing risk factors of dry eye. Second, due to information on a large number of medical comorbidities, we were able to correct for the 55 comorbidities associated with both WHS definition dry eye and alcohol intake. Third, both alcohol consumption and dry eye were assessed using validated questionnaires in a large sample representative for its geographical coverage [71].

This study also has some limitations. First, alcohol consumption and dry eye were not assessed simultaneously in all participants. In around one-third of participants, only past data on alcohol intake was available, obtained on average three years before dry eye assessment. Changes during this period could have led to a decreased power to detect the true association. However, studies have shown that alcohol consumption is quite stable over time in adults, so we do not expect a major bias from this time lag [72–74]. Second, due to the cross-sectional nature of this study, we cannot conclusively determine a causative effect of alcohol consumption on dry eye. Finally, the presence of a clinical diagnosis of dry eye, comorbid conditions, and alcohol consumption were retrospectively self-reported and recall bias is possible. Future longitudinal studies on the use of alcohol and dry eye should, if possible, include objective and subjective measures of both alcohol consumption and dry eye. For alcohol intake, this could be the addition of phosphatidyl ethanol or carbohydrate-deficient transferrin measurements [75]. Dry eye disease should ideally be diagnosed in accordance with the TFOS DEWS II guidelines [76]. The diagnosis is based on both symptomatology, assessed by either the Ocular Surface Disease Index (OSDI) or the Dry Eye Questionnaire-5 (DEQ-5), and markers of loss of homeostasis of the tear film, such as break-up time, tear film osmolarity, or ocular surface staining. Furthermore, studies investigating symptoms and signs of dry eye after stopping alcohol consumption or overcoming alcohol addiction are warranted.

In conclusion, alcohol use appears to be a mild risk factor for symptomatic dry eye in females, but not in males. The effects of alcohol on dry eye are highly dependent on sex, with females being significantly more at risk than males. In male drinkers, increased alcohol intake was

even found protective for symptomatic dry eye. These findings highlight the importance of stratification by sex in studies on dry eye disease. Our results also indicate that future studies should aim to include both objective and subjective assessment of both dry eye disease and alcohol use to uncover its complex relationship including the role of any possible neuropathic mechanisms masking dry eye symptoms.

Declaration of competing interest

The authors have no conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jtos.2021.05.005.

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