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Prevalence and risk factors of dry eye in 79,866 participants of the population-based Lifelines cohort study in the Netherlands

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ABSTRACT

Purpose: To investigate the prevalence of dry eye among all adult age categories and to discover independent risk factors by investigating a wide range of etiological categories.
Methods: A cross-sectional association study including 79,866 voluntary participants aged 20–94 years of the population-based Lifelines Cohort Study in the Netherlands.
Results: Overall, 9.1% of participants had dry eye disease as measured by the Women's Health Study dry eye questionnaire. Prevalence of dry eye symptoms were particularly prevalent in 20–30 years olds. Dry eye was associated with comorbidities in almost all body systems, including musculoskeletal, gastro-intestinal, ophthalmic, autoimmune, psychiatric, pain, functional, dermatological and atopic disorders. Numerous independent risk factors were discovered or confirmed, with strong associations for female sex, contact lens use, irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, eye surgery including cataract and laser refractive surgery, keratoconus, osteoarthritis, connective tissue diseases, atherosclerosis, Graves' disease, autistic disorder, depression, 'burnout', Crohn's disease, sarcoid, lichen planus, rosacea, liver cirrhosis, sleep apnea, sinusitis, thyroid function, and air pollution (NO_2). High blood pressure and high BMI were strongly associated with less dry eye, as was current smoking, while ex-smokers had more dry eye. No clear link between dry eye and lipid or blood glucose levels was found.
Conclusions: This study on dry eye confirmed but also refuted many risk factors from smaller epidemiological studies, and discovered numerous new risk factors in multiple etiological categories. The finding that dry eye symptoms are particularly common in young adults is concerning, and warrants further study.

1. Introduction

The recognition of dry eye as a global health problem, and consequent research studies, has greatly increased over the last decade, but its multi-factorial etiology and pathophysiology are still poorly understood [1]. Epidemiological studies that identify risk factors of disease are important, especially in complex diseases such as dry eye. They not only provide clues about underlying pathophysiological mechanisms, but also provide possible new treatment and prevention strategies if risk factors can be identified and modified. There have been several population-based studies investigating prevalence and risk factors of dry eye around the world [2]. However, these have mostly focused on older people, and are limited by small sample sizes and a limited set of risk factors, limiting the understanding of relative contributions of risk factors at a population level. Indeed, the TFOS DEWS II Epidemiology Report concludes that appropriately powered studies are highly needed to address major and important risk factors and that there remains a particular need for studies in populations below 40 years of age [2]. The aims of this large study were to ascertain the prevalence of dry eye disease in men and women across the whole adult age spectrum, and to identify new and confirm or refute previously reported associations by investigating a broad range of risk factors. For this purpose, we set up a

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cross-sectional association study and used data of almost 80,000 participants from the population-based Lifelines cohort study.

2. Methods

2.1. 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 [3]. 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 [4]. The study was carried out in accordance to the Declaration of Helsinki, institutional review board (IRB) approval was obtained, and all participants provided written informed consent. For the purpose of this study we assessed dry eye using a questionnaire during their first follow-up visit between 2014 and 2017. We aimed to include at least 70,900 participants to be able to detect an odds ratio of 1.33 for risk factors with a prevalence as low as 1%, with a power of 80%, an alpha of 0.05, and an estimated prevalence of dry eye of 10%.

2.2. Assessment of dry eye disease

In this study cases of dry eye were assigned via the Women's Health Study dry eye questionnaire [5]. This short questionnaire with 3 questions has been validated against a standardized clinical exam [6] and showed similar sensitivity and specificity as a 16 item instrument [5]. It is the most widely used dry eye questionnaire in population-based studies [2]. The questionnaire includes two symptom questions: (1) "How often do your eyes feel dry (not wet enough)?" and (2) "How often do your eyes feel irritated?" (both with possible answers: 0 never, 1 sometimes, 2 often, or 3 constantly), and a third question about a previous clinical diagnosis of dry eye: (3) "Have you ever been diagnosed (by a clinician) as having dry eye syndrome?" (with possible answers: yes or no). A subject is considered as having dry eye if there is the presence of both dryness and irritation either 'constantly' or 'often', and/or a report of a previous diagnosis of dry eye [5]. This definition was used as the primary outcome variable of our analysis and is further regarded as a 'case of dry eye'. As a secondary outcome variable, we assessed the presence of dryness symptoms either 'constantly' or 'often' (using question 1 of the questionnaire only). This outcome variable is a measure of *current* 'symptomatic dry eye', and is not affected by a potential cumulative effect of age on the diagnosis of dry eye (e.g. the older you are the higher the likelihood you will have been diagnosed). In addition to questions above, subjects were asked about current use of ocular lubricants for dry eye disease, the mainstay of therapy for dry eye [7]. Participants that did not complete one or more questions of the dry eye questionnaire which made classification of any of the two outcome variables impossible, were not included in this study (this was the case for only 0.26% of participants).

2.3. Assessment of risk factors

All participants were asked to complete a self-administered questionnaire, with information about medical history and current diseases, at both baseline (2006–2013) and follow-up visit (2014–2017). They were asked about 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 dry eye questions. In addition to the self-reported diagnoses, a brief standardized diagnostic interview (Mini International Neuropsychiatric Interview (MINI)) was performed to assess a range of current psychiatric disorders (depressive disorder, dysthymia, and anxiety disorders) [8], and a questionnaire using the ROME III criteria assessed diagnosis of concurrent irritable bowel syndrome (IBS) [9]. Participants also answered if they used any prescription medication at the time of dry eye assessment. However, no information on type of medication was available.

Demographic variables included in this study were age, sex, relationship status (partnered or not), and completion of higher education (higher vocational or university education diploma). Smoking behavior was categorized from multiple questions into current smoker, ex-smoker (having smoked at least a full year) or never smoked. Total physical activity score was calculated by multiplying the amount of minutes of physical activity per week (e.g., walking, household activities, sports, and gardening) with a factor for intensity, using the SQUASH questionnaire [10]. Environmental variables that were investigated were the presence of cats and dogs as pets, and residential air pollution, by using annual average concentrations of nitrogen dioxide (NO_2), and particulate matter with aerodynamic diameter <10 μM (PM10), and fine particles with diameter <2.5 μM (PM2.5) for the period 2009–2010 [11]. These estimates were generated using a standardized land-use regression modeling approach which was developed in the context of the European Study of Cohorts for Air Pollution Effects (ESCAPE) [12].

Body weight and height with participants wearing light clothing and without shoes were used to calculate body mass index (BMI). Blood pressure and heart rate were measured every minute over a period of 10 min with an automated DINAMAP Monitor (GE Healthcare), and the average of the final three readings was recorded. Hypertension was defined as a systolic blood pressure of 140 mmHg or higher and/or a diastolic blood pressure of 90 mmHg or higher. Low blood pressure was defined as a systolic blood pressure of 90 mmHg or lower and/or a diastolic blood pressure of 60 mmHg or lower. Venous blood samples were collected between 8 and 10am after an overnight fast. Total cholesterol (TC) and high-density lipoprotein-cholesterol (HDL-C) were measured with an enzymatic colorimetric method, and triglycerides (TG) with ultraviolet colorometry, and low-density lipoprotein-cholesterol (LDL-C) using an enzymatic method (Roche Modular P chemistry analyser, Roche, Basel, Switzerland). HbA1c was measured with a turbidimetric inhibition immunoassay (Cobas Integra 800 CTS analyser, Roche Diagnostics Nederland BV, Almere, the Netherlands). Fasting blood glucose was measured using a hexokinase method. Levels of thyroid stimulating hormone (TSH), as well as free thyroxine (FT4) and free triiodothyronine (FT3) were assayed by electrochemiluminescent immunoassay (Roche Modular E170, Roche, Switzerland).

2.4. Statistics

Descriptive statistics were used to describe the characteristics of the study population. Prevalence rates including 95% confidence intervals were calculated for the dry eye definitions, stratified by age decade and sex. Logistic regression was used to calculate odds ratios (OR) of risk factors for dry eye, corrected for age and sex. Unless the determinant was previously known or suspected to have a highly increased risk of dry eye (e.g., connective tissue diseases), only risk factors with a prevalence of $n = 62$ or more were included, to ensure a power of 80% to detect an OR of 2.5 with an alpha of 0.05. Next, a backward stepwise multivariable logistic regression model was used to identify independent risk factors for dry eye, starting with all risk factors that were previously associated with a P-value lower than 0.10. For this multivariable analysis, only dichotomous variables available in the total sample were included (self-reported comorbidities, and hypertension and hypotension), in addition to age, sex and BMI. Subsequently, the independently associated risk factors from this multivariable model were used as covariates in regression models of risk factors that were only available in

a subsample (blood tests, environmental factors). Of the final set of comorbidities that turned out to be independent risk factors, odds ratios were calculated stratified by age group (20–40, 40–60, 60+ yrs) and by sex. All analyses were performed with IBM SPSS Statistics 22.

3. Results

3.1. Population characteristics and prevalence of dry eye

A total of 79,866 participants were included in this study (mean age of 50.4 years (range 20–94); 59.2% women). Table 1 presents the characteristics of the study population. Overall, 9.1% (n = 7230) of participants were designated as a case of dry eye (primary outcome variable). Participants with dry eye were more likely to be female, older, not in a relationship and non-smoker. A total of 3.7% of participants had symptoms of dryness of the eyes 'often' or 'constantly' (secondary outcome variable), 8.5% had a previous clinical diagnosis of dry eye and 3.2% used ocular lubricants for dry eye disease. Prevalence of these dry eye outcomes, stratified by age decade and sex, is depicted in Fig. 1a–d. These figures show that while a clinical diagnosis of dry eye (Fig. 1b) and particularly the use of ocular lubricants (Fig. 1d) become more common with increasing age, symptomatic dry eye appears particularly prevalent in younger age categories (Fig. 1c). Indeed, for men symptoms were more common in 20–30 years olds than any other age decade.

3.2. Risk factors of dry eye

Table 2 shows the association between dry eye and comorbidities, corrected for age and sex only. All comorbidities that were independently associated with dry eye after a stepwise multivariable regression analysis are graphically depicted in Fig. 2. Appendices Table A and B show the association results of these comorbidities stratified by age group and sex, respectively.

Table 3 shows the associations with demographic, environmental, and other systemic risk factors investigated, corrected for age and sex only and corrected for age, sex, BMI and comorbidities as well.

Similarly, the results for current *symptomatic* dry eye (secondary outcome) are shown in appendix Table C (the association with self-reported comorbidities), D (the association with demographic, environmental and other systemic risk factors) and appendix Fig. A (independently associated comorbidities). In the text below we focus on odds ratios (95% CI) of the associations found for dry eye (primary outcome variable, i.e. Tables 2 and 3) corrected for age and sex only, unless specified otherwise.

Women had a much higher risk of dry eye compared to men (OR 2.68 (95% confidence interval 2.53 to 2.84)) and this sex difference was present across all age groups, but more pronounced after the age of 40 years (Fig. 1 and Table A). Participants with a partner were less likely to have dry eye compared to those without a partner (OR 0.84 (0.79–0.91)), but after correction for comorbidities this association was only borderline significant (OR 0.93 (0.86–0.999)). Participants with a higher education diploma showed an increased risk of dry eye, independent of comorbidities. Interestingly, current smoking was associated with lower rates of dry eye compared to never smokers (OR 0.89 (0.82–0.96)), and this relationship was even stronger after correction for other associated comorbidities (OR 0.87 (0.80–0.94)). On the other hand, ex-smokers showed higher rates of dry eye compared to never smokers (OR 1.11 (1.06–1.18)). Greater physical activity was associated with fewer dry eye, but this association was no longer significant when corrected for comorbidities. The presence of pets was not associated with increased dry eye, and even showed a mildly protective effect. Air pollution, as reflected by NO_2 and PM_{10}, was associated with more dry eye; only NO_2 remained significant after correction for comorbidities.

Many systemic disorders showed strong associations with dry eye. High odds ratios were found for autoimmune disorders, such as Sjögren's syndrome (OR 60.3 (27.0–134.5)), rheumatoid arthritis (OR 1.9 (1.8–2.2)), systemic lupus erythematosus (SLE) (OR 4.2 (2.1–8.5)), systemic sclerosis (OR 3.0 (1.4–6.5)), sarcoid (OR 1.9 (1.4–2.7)), and Graves' disease (OR 4.6 (3.2–6.5)). Similarly, pain disorders and musculoskeletal disorders showed a higher risk of dry eye, including osteoporosis (OR 1.8 (1.6–2.0)), osteoarthritis (OR 1.6 (1.5–1.7)), carpal tunnel syndrome (OR 1.7 (1.2–2.2)) and fibromyalgia (OR 2.2 (2.0–2.4)). IBS was associated with dry eye, either with a self-reported diagnosis (OR of 1.9 (1.7–2.0)), or a current clinical diagnosis of IBS based on the Rome-III criteria questionnaire (OR 2.2 (1.9–2.6), see appendix Table E.

All ophthalmic disorders and types of ophthalmic surgery investigated in this study were highly associated with dry eye, with high ORs for disorders keratoconus (OR 10.8 (5.1–22.8)), allergic conjunctivitis (OR 3.8 (3.3–4.5)), Bell's palsy (OR 2.9 (1.8–4.6)), and glaucoma (OR 2.8 (2.5–3.1)). The strong association found in keratoconus patients was still present after correction for other traits, such as allergic conjunctivitis and contact lens use that often coexist in these patients. Glaucoma surgery (OR 4.2 (2.8–6.4)) and surgery for diabetic retinopathy (OR 4.2 (1.5–11.5)) had the highest point estimates of odds ratios for dry eye among ophthalmic surgeries, but more common procedures such as cataract surgery (OR 2.2 (2.0–2.5)) and laser refractive surgery (OR 3.5 (3.0–4.1)) were also highly associated with dry eye. This increased risk was even more pronounced for symptomatic dry eye (see appendix Table C), indicating an effect not purely driven by a bias of increased likelihood of diagnosis of dry eye because these participants were under ophthalmological care. The use of contact lenses was also found to be an important risk factor (OR 1.9 (1.8–2.1)), especially because their use was highly prevalent (12.9%). Contact lens use was most prevalent in participants under 40 years of age (19.3%), and it was this age group that showed the strongest association between contact lens use and dry eye (OR 4.0 (3.5–4.5)) (see appendix Table A).

Disorders related to atopy or allergy were also associated with increased risk of dry eye. The presence of allergy, hay fever, eczema, and asthma showed ORs between 1.3 and 1.6. Looking at the specific allergies, there were no great differences in type of allergy and risk of dry eye: medication allergy (OR 1.5 (1.4–1.7)) showed the highest risk and animal allergy the lowest risk (OR 1.2 (1.1–1.3)), and an allergy for dust, pollen, food, insects, and contact allergy were in between these risks.

Of the self-reported psychiatric disorders, the majority was associated with increased risk of dry eye. Highest odds ratios were found for autistic disorders (OR 2.8 (1.8–4.3)), chronic fatigue syndrome (OR 2.3 (2.0–2.6)), ADHD (OR 1.9 (1.5–2.5)), agoraphobia (OR 1.9 (1.5–2.4)), and manic depressive disorder (OR 1.7 (1.2–2.5)). The current presence of a major depressive disorder (OR 1.7 (1.5–2.0)) or a generalized anxiety disorder (OR 1.6 (1.4–1.8)), as assessed by the MINI-interview (see appendix Table E), showed ORs approximately similar to self-reported diagnoses (i.e. OR 1.5 (1.4–1.6) for depression, and OR 1.3 (1.1–1.4) for anxiety disorder). Interestingly, in participants who did not take any prescription medication at the time of dry eye assessment, point estimates of odds ratios between dry eye and depression (OR 1.6 (1.4–1.8) and anxiety disorder (OR 1.4 (1.1–1.7) were also similar to in the total group, indicating that the disorders itself increase the odds of dry eye, and that the association is not highly mediated by use of

Table 1
Characteristics of the study population (n = 79,866).

	No dry eye	Dry eye	P value
No. of participants (%)	72,636 (90.9%)	7230 (9.1%)	–
Age (years) (mean (SD))	50.1 (12.4)	53.3 (13.0)	<0.001
Women (%)	57.4%	77.6%	<0.001
BMI (kg/m^2) (mean (SD))	26.3 (4.2)	26.1 (4.8)	0.22
Higher education diploma (%) (n = 78,673)	29.6%	29.9%	0.68
Partnered (yes) (%) (n = 75,000)	85.8%	83.9%	<0.001
Current smoker (%) (n = 79,481)	16.1%	12.6%	<0.001

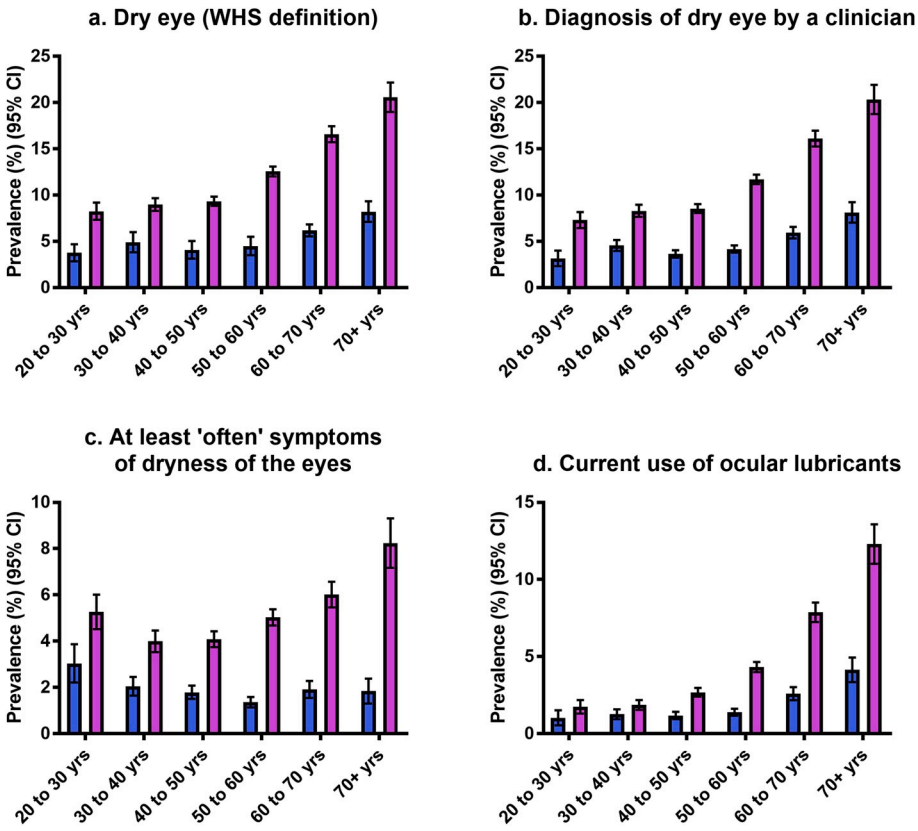

Fig. 1. Prevalence of dry eye stratified by age and sex (women pink, men blue).
(a) dry eye as defined by the Women's Health Study (WHS) questionnaire (either a clinical diagnosis of dry eye and/or symptoms of both dryness and irritation of the eyes 'often' or 'constantly'; primary outcome); (b) diagnosis of dry eye by a clinician; (c) symptomatic dry eye (defined as 'often' or 'constantly' symptoms of dryness of the eyes; secondary outcome); (d) current use of ocular lubricants for dry eye. Error bars indicate 95% confidence interval.

antidepressants or anxiolytics that can have anticholinergic side-effects.

Participants with diabetes mellitus (DM) had a moderate but significantly increased risk of dry eye (OR 1.3 (1.1–1.5)). There was no great difference in risks between DM1 and DM2 patients. We found no clear association between glucose or HbA1C levels and dry eye in both DM and non DM patients (Table 3). Thyroid function tests were only available in a smaller subsample of participants (n = 25,543), and higher levels of FT4 were significantly associated with increased risk of dry eye. The opposite was found for FT3 levels. There was no clear association between cholesterol levels and dry eye. Interestingly, the presence of hypertension (OR 0.85 (0.80–0.90)) was clearly associated with less dry eye, as were higher systolic and diastolic blood pressure.

4. Discussion

This study found that dry eye is highly prevalent in the adult population, in both young and old age groups, and is associated with comorbidities in all organ systems, underlining its highly multifactorial etiology. In addition to auto-immune disorders and diseases that directly affect the ocular surface, this study has shown that numerous functional and psychiatric disorders are also highly associated with dry eye, independent of medication use, and that virtually every type of eye surgery increases the risk of dry eye dramatically. Based on these results we might rephrase the old aphorism 'a sick eye in a sick body', originally made in relation to systemic associations with glaucoma [13], to 'a dry eye in a sick body'. The multifactorial risks of dry eye found in this study emphasize the importance of taking a holistic view when health care physicians assess dry eye patients.

Studies on the prevalence of dry eye have largely focused on older age groups and there has been a need for studies in populations below 40 years of age [2]. Strikingly, this study showed a relatively high prevalence of symptomatic dry eye in adults aged 20–30 years. This age group had the highest prevalence among men of all age groups and among women under 60 years of age; as many as 5% of women and 3% of men aged 20–30 years had either 'often' or 'constant' symptoms of dry eye. This remarkable peak was associated with contact lens use, which appeared to be a strong risk factor in the younger age categories in particular (see Appendix Table A). The high prevalence of symptomatic dry eye could possibly also be associated with the increased use of handheld devices such as smartphones or tablet use in this age group, which has been shown to be associated with signs and symptoms of dry eye in children and adults [14,15]. The use of visual displays can lead to diminished blink frequency and incomplete blinks causing accelerated tear evaporation and tear film instability [16] and prevalence of dry eye symptoms has been shown to be high among visual display users [2]. Unfortunately, no data on screen use was available in our cohort, but in a previous study in this cohort we did find a relation between dry eye and occupations with high screen use, such as clerical support workers and business and administration professionals [17].

This study also showed a step change in dry eye prevalence for women over 50 years of age, and continuing beyond. This age effect is well-known [2,18,19] and thought to be caused by hormonal changes after the menopause, such as androgen deficiency [20,21]. Other causes for the higher prevalence of dry eye in women compared to men are the increased prevalence of risk factors for dry eye in women, such as autoimmune disorders, functional disorders, atopic diseases and allergy, and most psychiatric disorders, which was also evident in our study population (see appendix Table B) [2,20]. Medications have been related to dry eye and their increasing use may be another factor explaining the increase of dry eye with age [22]. Interestingly, the use of ocular lubricants for dry eye disease showed a sharp increase with age, especially after age 50, much steeper than the increase in rate of diagnosis of dry eye disease. The use of these lubricants does not follow the trend of symptomatic dry eye at all, with only less than 2% of 20–40 years olds using eyedrops. Future studies should investigate whether dry eye in the young adults, including its possible under-treatment, might lead to increased problems at later age. Studies have shown that chronic ocular surface damage can lead to self-perpetuating dry eye disease,

Table 2
Associations between dry eye and comorbidities/traits, corrected for age and sex.

Risk factor (total n = 79,866)	Prevalence of risk factor n(%)	Prevalence of dry eye (overall 9.1%)	Odds Ratio (95% CI)	P value
Age (years)	–	–	1.023 (1.021–1.025)	<0.001
Female sex	47294 (59.2%)	11.9%	2.68 (2.53–2.84)	<0.001
Ophthalmic disorders and traits				
Contact lens use	10310 (12.9%)	14.1%	1.94 (1.82–2.07)	<0.001
Macular degeneration	1038 (1.4%)	22.4%	2.54 (2.17–2.96)	<0.001
Glaucoma/ocular hypertension	2116 (2.9%)	22.1%	2.79 (2.50–3.11)	<0.001
including IOP lowering drops	635 (0.8%)	23.9%	2.70 (2.23–3.26)	<0.001
including laser	223 (0.3%)	27.8%	3.11 (2.30–4.21)	<0.001
Allergic conjunctivitis using drops	778 (1.0%)	28.4%	3.82 (3.25–4.50)	<0.001
Keratoconus	30 (<0.1%)	40.0%	10.8 (5.10–22.8)	<0.001
Bell's palsy	114 (0.1%)	21.9%	2.90 (1.84–4.57)	<0.001
Ophthalmic surgery				
Any eye surgery	5332 (6.7%)	17.9%	2.03 (1.88–2.20)	<0.001
Cataract surgery	2499 (3.1%)	22.3%	2.22 (1.99–2.47)	<0.001
Retinal detachment surgery	406 (0.5%)	18.4%	2.04 (1.57–2.64)	<0.001
Glaucoma surgery	113 (0.1%)	32.1%	4.23 (2.80–6.37)	<0.001
Diabetic retinopathy surgery	18 (<0.1%)	33.3%	4.18 (1.52–11.5)	0.006
Refractive surgery - non-laser	301 (0.4%)	22.6%	2.98 (2.26–3.93)	<0.001
Refractive surgery - laser	900 (1.1%)	23.8%	3.51 (2.99–4.11)	<0.001
Pain disorders				
Irritable bowel syndrome	9042 (11.3%)	16.1%	1.85 (1.74–1.98)	<0.001
Fibromyalgia	3402 (4.3%)	21.6%	2.21 (2.03–2.41)	<0.001
Osteoarthritis	12744 (16.0%)	15.2%	1.60 (1.50–1.70)	<0.001
Intervertebral disc herniation	5645 (7.1%)	11.4%	1.28 (1.17–1.40)	<0.001
RSI	2738 (3.4%)	13.8%	1.61 (1.43–1.80)	<0.001
Back pain	1650 (2.1%)	11.9%	1.42 (1.22–1.65)	<0.001
Carpal tunnel syndrome	311 (0.4%)	16.1%	1.65 (1.21–2.24)	0.001
Whiplash	400 (0.5%)	13.0%	1.34 (1.00–1.80)	0.05
Tietze syndrome	155 (0.2%)	14.2%	1.50 (0.95–2.36)	0.08
Musculoskeletal disorders				
Rheumatoid arthritis	2822 (3.5%)	18.8%	1.94 (1.76–2.15)	<0.001
Systemic sclerosis	31 (<0.1%)	30.0%	2.96 (1.35–6.50)	0.007
SLE	35 (0.1%)	34.3%	4.21 (2.09–8.51)	<0.001
Sjögren's syndrome	59 (0.1%)	88.1%	60.3 (27.0–135)	<0.001
Polymyalgia rheumatica	109 (0.1%)	17.6%	1.44 (0.87–2.39)	0.15
Ankylosing spondylitis	157 (0.2%)	13.4%	1.74 (1.09–2.78)	0.02
Sarcoid	311 (0.4%)	16.1%	1.94 (1.43–2.65)	<0.001
Gout	326 (0.4%)	7.4%	1.15 (0.76–1.74)	0.51
Cardiovascular disorders				
Heart valve disease	930 (1.2%)	11.7%	1.20 (0.98–1.47)	0.08
Atherosclerosis	411 (0.5%)	16.2%	1.79 (1.37–2.35)	<0.001
Pulmonary embolism	672 (0.8%)	11.8%	1.17 (0.92–1.48)	0.21
Myocardial infarction	612 (0.8%)	11.2%	1.29 (0.99–1.67)	0.06
Stroke	442 (0.5%)	12.4%	1.20 (0.90–1.61)	0.22
Heart failure/ muscle disease	1229 (1.5%)	11.4%	1.14 (0.95–1.37)	0.16
Thrombosis	835 (1.0%)	14.0%	1.37 (1.12–1.68)	0.002
Blood clotting disorder	494 (0.6%)	11.6%	1.20 (0.91–1.59)	0.2
Arrhythmia heart	6462 (8.1%)	14.3%	1.53 (1.42–1.65)	<0.001
Aorta aneurysm	233 (0.3%)	14.3%	1.71 (1.17–2.49)	0.005
Carotid stenosis	216 (0.3%)	12.2%	1.25 (0.83–1.90)	0.29
Varicose veins	906 (1.1%)	9.7%	0.95 (0.76–1.19)	0.66
Hepatic disorders				
Any hepatitis	983 (1.2%)	11.5%	1.05 (0.86–1.28)	0.64
Hepatitis B	66 (0.1%)	9.2%	0.96 (0.41–2.25)	0.92
Liver cirrhosis	74 (0.1%)	27.0%	3.38 (1.99–5.72)	<0.001
Gall stones	3724 (4.7%)	13.4%	1.22 (1.10–1.34)	<0.001
Renal/urinary tract disorders				
Kidney stones	3019 (3.8%)	10.8%	1.23 (1.09–1.38)	0.001
Renal failure	134 (0.2%)	14.7%	1.49 (0.91–2.44)	0.12
Chronic cystitis	1367 (1.7%)	18.6%	1.72 (1.49–1.98)	<0.001
Urine incontinence	1828 (2.3%)	17.4%	1.52 (1.34–1.72)	<0.001
Neurological disorders				
Parkinson	116 (0.1%)	13.3%	1.28 (0.73–2.22)	0.39
Epilepsy	1042 (1.3%)	10.4%	1.17 (0.95–1.43)	0.14
Multiple sclerosis	214 (0.2%)	11.7%	1.16 (0.76–1.77)	0.49
Spasticity	99 (0.1%)	16.2%	2.22 (1.29–3.83)	0.004
Cluster headache	75 (0.1%)	14.7%	2.12 (1.10–4.06)	0.02
Migraine	15865 (19.9%)	11.9%	1.27 (1.20–1.34)	<0.001
Psychiatric disorders				
Social phobia	686 (0.9%)	13.3%	1.61 (1.29–2.02)	<0.001
Anxiety disorder	2309 (2.9%)	11.5%	1.26 (1.10–1.43)	0.001
Manic depression	239 (0.3%)	15.1%	1.71 (1.19–2.45)	0.003

(*continued on next page*)

Table 2 (*continued*)

Risk factor (total n = 79,866)	Prevalence of risk factor n(%)	Prevalence of dry eye (overall 9.1%)	Odds Ratio (95% CI)	P value
Schizophrenia	66 (0.1%)	6.1%	0.79 (0.29–2.20)	0.66
Eating disorder	1122 (1.4%)	15.9%	1.64 (1.39–1.93)	<0.001
Obsessive compulsive disorder	296 (0.4%)	10.5%	1.25 (0.85–1.82)	0.25
ADHD	651 (0.7%)	12.6%	1.93 (1.52–2.45)	<0.001
Addiction	452 (0.6%)	10.6%	1.55 (1.14–2.11)	0.005
Agoraphobia	557 (0.7%)	16.0%	1.86 (1.48–2.35)	<0.001
Panic disorder	3495 (4.4%)	12.7%	1.41 (1.27–1.57)	<0.001
Chronic fatigue syndrome	1323 (1.7%)	19.2%	2.28 (1.98–2.62)	<0.001
Depression	9494 (11.9%)	13.2%	1.52 (1.42–1.62)	<0.001
'Burnout'	10314 (12.9%)	12.0%	1.44 (1.35–1.54)	<0.001
PTSD	205 (0.3%)	11.2%	1.23 (0.79–1.90)	0.36
Borderline PD	96 (0.1%)	14.6%	1.62 (0.91–2.86)	0.10
Dementia	73 (0.1%)	14.5%	1.52 (0.77–3.02)	0.23
Autistic disorder	163 (0.2%)	14.9%	2.75 (1.76–4.28)	<0.001
Gastro-intestinal disorders				
Stomach ulcer	3290 (4.1%)	14.7%	1.68 (1.52–1.86)	<0.001
Crohn	328 (0.4%)	17.5%	2.01 (1.51–2.70)	<0.001
Ulcerative colitis	642 (0.8%)	14.5%	1.61 (1.29–2.01)	<0.001
Celiac disease	379 (0.5%)	17.0%	1.66 (1.27–2.19)	<0.001
Lactose intolerance	68 (0.1%)	16.2%	1.84 (0.96–3.54)	0.07
Diverticulosis	210 (0.3%)	18.1%	1.71 (1.20–2.44)	0.003
Pulmonary disorders				
COPD	3446 (4.3%)	14.5%	1.53 (1.39–1.69)	<0.001
Asthma	3974 (5.0%)	14.0%	1.62 (1.48–1.78)	<0.001
Sleep apnea	265 (0.3%)	13.1%	1.90 (1.32–2.73)	0.001
Hyperventilation syndrome	951 (1.2%)	10.6%	1.14 (0.93–1.41)	0.22
Dermatological disorders				
Severe acne	2182 (2.7%)	11.4%	1.41 (1.23–1.61)	<0.001
Psoriasis	2282 (2.9%)	11.2%	1.32 (1.15–1.51)	<0.001
Eczema	12096 (15.1%)	10.8%	1.29 (1.21–1.37)	<0.001
Rosacea	267 (0.3%)	17.6%	1.95 (1.28–2.97)	0.002
Alopecia areata	54 (0.1%)	13.0%	1.47 (0.66–3.29)	0.34
Lichen planus	91 (0.1%)	17.6%	1.65 (0.96–2.86)	0.07
Lichen sclerosus	144 (0.2%)	18.8%	1.61 (1.05–2.45)	0.03
Vitiligo	131 (0.2%)	10.8%	1.23 (0.70–2.16)	0.47
Allergies				
Nasal allergy/hay fever	18662 (23.4%)	10.8%	1.38 (1.30–1.46)	<0.001
Any allergy	37084 (46.4%)	10.8%	1.37 (1.30–1.44)	<0.001
Dust	11700 (14.7%)	10.9%	1.33 (1.25–1.42)	<0.001
Pollen	14442 (18.1%)	10.0%	1.22 (1.14–1.29)	<0.001
Animals	8325 (10.4%)	10.0%	1.16 (1.07–1.25)	0.0002
Foods	3192 (4.0%)	13.5%	1.44 (1.30–1.60)	<0.001
Medication	6095 (7.6%)	14.9%	1.53 (1.42–1.65)	<0.001
Contact allergy	7072 (8.9%)	13.0%	1.24 (1.15–1.34)	<0.001
Insects	3013 (3.8%)	13.0%	1.33 (1.19–1.49)	<0.001
Other	7831 (9.8%)	11.6%	1.25 (1.16–1.35)	<0.001
Infectious diseases				
Lyme	423 (0.5%)	12.1%	1.34 (1.00–1.81)	0.05
Tuberculosis	140 (0.2%)	11.4%	1.13 (0.69–1.92)	0.64
Mononucleosis infectiosa	706 (0.9%)	8.4%	1.06 (0.81–1.39)	0.69
Other disorders				
Diabetes mellitus	2668 (3.3%)	12.6%	1.29 (1.15–1.46)	<0.001
Type 1	189 (0.2%)	11.6%	1.54 (0.98–2.42)	0.06
Type 2	2210 (2.8%)	12.9%	1.27 (1.11–1.44)	<0.001
Osteoporosis	2505 (3.1%)	21.1%	1.76 (1.59–1.96)	<0.001
Endometriosis	292 (0.4%)	16.4%	1.61 (1.18–2.20)	0.003
Thyroid disease	1344 (1.7%)	17.5%	1.73 (1.50–2.00)	<0.001
Graves disease	140 (0.2%)	35.7%	4.58 (3.22–6.50)	<0.001
Anemia	12788 (16.0%)	13.1%	1.27 (1.19–1.34)	<0.001
Hip fractures	526 (0.7%)	10.9%	1.06 (0.80–1.40)	0.71
Other fractures	2489 (3.1%)	13.2%	1.32 (1.17–1.49)	<0.001
Vitamin B12 deficiency	364 (0.5%)	15.1%	1.59 (1.19–2.13)	0.002
Ménière's disease	315 (0.4%)	16.6%	1.60 (1.18–2.17)	0.002
Tinnitus	265 (0.3%)	14.8%	1.78 (1.26–2.52)	0.001
Sinusitis	198 (0.2%)	18.7%	2.48 (1.72–3.57)	<0.001

ADHD = attention deficit hyperactivity disorder; CI = confidence interval; COPD = chronic obstructive pulmonary disease; IOP = intraocular pressure; PD = personality disorder; PTSD = posttraumatic stress disorder; RSI = repetitive strain injury; SLE = systemic lupus erythematosus.

caused by tear hyperosmolarity and inflammatory responses (the so called *vicious circle of dry eye*) [1]. Our results clearly indicate that more studies on dry eye are needed in younger adults of working age.

Air pollutants PM10 and NO_2 were strongly associated with dry eye in this study. Other studies in the United States and Asia have found varying positive associations between dry eye and air pollutants CO, NO_2, PM10, PM2.5, sulphur dioxide, ozone and aerosol optical depth [23–25]. These studies did however not correct for comorbidities at all or only for a limited set. In the present study, the effects of PM10 and NO_2 were reduced after additional correction for comorbidities, leaving only NO_2 significantly associated. So, the associations between air pollutants and dry eye are likely partly mediated by an increased prevalence of other diseases that have been directly linked to air pollution,

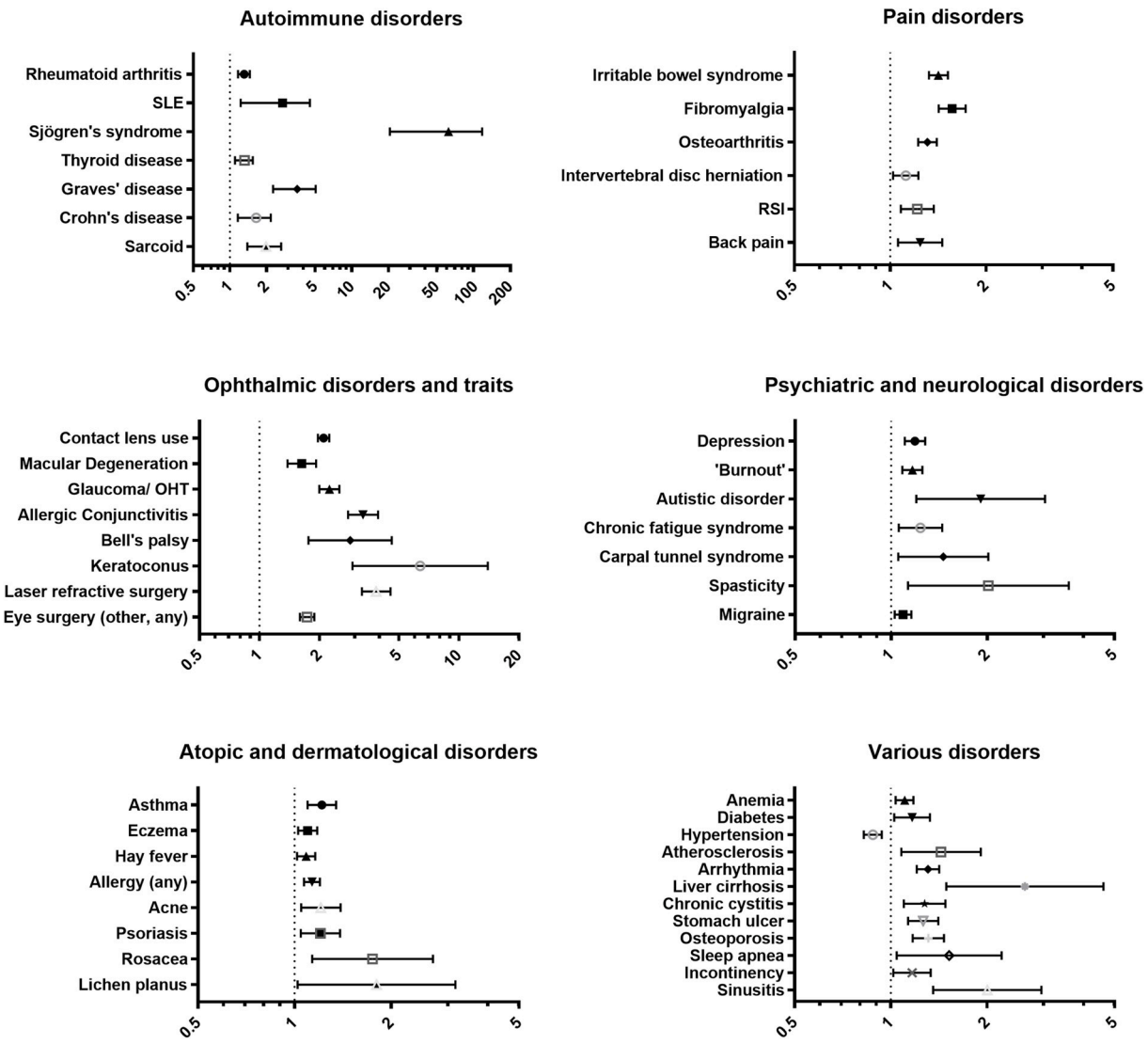

Fig. 2. Odds ratios of comorbidities and traits independently associated with dry eye.
All 48 comorbodities/traits in figures above were independently associated with dry eye in a stepwise multivariable logistic regression analysis, starting with 120 comorbidities/traits and age, sex and BMI. 95% confidence intervals of odds ratios are depicted by the lines. OHT = ocular hypertension; RSI = repetitive strain injury; SLE = systemic lupus erythematosus.

such as allergies and atopic disorders, atherosclerosis, and diabetes [26]. Our results, however, further indicate a likely detrimental effect on the ocular surface of NO_2, a chemical compound that is emitted when fuel is being burned, e.g. in transport or industrial processes. Kawashima et al. [27] and Hanyuda et al. [15] found higher levels of physical activity to be associated with less dry eye, but these cross-sectional studies did not correct for important confounding comorbidities, such as musculoskeletal disorders that are associated with both less physical activity and more dry eye. Indeed, in our study, after correction for other comorbidities the relationship between physical activity score and dry eye disappeared, indicating that a protective effect of activity on dry eye is less likely. These examples underline the importance of correction for possible confounding associated disorders in cross-sectional studies.

A recent systematic review looking at the effect of smoking on eye diseases concluded that smoking has a detrimental effect on most diseases of the anterior eye, but, however, the effect on dry eye remained unclear [28]. A meta-analysis of 10 studies that investigated the relation between dry eye and smoking concluded there was no statistical significant relationship between current or ex-smoking and the risk of dry eye [29]. The present study is larger than all these cross-sectional studies combined, which had individual sample sizes varying from 500 to 3703 participants. Interestingly, we found current smoking to be clearly associated with less dry eye. Although cigarette smoke is often associated with an irritating effect on the eyes for non-smokers and smoking has been associated with a lower quality of the tearfilm and higher osmolarity [30,31], this protective effect of smoking could be mediated by a reduced sensitivity of the ocular surface [30]. In addition, smoking and nicotine have been associated with protective and anti-inflammatory effects in auto-immune disorders such as ulcerative colitis and Behcet's disease, in part mediated via the cholinergic pathway [32], and this may apply to dry eye as well. The lower prevalence of dry eye in current smokers came particularly from a lower prevalence of clinical diagnoses, and to a lesser extent from fewer symptomatic dry eye, as this odds ratio did not reach statistical significance (see Suppl Table D). Any protective effect of smoking on dry eye seems to disappear after smoking cessation, as ex-smokers were more at risk for dry eye (including symptomatic dry eye). Because this association was unexpected, we have investigated the same relationship in the TwinsUK cohort where the same data were available [19]. In a total of 3889 twins current smokers showed an OR of 0.65 (P = 0.04) for dry eye, and ex-smokers an OR of 1.23 (P = 0.03),

Table 3
Associations between dry eye and demographic, environmental and systemic factors.

Risk factor (n = 79,866 unless otherwise specified)	Prevalence of risk factor n (%)	Prevalence of dry eye (overall 9.1%)	Corrected for age and sex only		Corrected for age, sex, BMI and 48 comorbidities[a]	
			Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value
Age (years)	–	–	1.023 (1.021–1.025)	<0.001	1.018 (1.016–1.021)	<0.001
Female sex	47,294 (59.2%)	11.9%	2.68 (2.53–2.84)	<0.001	2.06 (1.93–2.19)	<0.001
Partnered (n = 75,000)	64,175 (85.6%)	8.8%	0.84 (0.79–0.91)	<0.001	0.93 (0.86–1.00)	0.04
Higher education diploma (n = 78,673)	23,289 (29.6%)	9.1%	1.16 (1.10–1.23)	<0.001	1.11 (1.05–1.18)	<0.001
Smoking (n = 79,481)						
Yes	12,540 (15.8%)	7.3%	0.89 (0.82–0.96)	0.002	0.87 (0.80–0.94)	<0.001
Ever, but stopped	25,961 (32.7%)	10.3%	1.11 (1.06–1.18)	<0.001	1.09 (1.03–1.15)	0.003
Never	40,980 (51.6%)	8.8%	Reference group	–	Reference group	–
Total activity score (n = 72,535) (1000 units)	–	–	0.992 (0.986–0.998)	0.007	0.998 (0.992–1.004)	0.52
Pets: (n = 77,796)						
Cat	24,796 (31.9%)	8.4%	0.95 (0.90–1.00)	0.05	0.95 (0.89–1.00)	0.05
Dog	19,942 (25.7%)	8.4%	0.92 (0.87–0.98)	0.005	0.92 (0.86–0.98)	0.005
Air pollution (n = 47,869)						
Estimated PM10 (in Âµg/m3)	–	–	1.085 (1.036–1.135)	<0.001	1.038 (0.989–1.089)	0.13
Estimated PM2.5 (in Âµg/m3)	–	–	1.034 (0.952–1.123)	0.43	1.005 (0.922–1.096)	0.91
Estimated NO_2 (in Âµg/m3)	–	–	1.021 (1.013–1.030)	<0.001	1.011 (1.003–1.020)	0.008
Anthropometry						
BMI (kg/m2)	–	–	0.993 (0.987–0.998)	0.01	0.985 (0.979–0.991)	<0.001
Height (cm)	–	–	0.994 (0.990–0.998)	0.003	0.996 (0.992–1.000)	0.04
Waist circumference (cm)	–	–	0.998 (0.995–1.000)	0.02	0.995 (0.992–0.997)	<0.001
Blood pressure						
Diastolic (mmHg)	–	–	0.989 (0.987–0.992)	<0.001	0.991 (0.988–0.994)	<0.001
Systolic (mmHg)	–	–	0.994 (0.993–0.996)	<0.001	0.996 (0.994–0.997)	<0.001
Hypotension (≤90/60 mmHg)	3414 (4.3%)	11.1%	1.13 (1.01–1.26)	0.04	1.06 (0.94–1.19)	0.32
Hypertension (≥140/90 mmHg)	18,637 (23.4%)	8.8%	0.85 (0.80–0.90)	<0.001	0.88 (0.82–0.94)	<0.001
Thyroid function tests (n = 25,543)						
FT3 (pmol/l)	–	–	0.92 (0.86–0.98)	0.02	0.93 (0.86–0.99)	0.03
FT4 (pmol/l)	–	–	1.03 (1.01–1.05)	0.002	1.02 (1.001–1.04)	0.04
TSH (mu/l)	–	–	1.00 (0.99–1.01)	0.88	1.01 (0.995–1.02)	0.32
Blood glucose levels (n = 77,494)						
DM patients: Glucose (mmol/l)	–	–	1.01 (0.96–1.07)	0.61	1.02 (0.97–1.08)	0.43
Non DM patients: Glucose (mmol/l)	–	–	0.94 (0.91–0.98)	0.006	0.97 (0.92–1.01)	0.15
DM patients: HbA1c (%)	–	–	1.06 (0.94–1.21)	0.33	1.11 (0.98–1.26)	0.11
Non DM patients: HbA1C (%)	–	–	0.95 (0.88–1.02)	0.18	0.98 (0.91–1.06)	0.64
Duration diabetes mellitus (years)			1.006 (0.994–1.018)	0.35	1.004 (0.990–1.018)	0.57
Cholesterol levels (n = 77,712)						
Cholesterol (mmol/l)	–	–	0.97 (0.94–0.99)	0.009	0.98 (0.95–1.01)	0.16
High cholesterol (>6.2 mmol/l)	9585 (12.3%)	10.2%	0.98 (0.91–1.05)	0.54	0.99 (0.92–1.07)	0.83
Triglycerides (mmol/l)	–	–	1.01 (0.98–1.05)	0.49	0.99 (0.96–1.03)	0.70
High triglycerides (>2.25 mmol/l)	5592 (7.2%)	7.8%	1.05 (0.94–1.16)	0.40	1.01 (0.90–1.12)	0.89
HDL cholesterol (mmol/l)	–	–	0.99 (0.93–1.06)	0.80	1.00 (0.94–1.07)	0.99
Low HDL cholesterol (<1.03 mmol/l)	8749 (11.3%)	6.8%	1.06 (0.97–1.16)	0.23	1.03 (0.94–1.14)	0.49

BMI = body mass index; CI = confidence interval; DM = diabetes mellitus; HDL = high density lipoprotein; LDL = low density lipoprotein; NO_2 = nitrogen dioxide; PM10 = particulate matter less than 10 μm in diameter; PM2.5 = particulate matter less than 2.5 μm in diameter.

[a] Corrected for age and sex and 48 comorbidities/traits that were independently associated with dry eye disease (see Fig. 1). The associated self-reported risk factor was omitted per item (e.g. in the thyroid function tests analyses, the results were not corrected for self-reported thyroid disease).

confirming the results of the present study. Further longitudinal studies should investigate a potentially causal relationship.

Sjögren's syndrome showed the highest OR of all risk factors investigated, which is no surprise because the lacrimal glands are directly targeted in this auto-immune disorder. Dry eye signs and symptoms are part of the disease criteria [33]. Of the connective tissue diseases, we found SLE, systemic sclerosis and rheumatoid arthritis all to have a highly increased risk of dry eye. These autoimmune disorders have frequently been associated with dry eye and are also associated with secondary Sjögren's syndrome [2]. Osteoarthritis was also highly associated with dry eye, and our group has found this association before in a female cohort in the UK [19]. A possible link between osteoarthritis and dry eye could be an impaired function of the viscoelastic properties of both the tears and synovial fluid, via for example lubricin. Lubricin is a critical component of the healthy ocular surface glycocalyx, which plays a role in ocular surface friction [34], and has also has been shown to have an important role in joint lubrication and osteoarthritis [35,36]. In addition, both osteoarthritis and dry eye have been associated with increased pain sensitivity tested by quantitative sensory testing [37,39], so the association between the two could also be mediated by an

increased general pain sensitivity. In addition to the connective tissue diseases, a few other auto-immune disorders have been associated with dry eye in other studies, such as sarcoid and graft-versus-host disease [1,2]. In this study we also discovered strong associations with Crohn's disease, ulcerative colitis, celiac disease, and lichen planus, broadening the relationships between auto-immune disorders and dry eye. In addition, there were suggestive associations with alopecia areata, ankylosing spondylitis, and lichen sclerosus.

Disorders that have a strong psychological or psychogenic component are increasingly recognised as being associated with dry eye. This is also reflected in our study, with strong independent associations of dry eye with IBS, fibromyalgia, and chronic fatigue syndrome. A classical twin study by our group has shown that dry eye shares genetic factors with functional disorders including IBS, fibromyalgia and chronic pelvic pain [38]. In the same twin cohort we found these disorders to have the highest odds ratios for dry eye among 23 disorders investigated [19]. Recently, the more traditional classification of aqueous (tear) deficient and evaporative dry eye has been expanded to include neuropathic dry eye [40], reflecting the recognition that dry eye symptoms are often caused by more than tear film or ocular surface problems, and that neurosensory dysfunction, either at the periphery (cornea) or centrally, could also lead to dry eye symptoms [41]. Central neuropathic pain may explain our other associations with other diseases lacking clear objective pathology such as Tietze syndrome (costochondral junction syndrome) and tinnitus. Similarly, the strong association we found between sinusitis and dry eye could be the result of referred pain and/or trigeminal neuralgia. It is important for clinicians to recognize this, especially when ocular surface signs are limited in dry eye patients.

We found increased heart rate and higher blood pressure to be associated with less dry eye in this cohort. The role of blood pressure and heart rate on dry eye has not been investigated before. Interestingly, a recent meta-analysis that investigated a total of nine studies has reported a borderline significant *positive* association between *self-reported* hypertension and dry eye [42]. A possible link between blood pressure and dry eye could be via a role of the autonomous nerve system on lacrimation. The physiology of lacrimation is very complicated and still largely unclear, but activity of both the sympathetic and parasympathetic nervous system has been shown to play an important role [43], systems that also play a major role in regulation of blood pressure. Lower sympathetic activity has been linked to lower blood pressure and less lacrimation. Also, the influence of female sex hormones, such as estradiol that have been linked to both blood pressure and dry eye, could play a role in the association between the two. In this study, we had no contemporaneous data on type of medication used at the time of dry eye assessment, only at baseline on average 5 years earlier. Looking at these findings into more detail, we found hypertension to be significantly associated with less dry eye in both people who did use and who did not use antihypertensive medications at baseline. This suggests a protective association between high blood pressure and dry eye, independent of antihypertensive medication use. Our results indicate the importance of using accurate blood pressure measurements when studying hypertension, as opposed to using self-reported diagnosis, which is also shown in a recent systematic review on the accuracy of self-report of hypertension [44].

This is the first population-based study, to our knowledge, comparing different eye disorders and eye surgeries and their relative effects on dry eye. We found a strong association between all types of eye surgery investigated and dry eye. This is perhaps not surprising, because all eye surgery effectively starts at the ocular surface, but the risk of dry eye in this study turned out to be higher than expected. The presence of dry eye after laser refractive surgery has been studied in mostly short-term studies and is a notorious side-effect, particularly of LASIK. Pre-existing dry eye signs and symptoms are strong risk factors for post-surgical dry eye [22,45]. Most studies have shown that signs of dry eye and reduced corneal sensation recover to preoperative levels one year after surgery [45]. In the present study, patients who had laser refractive surgery showed an odds ratio of 3.8 for symptomatic dry eye: 9% reported dry eye symptoms 'often' or 'constantly'. This risk was even much higher in participants under age 40 (OR 7.1 (5.2–9.8), see appendix Table A). Moreover, these patients were unlikely to have had serious dry eye before, as dry eye is a relative contra-indication for laser refractive surgery [46]. Cataract surgery also increased odds (OR 2.6) for symptomatic dry eye. These findings underline the need to inform patients about risk of dry eye after any eye surgery, which is not common practice at present. Possible mechanisms for surgery-induced dry eye include use of topical anaesthetics, exposure desiccation, nerve transection, elevated inflammatory factors during and after surgery, conjunctival goblet cell loss, Meibomian gland dysfunction, use of topical antimetabolites in glaucoma surgery and possibly irritation of the conjunctiva with povidone iodine [22,45].

Many of the associations we found could be causally related with dry eye via medications used for the comorbidity. Medications that have been associated with dry eye are antihistamines, antidepressants, anxiolytics, and isotretinoin [2,22]. Isotretinoin, for example, could explain the relationship we found between dry eye and both acne and rosacea. However, this relationship could also be caused by meibomian gland dysfunction, which is an important cause of evaporative dry eye [47]. Antidepressants and anxiolytics all have anticholinergic side effects that reduce tear production and these could be partly responsible for the associations we found with psychiatric diseases. However, in participants that did not use any medication at all the strong association between dry eye and both depression and anxiety remained, indicating an effect independent of medication use. Among the psychiatric disorders with the highest risk of dry eye were autism and ADHD. Further studies are therefore warranted to investigate the role of psychostimulants such as methylphenidate on dry eye parameters, which is currently unknown. Similarly, the relation between allergy, hay fever, and other atopic disorders could also be partly explained by use of antihistamines. Other explanations could be increased sensitivity of the nerves on the ocular surface by inflammatory mediators or a possible misclassification of allergic conjunctivitis with dry eye [48].

Other notable strong associations with dry eye that were found in this study were with sleep apnea, which has been associated with floppy eyelid syndrome that can lead to exposure keratopathy during the night [49], but could also cause dry eye by a direct effect of leaking airstream of continuous positive airway pressure on the eyes; with spasticity and incontinence, often treated with anticholinergic medications; with stomach ulcers, lactose intolerance and vitamin B12 deficiency, which further adds evidence to the intriguing coexistence of gastro-intestinal disorders and dry eye, possibly independent of auto-immune processes; and with liver cirrhosis, an association not described before, that could possibly be linked via associated immune dysfunction or a consequence of jaundice.

The present study has some limitations. First, selection bias is a concern in most population based cohort studies. LifeLines has been shown to be broadly representative on socioeconomic characteristics, lifestyle, diseases, and general health [50]. Although this does not rule out selection bias, it is a strong indication that the LifeLines study population is a representative sample of the population in the north of the Netherlands. Participants of Lifelines are almost exclusively of Caucasian Northern/West European descent, which makes generalizability of the results to other ethnicities difficult. Second, self-reported diagnosis of comorbidities is prone to recall bias. When we assessed psychiatric disorders and IBS using validated interviews and an extensive questionnaire, respectively, OR's were broadly similar to those of self-report in this study. However, some of the other comorbidities we investigated might be more prone to bias. Similarly, the WHS questionnaire asks about a previous diagnosis of dry eye from a clinician. This definition could have led to an under- or overestimation of dry eye, as diagnostic criteria were less clear in the past and could have differed per clinician. However, this questionnaire has been shown to have a good specificity and sensitivity versus clinical examination. Finally, we

conducted multiple tests in this study and this could have led to false positive results, important to consider when interpreting results, particularly for risk factors that were at or just below nominal significance level. We believe it is important that future studies confirm observed associations in the current study that were not highly significant. Until then these associations can only be considered suggestive. Because of the cross-sectional design of this study, we have tried to avoid any implication of causation between risk factor and dry eye as much as possible. The major strengths of this study are the large sample size and the investigation of multiple risk factors at once. This allowed us to correct for multiple confounding factors, which is generally lacking in other studies. It also allowed us to look at differences in the epidemiology of dry eye between men and women and between different age categories (see Appendices Tables A and B), which is important to better understand the pathophysiology of dry eye and to improve personalized treatment.

5. Conclusions

This study is the first to report that symptoms are particularly frequent in young adults. Future studies in younger age groups are warranted to investigate long-term consequences and the influence of screen use. The large scale of this study has allowed confirmation, clarification (and rejection) of previous reported risk factors, such as an apparent protective effect of smoking and hypertension on dry eye, and has found numerous new risk factors, of which several are potentially modifiable. It underlines the importance of informing patients and screen for dry eye when ocular surgery is considered. These findings expand our knowledge of the multifactorial etiology and pathophysiology of dry eye. For doctors that treat patients this study underlines the importance of taking a holistic view and considering environmental, systemic, and iatrogenic risks of dry eye, instead of focusing only on the ocular surface and lubricants.

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Declaration of competing interest

No conflicting relationship exists for any author.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jtos.2020.04.005.

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