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Medication use and dry eye symptoms: A large, hypothesis-free, population-based study in the Netherlands

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ABSTRACT

Purpose: To date, population-based studies reporting associations between dry eye disease and medications were hypothesis-driven, did not take into account underlying comorbidities, and did not investigate individual drugs. The purpose of this study was to clarify the association of dry eye symptoms with medication classes and individual drugs, using a hypothesis-free approach.

Methods: 79,606 participants (age 20–97 years, 59.2% female) from the population-based Lifelines cohort in the Netherlands were cross-sectionally assessed for dry eye symptoms using the Womens' Health Study dry eye questionnaire. All medications used were coded with the ATC classification system. Logistic regression was used to assess the risk of the 59 most-used therapeutic/pharmacological subgroups and the 99 most-used individual drugs (all $n > 200$) on dry eye symptoms, correcting for age, sex, body mass index, and 48 comorbidities associated with dry eye.

Results: Thirty-eight (64%) medication subgroups and fifty-two (53%) individual drugs were associated with dry eye symptoms ($P < 0.05$), after correction for age and sex only. A multivariable model correcting for comorbidities revealed highly significant associations between dry eye symptoms and drugs for peptic ulcer (particularly proton pump inhibitors (PPIs)), antiglaucoma and anticholinergic medications.

Conclusions: This study underlines that medication use is highly informative of risk of dry eye symptoms. Correction for underlying comorbidities is critical to avoid confounding effects. This study confirms suggested associations between medications and dry eye symptoms at a population level and shows several new associations. The novel link between PPIs and dry eye symptoms deserves particular attention given how commonly they are prescribed.

1. Introduction

Dry eye disease (DED) is a common, complex and multifactorial disease that results in ocular discomfort with symptoms of dryness, burning, and grittiness [1]. DED can have a significant impact on quality of life [1,2]. The precise aetiology of DED is multifactorial and not well understood but it is thought to be mediated by several modifiable and non-modifiable risk factors, including but not limited to older age, female sex, autoimmune and other systemic medical disorders, environmental exposures, and medication use [1]. A number of topical and systemic medications have been associated with symptoms and signs of DED, including antidepressants [3–6], antihypertensives [3,5], antiglaucoma medications [7–9], and anticholinergics [10]. However, to date, studies that have linked DED to medication use were hypothesis-driven, only corrected for a few possible confounding underlying comorbidities or did not investigate individual drugs but rather drug classes. Understanding the exact role of systemic and topical medications in the aetiology of DED is important because it can give clues as to the multifactorial pathophysiology of DED, and it might help alleviate DED in patients by modifying these medications. Therefore, the

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purpose of this large, population-based study was to investigate the association between dry eye symptoms and both medication classes and individual drugs, using a hypothesis-free approach to allow for identification of new associations, whilst correcting for underlying comorbidities.

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 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 [11]. Participants, almost exclusively of European ancestry, were included via general practitioners or self-enrolment between 2006 and 2013 for the baseline visit and will be followed for at least 30 years. The cohort is described in detail elsewhere [12]. The study protocol was approved by the medical ethics committee of the University Medical Center Groningen, was carried out in accordance with the Declaration of Helsinki, and all participants provided written informed consent. For the current study, we included participants at least 18 years of age who had completed the Women's Health Study (WHS) dry eye questionnaire, (see below), which was taken during the first follow-up assessment round (2014–2017). Power analysis showed that at least 73,605 participants are needed to be able to detect an odds ratio of 1.5 for medications with a prevalence as low as 0.3% (i.e. n = 200) with a power of 80%, an alpha of 0.05, and an estimated prevalence of dry eye symptoms of 30% [13].

2.2. Assessment of dry eye symptoms

No gold standard for a diagnosis of DED exists, making it difficult to investigate [14]. In this study dry eye symptoms were assessed during the first follow-up assessment round, between 2014 and 2017, with the Women's Health Study (WHS) dry eye questionnaire [15]. This short questionnaire with 3 questions has been validated against a standardized clinical exam [16] and showed similar sensitivity and specificity as a 16 item instrument [15]. It is the most widely used dry eye questionnaire in population-based studies [1]. 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 DED: (3) "Have you ever been diagnosed (by a clinician) as having dry eye syndrome?" (with possible answers: yes or no). For the purpose of this study, we looked at current dry eye symptoms only, making use of a combination of the first two questions. As a primary outcome variable, we defined dry eye symptoms 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 or irritation) [13]. We have not assessed the relation of medication use with a diagnosis of DED (third question of the WHS dry eye questionnaire) because this diagnosis could have been present long before the medication was started. A sensitivity analysis was conducted, measuring highly symptomatic dry eye as a score of 3 or higher in the WHS questionnaire.

2.3. Assessment of medication and possible confounding factors

Participants were asked to bring all their medications at their baseline visit, between 2006 and 2013. Subsequently, these medications were registered and coded via the Anatomical Therapeutic Chemical (ATC) drug classification system by a trained research nurse. This classification system categorises the active ingredients of drugs according to the organ or anatomical system on which they act and on their therapeutic and chemical characteristics. This system is hierarchical, and drugs are classified at five different levels: the first level of the code indicates the anatomical main groups (one letter), the second level the therapeutic subgroup (two digits), the third level the therapeutic/pharmacological subgroup (one letter), the fourth level the chemical/therapeutic/pharmacological subgroup (one letter), and the fifth level the chemical substance (two digits). An example would be the ATC code S01EE03: S Sensory organs => S01 Ophthalmologicals => S01E Antiglaucoma preparations and miotics => S01EE Prostaglandin analogues => S01EE03 Bimatoprost [17].

In addition, all participants completed questionnaires at baseline and at a follow-up visit. At both of these visits participants were asked 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 dry eye questions. Of these disorders and traits 48 were independently associated with DED, see Vehof et al. [18] These disorders were contact lens use, macular degeneration, glaucoma/ocular hypertension, allergic conjunctivitis, Bell's paralysis, keratoconus, eye surgery (any), laser refractive surgery, hypotension, irritable bowel syndrome (IBS), fibromyalgia, Tietze syndrome, osteoarthritis, hernia back or neck, repetitive strain injury (RSI), rheumatoid arthritis, Sjögren's syndrome, arrhythmia, liver cirrhosis, gallstones, chronic cystitis, incontinence, spasticity, migraine, eating disorder, attention deficit hyperactivity disorder (ADHD), depression, burnout, stomach ulcer, asthma, acne, rosacea, hay fever, allergy (any), anaemia, osteoporosis, vitamin B12 deficiency, Graves' disease, obstructive sleep apnoea syndrome, lichen planus, sarcoidosis, back pain, chronic fatigue syndrome, chronic obstructive pulmonary disease (COPD), psoriasis, and atherosclerosis. Other variables corrected for in this study were age and sex, and body mass index (BMI).

2.4. Statistics

Descriptive statistics were used to describe the characteristics of the study population. Only medications that were used by 200 or more participants were included in the analyses to ensure sufficient power to detect an association. First, logistic regression, corrected for age and sex only, was used to assess the individual association of a certain medication with dry eye symptoms. Next, a forward stepwise multivariable logistic regression model was used to identify all independently associated medications, starting with all medications that were individually associated with a P-value lower than 0.10. For this analysis, we excluded medications that are used to treat: (i) DED or (ii) diseases clearly known to cause DED (e.g. for allergy/allergic conjunctivitis and autoimmune disorders such as rheumatoid arthritis or Sjögren's syndrome), as independent variables in analysis. To correct for multiple testing in the univariable analysis, we used a false discovery rate (FDR) corrected P-value to assess significance for every ATC level we investigated. In addition, to better assess the true effect of medication instead of its underlying disorder, the same multivariable logistic regression analysis was run including BMI and the 48 disorder or traits that were independently associated with DED. These analyses were performed separately for 3rd (therapeutic/pharmacological subgroups), 4th (chemical/therapeutic/pharmacological subgroups), and 5th (individual drugs, i.e. chemical substance) level medications of the ATC classification system. The 1st and 2nd level ATC classes were not analysed as these classes were considered to be too broad.

We performed additional exploratory subgroup analyses of two medication groups that are often linked to dry eye: antihypertensives and antidepressants. Odds ratios of dry eye symptoms of the main antihypertensive groups were calculated, while correcting for age, sex, BMI, hypertension, hypotension and all other comorbidities of dry eye

presented before. In persons with known depression, we calculated odds ratios of dry eye symptoms of the main antidepressant groups and subgroups while correcting for age, sex, BMI, and all comorbidities of dry eye excluding depression. A (corrected) P-value lower than 0.05 was regarded as statistically significant for all analyses. Fig. 1 provides an overview of the study analyses.

3. Results

Table 1 describes the characteristics of the study population (n = 79,606 with complete information on WHS questionnaire). A total of 53.1% of all participants were using at least one type of medication. In this group, 33.5% of participants had dry eye symptoms compared to only 26.1% in participants using no medication at all (P < 0.0001 for a difference). In total, 59 ATC 3rd level medication groups, 76 ATC 4th level medication groups, and 99 ATC 5th level individual drugs were included in the association analysis (all with more than 200 users). Of these, a total of 38 (64%) ATC 3rd level medication subgroups, 48 (63%) 4th ATC level medication subgroups, and 52 (53%) ATC 5th level individual drugs were individually associated with dry eye symptoms, when only corrected for age and sex (P < 0.05) (appendix tables A, B and C). Fig. 2 shows all medication groups (ATC 3rd level) that were significantly associated (after FDR correction for multiple testing) with dry eye symptoms, corrected for age and sex, excluding ATC code S01X 'other ophthalmologicals', the ATC class including artificial tears.

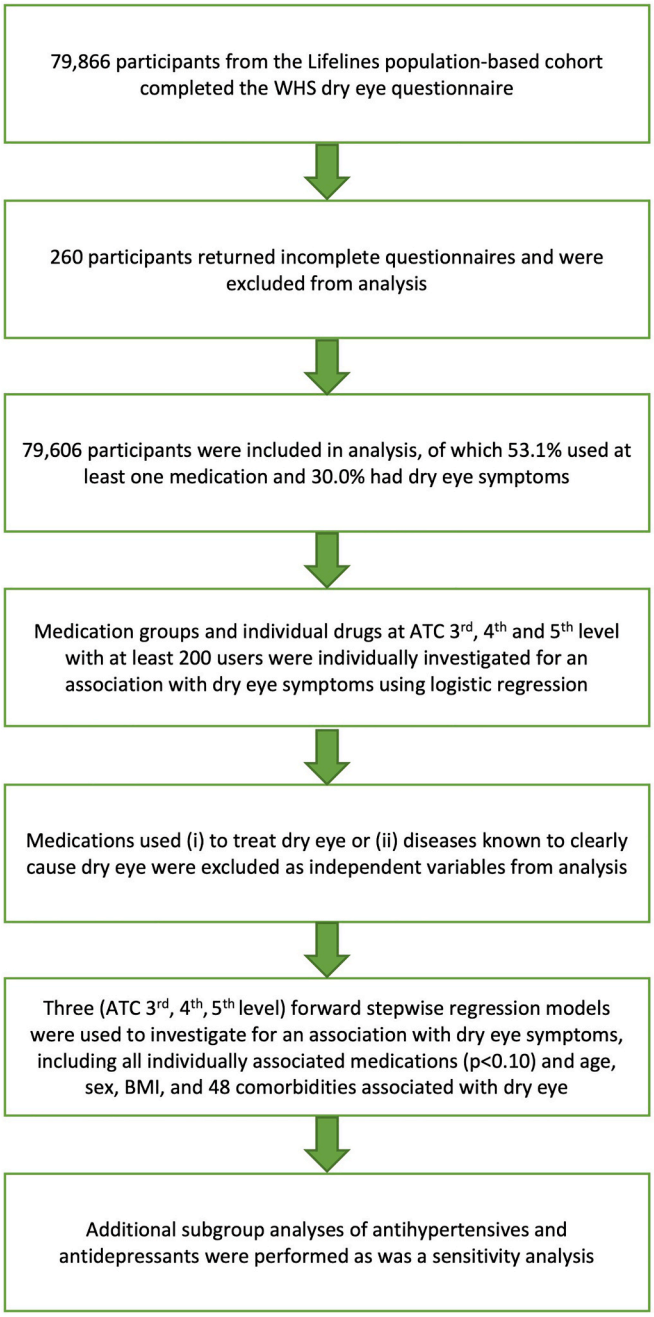

Fig. 1. Overview of study.

Table 1
Characteristics of the study population (n = 79,606).

	All (n = 79,606)	On any medication (n = 42,275)	No medication (n = 37,321)
Age (mean, s.d.)	50.4 (12.6)	51.7 (13.5)	48.9 (11.2)
Female sex (%)	59.2%	67.7%	49.5%
BMI (kg/m^2) (mean, s.d.)	26.1 (4.3)	26.6 (4.6)	25.7 (3.9)
Number of medications used (n, %)			
0	37,331 (46.9%)	–	37,331 (100%)
1	19,340 (24.3%)	19,340 (45.7%)	–
2	9652 (12.1%)	9652 (22.8%)	–
3	5301 (6.7%)	5301 (12.5%)	–
4 or more	7982 (10.1%)	7982 (18.9%)	–
Symptomatic dry eye (%)	30.0%	33.5%	26.1%

BMI = body mass index; s.d. = standard deviation.

Medications used for DED or causally related disorders (ATC 3rd level, n = 14; ATC 4th level, n = 19, ATC 5th level, n = 25) were then excluded (see appendix tables A, B and C for details). Subsequently, multivariable analyses including all remaining medications (ATC 3rd level n = 24; ATC 4th level n = 29; ATC 5th level n = 27) as independent variables, corrected for age, sex, BMI and 48 comorbidities, were performed. The total number of significantly associated medications largely decreased (Table 2). At the ATC 3rd level, drugs for peptic ulcer and GORD (OR 1.24, 95% CI 1.17–1.31) had the strongest association with dry eye symptoms. At the ATC 4th level proton pump inhibitors (PPIs) (OR 1.24, 95% CI 1.16–1.32) showed the highest risk of dry eye symptoms. At ATC 5th level omeprazole (OR 1.23, 95% CI 1.15–1.32), pantoprazole (OR 1.24, 95% CI 1.09–1.42) and esomeprazole (OR 1.19, 95% CI 1.01–1.40) all showed an association with dry eye symptoms. Drugs for functional gastrointestinal disorders (OR 1.33, 95% CI 1.02–1.74) were associated with dry eye symptoms at the ATC 3rd level, with mebeverine (OR 1.36, 95% CI 1.04–1.78) and ispaghula (OR 1.22, 95% CI 1.04–1.44) being associated with dry eye symptoms at the ATC 5th level. Antiglaucoma preparations and miotics (OR 1.32, 95% CI 1.06–1.66) were associated with an increased risk of dry eye symptoms. At ATC 3rd level vitamin B12 and folic acid (OR 1.18, 95% CI 1.02–1.36) were associated with dry eye symptoms. Low-ceiling diuretics, thiazides (OR 0.90, 95% CI 0.82–0.99) were associated with a small protective effect. Synthetic anticholinergics (OR 1.36, 95% CI 1.03–1.78) and 'other antiepileptics' (OR 1.29, 95% CI 1.01–1.65) showed an increased risk of dry eye symptoms at ATC 4th level.

Prevalence of highly symptomatic dry eye, used for the sensitivity analysis, was low (4.7%), resulting in less power to detect associations. However, similar to the main analysis, the sensitivity analysis showed highly significant associations with PPIs, antiglaucoma preparations and miotics, antiepileptics and vitamin B12 and folic acid. In addition, there were also associations with osmotically acting laxatives (OR 1.35, 95% CI 1.20–1.51), macrogol (OR 1.47, 95% CI 1.16–1.87), other antidepressants (OR 1.34, 95% CI 1.05–1.71) and methylphenidate (OR 1.69, 95% CI 1.01–2.85) (appendix table DTable Appendix D).

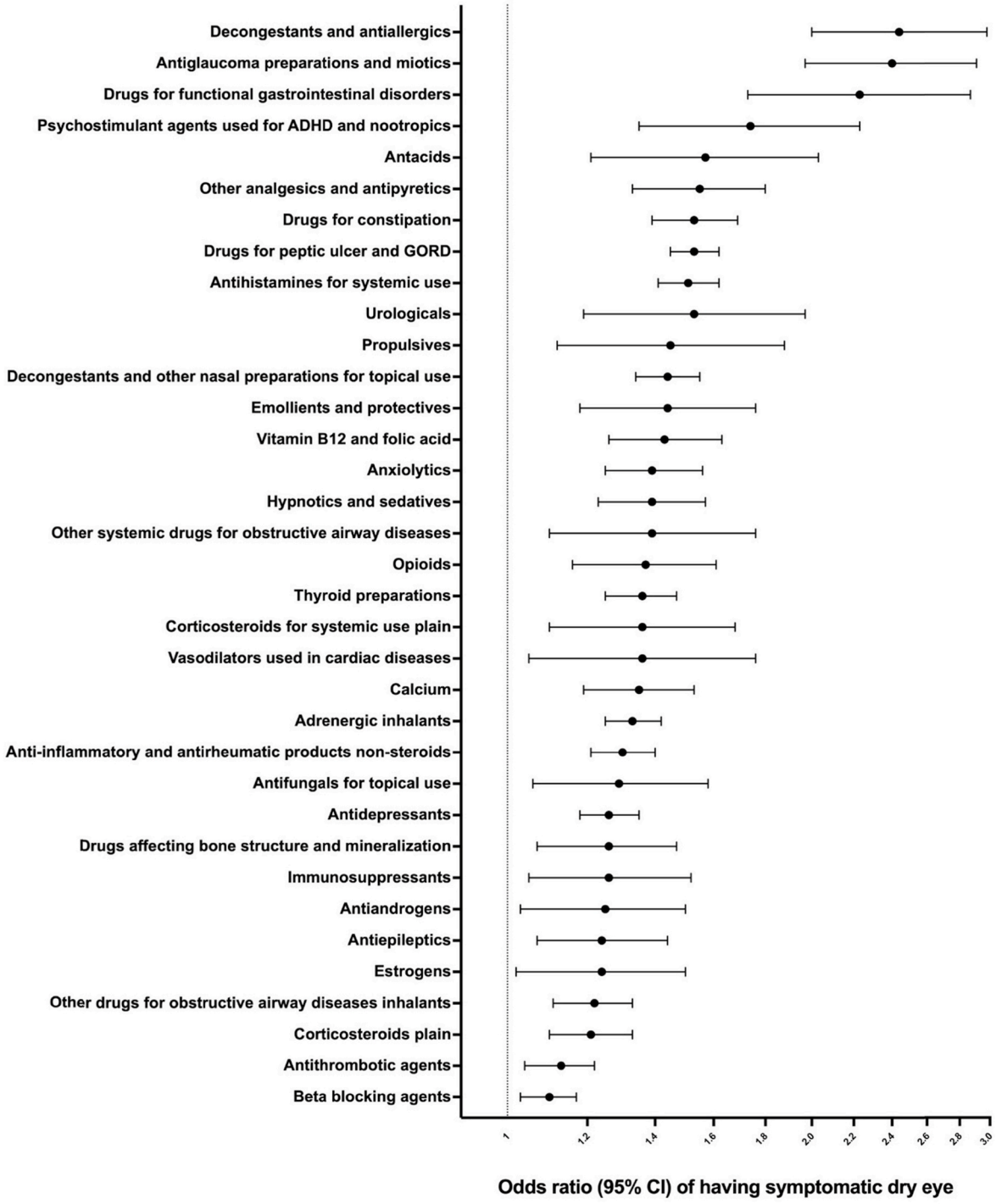

Fig. 2. Significant associations between dry eye symptoms and medication groups (ATC 3rd level), corrected for age and sex only.

Table 3 shows that in participants with a diagnosis of depression (n = 9425), patients taking no antidepressants had more dry eye symptoms than those on medications. Moreover, there were less dry eye symptoms in participants using selective serotonin reuptake inhibitors (P = 0.02). Similarly, a trend was found for non-selective monoamine reuptake inhibitors to be associated with less dry eye symptoms (P = 0.08). This is in line with our main analyses, in which we found antidepressants to be mildly protective of dry eye symptoms after correction for systemic comorbidities including depression (Table 2). Thus, these results indicate that depression itself is the risk factor for dry eye and that use of antidepressants does not carry an additional increased risk of dry eye symptoms. Also, none of the antihypertensive medication groups were clearly associated with dry eye symptoms after correction for confounding factors including hyper- and hypotension (Table 4).

In persons with known glaucoma or ocular hypertension, the use of any antiglaucoma preparation was associated with an increased risk of dry eye symptoms compared to no use of antiglaucoma drops (OR 1.30 (95% CI 1.05 to 1.61), P = 0.02), indicating that antiglaucoma drops do contribute to an increased risk of dry eye symptoms, independent of underlying glaucoma and ocular hypertension. Two 4th level ATC subgroups of the 3rd level ATC group 'antiglaucoma preparations and miotics' had over 200 users; prostaglandin analogues S01EE (OR 1.09

Table 2
Associations between dry eye symptoms and medication groups (for ATC 3rd, 4th and 5th level), corrected for age, sex, BMI and 48 comorbidities associated with dry eye, using forward stepwise regression models.

ATC code	Name	Odds ratio (95% CI)*	P-value
ATC 3rd level			
A02B	Drugs for peptic ulcer and GORD	1.24 (1.17–1.31)	<0.001
S01E	Antiglaucoma preparations and miotics	1.32 (1.06–1.66)	0.014
B03B	Vitamin B12 and folic acid	1.18 (1.02–1.36)	0.026
C03A	Low-ceiling diuretics, thiazides	0.90 (0.82–0.99)	0.033
A03A	Drugs for functional gastrointestinal disorders	1.33 (1.02–1.74)	0.039
ATC 4th level			
A02BC	Proton pump inhibitors	1.24 (1.16–1.32)	<0.001
G04BD	Drugs for urinary frequency and incontinence	1.41 (1.05–1.89)	0.024
A03AA	Synthetic anticholinergics	1.36 (1.03–1.78)	0.028
N03AX	Other antiepileptics	1.29 (1.01–1.65)	0.038
C03AA	Thiazides	0.91 (0.82–1.00)	0.043
ATC 5th level			
A02BC01	Omeprazole	1.23 (1.15–1.32)	<0.001
A02BC02	Pantoprazole	1.24 (1.09–1.42)	0.001
C03AA03	Hydrochlorothiazide	0.89 (0.81–0.98)	0.017
A06AC01	Ispaghula (psylla seeds)	1.22 (1.04–1.44)	0.018
G03AA09	Desogestrel and oestrogen	0.80 (0.65–0.97)	0.025
A03AA04	Mebeverine	1.36 (1.04–1.78)	0.027
A02BC05	Esomeprazole	1.19 (1.01–1.40)	0.035
B01AC08	Carbasalate calcium	1.14 (1.00–1.29)	0.047

BMI = body mass index.
ATC = anatomical therapeutic chemical, BMI = body mass index, CI = confidence interval, GORD = gastro-oesophageal reflux disease.

(95% CI 0.82–1.46), P = 0.56) and beta blocking agents S01ED (OR 1.33 (95% CI 0.98–1.80), P = 0.06).

4. Discussion

This large population-based hypothesis-free study found medication use to be highly informative of the risk of dry eye symptoms. Strikingly, after correction for underlying comorbidities, the majority of associations between medications and dry eye symptoms disappeared. This may indicate that most of the associations seen between medications and dry eye are caused instead by the disease being treated and not the medications used for the disease themselves. Our results did not support suggested causal links between dry eye symptoms and antihypertensives and antidepressants or any of their subgroups from smaller studies [3–6] that did not incorporate underlying comorbidities. A new finding was the clear association of dry eye symptoms with PPI use, which was found to be independent of underlying comorbidities and other medications. Further medications that increased the risk of dry eye symptoms were antiglaucoma drugs, anticholinergics and antiepileptics.

This study found PPIs to be the most significant independent risk factor of dry eye symptoms of all commonly used medications. PPIs are frequently prescribed, with 8.3% of our study population reporting PPI use, amounting to a population attributable fraction of dry eye symptoms of 1.9%. In the same population as the current study, stomach ulcer was found to be highly associated with dry eye symptoms and dry eye diagnosis [18]. Similarly, a population-based study in Taiwan of over 48,000 participants found a significant association between stomach ulcer disease and a clinical diagnosis of DED [19]. In both of these studies effects of PPI use was not assessed. A population-based study of almost 2000 participants in Germany showed an association between drugs for peptic ulcer/gastro-oesophageal reflux disease and a reduced Schirmer test, however this study did not correct for comorbidities associated with dry eye in which PPIs may be used (e.g. in anti-inflammatory drug treatment for rheumatic diseases, which are highly associated with dry eye) [20]. A population-based study on oral and ocular dryness and medications by Smidt et al. [21] (n = 668) did not find an association between ocular dryness and PPIs. This may be due to the stricter dry eye definition, or the smaller study size.

Table 3
Association between dry eye symptoms and antidepressant use, after correction for age, sex, BMI, and 47 comorbidities associated with dry eye, in participants with a diagnosis of depression.

Antidepressant (ATC code)	Name	Number of users (n)	OR (95% CI) *	P-value
N06AA	Non-selective monoamine reuptake inhibitors	336	0.81 (0.63–1.03)	0.08
N06AB	Selective serotonin reuptake inhibitors	1673	0.87 (0.77–0.98)	0.02
N06AX	Other antidepressants	647	0.97 (0.81–1.15)	0.71
N06AB05	Paroxetine	675	0.84 (0.71–1.01)	0.06
N06AB04	Citalopram	484	0.83 (0.68–1.02)	0.07
N06AX16	Venlafaxine	367	0.97 (0.78–1.22)	0.82
N06AA09	Amitriptyline	208	0.93 (0.69–1.26)	0.65
N06AB03	Fluoxetine	190	1.01 (0.74–1.38)	0.97
N06AX11	Mirtazapine	177	0.93 (0.67–1.28)	0.65
N06AB10	Escitalopram	139	0.86 (0.59–1.24)	0.41
N06AB06	Sertraline	116	0.84 (0.56–1.26)	0.39
N06AA04	Clomipramine	74	0.65 (0.39–1.10)	0.11
N06AB08	Fluvoxamine	78	1.01 (0.63–1.63)	0.95
N06AX21	Duloxetine	73	0.92 (0.55–1.53)	0.75

ATC = anatomical therapeutic chemical, BMI = body mass index, CI = confidence interval.
47 comorbidities were included in this subgroup analysis as opposed to 48 in the main analysis as depression was not adjusted for given that this analysis only examined depressed participants.

Whilst the precise mechanism by which PPIs may predispose to dry eye is not known, long term PPI use has been shown to affect absorption of vitamin B12 [22]. This increases the risk of vitamin B12 deficiency [23], which has been associated with dry eye and other chronic pain disorders [18,24]. Chronic pain predisposition has been implicated in the aetiology of DED [25–27]. Indeed, in this study we found vitamin B12 (used to treat vitamin B12 deficiency) to be associated with dry eye symptoms. Otherwise, PPIs may predispose to dry eye through their effects on the gut microbiome [28], which maintains mucosal immune function outside of the gut [29]. The conjunctival microbiome may therefore be affected by these changes, thus predisposing to dry eye [30]. In addition, the gastro-intestinal medications isphagula and mebeverine were also associated with dry eye symptoms in this study (Table 2), and osmotically acting laxatives were associated with highly frequent dry eye symptoms. PPI use has also been associated with an increased risk of glaucoma, proposed to be caused by effects on the nitrate-nitrite-nitric oxide pathway due to higher stomach pH, again suggesting a role of the gut system in ocular health and disease [31]. Nitric oxide is present in the tear film and maintains ocular surface homeostatic functions [32]. Impairment of the nitrate-nitrite-nitric oxide pathway may result in functional dysregulation. Nitric oxide isomers have been implicated in the pathogenesis of DED in Sjögren's syndrome [33]. Our findings further add to the evidence of a possible important role of the gut system in the aetiology of dry eye, which was also previously reflected by several gastro-intestinal disorders being associated with dry eye in this cohort, such as Crohn's disease, IBS,

Table 4
Association between dry eye symptoms and antihypertensive use, after correction for age, sex, BMI, and 48 comorbidities associated with dry eye, including hypertension.

Antihypertensive (ATC code)	Name	Number of users (n)	OR (95% CI)*	P-value
C03A	Low-ceiling diuretics, thiazides	2514	0.93 (0.84–1.03)	0.14
C03C	High-ceiling diuretics	314	1.11 (0.86–1.43)	0.45
C03D	Potassium sparing agents	191	0.79 (0.55–1.11)	0.17
C03E	Diuretics and potassium-sparing agents in combination	185	1.19 (0.86–1.64)	0.29
C07A	Beta-blocking agents	4927	1.02 (0.94–1.90)	0.67
C07B	Beta blocking agents and thiazides	77	0.63 (0.36–1.12)	0.12
C08C	Selective calcium channel blockers with mainly vascular effects	1387	1.04 (0.91–1.18)	0.58
C08D	Selective calcium channel blockers with direct cardiac effects	412	1.01 (0.81–1.26)	0.93
C09A	ACE inhibitors, plain	2948	0.92 (0.83–1.01)	0.07
C09B	ACE inhibitors, combinations	353	0.91 (0.71–1.17)	0.48
C09C	Angiotensin II receptor blockers (ARBs), plain	2005	0.96 (0.86–1.07)	0.41
C09D	Angiotensin II receptor blockers (ARBs), combinations	648	0.97 (0.81–1.17)	0.77

ACE = Angiotensin-converting enzyme, ATC = anatomical therapeutic chemical, BMI = body mass index, CI = confidence interval.
* Corrected for age, sex, BMI and 48 comorbidities associated with dry eye including hypertension.

eating disorder, lactose intolerance and gallstones [18]. Future studies on the association between dry eye and PPIs may also with to explore other possible confounding factors such as functional dyspepsia, for which PPIs may be used [34].

This study confirmed well known associations between anti-glaucoma drugs and anticholinergics with dry eye symptoms [10]. Previous studies have shown greater dry eye signs in people on topical anti-glaucomatous treatment [9,20], and concurrent use of multiple drops is associated with significantly higher symptom scores and prevalence of dry eye signs than use of single pressure lowering agents [7,35]. Non-preservative-free drops are associated with significantly more ocular symptoms compared with preservative-free drops [8,36–39], with patients using benzalkonium chloride having greater clinical signs of dry eye [8,9,40].

Anticholinergics decrease aqueous and mucous secretions by affecting lacrimal gland and conjunctival goblet cell receptors [10]. At every ATC level we found anticholinergic medications associated with dry eye symptoms; at the 3rd level ATC drugs for functional gastrointestinal disorders, at 4th level ATC synthetic anticholinergics and drugs for urinary frequency, and at the 5th level ATC mebeverine.

Antidepressant use has been linked to dry eye in many studies [3–6,41–44]. Whilst some of the first-generation tricyclic antidepressants have anticholinergic activity, many newer antidepressants have limited or no anticholinergic activity [45,46]. The TFOS DEWS II Epidemiology Report concluded that future studies should investigate whether depression itself or antidepressants are risk factors for dry eye [1]. We did not find any antidepressant to be associated with dry eye symptoms in the general population when correcting for comorbidities including depression and several other psychiatric disorders, nor in a subgroup analysis in patients with a clinical diagnosis of depression. In a cross-sectional study (n = 190) Işik-Ulusoy et al. found that depressed patients treated with antidepressants had higher ocular surface disease index (OSDI) scores and more severe dry eye signs than healthy controls [44]. However, no participants with depression not receiving anti-depressant treatment were included in the study. Many previous studies did not adjust for depression in their analyses, so the association between anti-depressants and dry eye seen could be due to the association between depression and dry eye, and not the medication itself. Depression has been shown to be significantly associated with dry eye symptoms [1,19,25,47], but not clinical signs of DED [47]. A population-based study did not find any association between Schirmer test and antidepressants [20]. Depression can affect pain experience, with depressed persons reporting more frequent and severe pain than non-depressed people, and having a poorer response to pain treatment [48]. There may also be a neuropathic pain component to DED [49], which often coexists with neuropathic pain disorders [50]. This may also explain the association seen between dry eye symptoms and the 'other antiepileptics' group in our study, as 'other antiepileptics' includes medications such as gabapentin and pregabalin, which are commonly used to treat neuropathic pain and to a lesser degree, but increasingly, for neuropathic DED as well [51]. In addition, 'other antidepressants' were associated with highly symptomatic dry eye, possibly due to the presence of medications used in chronic pain disorders, such as duloxetine [52].

Whereas previous studies - not adjusting for underlying comorbidities-have found several antihypertensive medications to be associated with dry eye [3,5,41], our study did not find any significant association with antihypertensives after correction for comorbidities including hypotension, hypertension, arrhythmia, and atherosclerosis. With correction for *age and sex only*, we found beta blocking agents to be modestly associated with dry eye symptoms (OR 1.10, P = 0.004), indicating the importance of correction for underlying disorders as well. Of note, *self-reported* hypertension has been found to be associated with dry eye in several studies [19,41,53]. However, *measured* hypertension and higher blood pressure were found to be a highly significant protective factor for dry eye in the current population, showing the importance of true measurement versus self-reported outcomes in these studies too [18]. In our main analysis (Table 2), there was a trend of low-ceiling diuretics to be associated with a mildly protective effect. Looking at Table 4, however, no large differences in odds ratios of dry eye symptoms are found between the different antihypertensives. This suggests that antihypertensives do not play an important role in causing dry eye symptoms.

The psychostimulant methylphenidate was borderline significantly associated with highly frequent dry eye symptoms in the sensitivity analysis (p = 0.048) and was almost significantly associated in the main analysis (p = 0.06). In population-based studies psychoanaleptics including methylphenidate have been reported to be associated with ocular and oral dryness [21] and lower salivary flow rates [54]. Further studies are warranted to explore the biological basis of this association.

This study has several limitations. First, because of the cross-sectional assessment of dry eye symptoms and medication use it is impossible to imply causation. Second, because several medications are used to treat disorders that have also been associated with DED, it is difficult to clearly segregate the risk of dry eye of the medication and the disorder associated. However, the availability of data on comorbid disorders allowed for the correction for these disorders, taking away confounding effects at least partially. Third, the median 3.8 year time lag between assessment of medication use and assessment of dry eye symptoms might have potentially led to decreased power to find a true association between risk factor and outcome, because some of the patients might have stopped the medication at the time of dry eye

assessment. True odds ratios might therefore be stronger if medication and dry eye symptoms would have been assessed at the same time. However, to have a certain amount of time between exposure and outcome is an advantage because exposure to a possible risk factor (i.e. medication) will not immediately lead to a resulting outcome (i.e. dry eye symptoms). Fourth, the WHS questionnaire assesses only frequency of dry eye symptoms. Use of an alternative questionnaire such as the Symptom Assessment in Dry Eye Questionnaire, Dry Eye Questionnaire −5 or OSDI would have provided more information on presence, frequency and severity of other dry eye symptoms [1]. The strengths of this study are the unprecedented sample size, the systematic registration and classification of all used medications into the ATC-classification system, and the hypothesis-free approach used.

In conclusion, this hypothesis-free study described a new, highly significant association between dry eye symptoms and PPIs, a commonly prescribed medication all over the world. Future longitudinal studies are warranted to further clarify this relationship and to investigate whether stopping or reducing the dose of PPIs could help in relieving dry eye symptoms. This study also found medication classes previously thought to be linked to dry eye, such as antidepressants and antihypertensives, were not associated with dry eye symptoms after adjustment for underlying comorbidities. We also confirmed previously suggested associations of certain medications with dry eye symptoms, such as anticholinergic and anti-glaucoma medications. Lastly, our study showed that medication use is highly informative of the risk of dry eye symptoms, either independently associated or reflecting underlying disorders that can cause dry eye. Therefore, medication use should always be assessed in every dry eye patient.

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Declaration of competing interest

Laura Wolpert, Nomdo Jansonius, Harold Snieder and Chris Hammond declare no conflicts of interest.

Although not considered to be a conflict of interest in the present work, Tor Paaske Utheim would for the sake of transparency state that he is co-founder and co-owner of the Norwegian Dry Eye Clinic, which has received financial support from several companies as specified on the webpage. Moreover, he has served as a Consultant on Alcon and Novartis Global Scientific Advisory Board as well as Takeda/Shire European Scientific Advisory Board. In addition, Utheim is the Norwegian Global Ambassador of the Tear Film and Ocular Surface Society and Member of Board of Directors of The International Ocular Surface Society.

Although not considered to be a conflict of interest in the present work, Jelle Vehof would for the sake of transparency state that he served as a Consultant for Santen. In addition, Vehof is the Dutch Global Ambassador of the Tear Film and Ocular Surface Society (TFOS).

Appendix

Appendix Table A
Associations between dry eye symptoms and medication groups (ATC 3rd level), corrected for age and sex only

ATC-code	Name	Used in treatment of dry eye or causally related disorders?	n	Odds ratio (95% CI)	P-value
S01X	Other ophthalmologicals	Yes, treatment of dry eye	552	14.77 (11.50–18.96)	<0.001*
S01G	Decongestants and antiallergics	Yes, treatment of allergy/allergic conjunctivitis	396	2.44 (2.00–2.98)	<0.001*
S01E	Antiglaucoma preparations and miotics	No	427	2.40 (1.97–2.91)	<0.001*
A06A	Drugs for constipation	No	1805	1.53 (1.39–1.69)	<0.001*
A02B	Drugs for peptic ulcer and GORD	No	6944	1.53 (1.45–1.62)	<0.001*
R06A	Antihistamines for systemic use	Yes, treatment of allergy/allergic conjunctivitis	3453	1.51 (1.41–1.62)	<0.001*
R01A	Decongestants and other nasal preparations for topical use	Yes, treatment of allergy/allergic conjunctivitis	3286	1.44 (1.34–1.55)	<0.001*
R03A	Adrenergic inhalants	Yes, treatment of allergy/allergic conjunctivitis	4480	1.33 (1.25–1.42)	<0.001*
H03A	Thyroid preparations	No	2583	1.36 (1.25–1.47)	<0.001*
M01A	Anti-inflammatory and antirheumatic products non-steroids	Yes, treatment for pain symptoms	3408	1.30 (1.21–1.40)	<0.001*
N06A	Antidepressants	No	4115	1.26 (1.18–1.35)	<0.001*
A03A	Drugs for functional gastrointestinal disorders	No	249	2.23 (1.73–2.87)	<0.001*
N05B	Anxiolytics	No	1394	1.39 (1.25–1.56)	<0.001*
N02B	Other analgesics and antipyretics	Yes, treatment for pain symptoms	726	1.55 (1.33–1.80)	<0.001*
B03B	Vitamin B12 and folic acid	No	1005	1.43 (1.26–1.63)	<0.001*
N05C	Hypnotics and sedatives	No	1174	1.39 (1.23–1.57)	<0.001*
A12A	Calcium	No	1083	1.35 (1.19–1.53)	<0.001*
N06B	Psychostimulant agents used for ADHD and nootropics	No	260	1.74 (1.35–2.23)	<0.001*
R03B	Other drugs for obstructive airway diseases inhalants	Yes, treatment of allergy/allergic conjunctivitis	2119	1.22 (1.11–1.33)	<0.001*
D07A	Corticosteroids plain	Yes, treatment of allergy/allergic conjunctivitis	1909	1.21 (1.10–1.33)	<0.001*
N02A	Opioids	Yes, treatment for pain symptoms	645	1.37 (1.16–1.61)	<0.001*
D02A	Emollients and protectives	Yes, treatment of allergy/allergic conjunctivitis	413	1.44 (1.18–1.76)	<0.001*
A02A	Antacids	No	238	1.57 (1.21–2.03)	<0.001*
G04B	Urologicals	No	258	1.53 (1.19–1.97)	0.001*
B01A	Antithrombotic agents	No	3390	1.13 (1.04–1.22)	0.002*
C07A	Beta blocking agents	No	4923	1.10 (1.03–1.17)	0.004*
H02A	Corticosteroids for systemic use plain	Yes, treatment for autoimmune disorders	383	1.36 (1.10–1.68)	0.005*
A03F	Propulsives	No	240	1.45 (1.12–1.88)	0.005*
M05B	Drugs affecting bone structure and mineralization	No	695	1.26 (1.07–1.47)	0.005*
N03A	Antiepileptics	No	785	1.24 (1.07–1.44)	0.005*
R03D	Other systemic drugs for obstructive airway diseases	Yes, treatment of allergy/allergic conjunctivitis	305	1.39 (1.10–1.76)	0.006*
D01A	Antifungals for topical use	No	437	1.29 (1.06–1.58)	0.012*
L04A	Immunosuppressants	Yes, treatment for autoimmune disorders	494	1.26 (1.05–1.52)	0.015*
C01D	Vasodilators used in cardiac diseases	No	273	1.36 (1.05–1.76)	0.021*

(*continued on next page*)

Appendix Table A (*continued*)

ATC-code	Name	Used in treatment of dry eye or causally related disorders?	n	Odds ratio (95% CI)	P-value
G03H	Antiandrogens	No	466	1.25 (1.03–1.50)	0.022*
G03C	Estrogens	No	433	1.24 (1.02–1.50)	0.030*
C10A	Lipid modifying agents plain	No	5424	1.07 (1.00–1.14)	0.046
C03C	High-ceiling diuretics	No	320	1.26 (1.00–1.60)	0.049
G04C	Drugs used in benign prostatic hypertrophy	No	647	1.19 (1.00–1.43)	0.06
N05A	Antipsychotics	No	433	1.21 (0.99–1.48)	0.06
C08D	Selective calcium channel blockers with direct cardiac effects	No	412	1.22 (0.99–1.51)	0.06
C03A	Low ceiling- diuretics thiazides	No	2509	0.92 (0.84–1.01)	0.08
N07C	Antivertigo preparations	No	297	1.23 (0.97–1.57)	0.09
B03A	Iron preparations	No	365	1.20 (0.97–1.49)	0.09
A10B	Blood glucose lowering drugs excluding insulin	No	1272	1.11 (0.98–1.25)	0.10
A10A	Insulins and analogues	No	445	1.17 (0.96–1.44)	0.12
J01C	Beta-lactam antibacterials penicillins	No	213	1.25 (0.94–1.66)	0.13
G03A	Hormonal contraceptives for systemic used	No	6824	0.96 (0.91–1.02)	0.19
C09A	ACE inhibitors plain	No	2948	0.94 (0.87–1.03)	0.19
A07E	Intestinal anti-inflammatory agents	No	405	1.13 (0.92–1.40)	0.24
C09C	Angiotensin II antagonists plain	No	2005	1.04 (0.94–1.15)	0.41
C08C	Selective calcium channel blockers with mainly vascular effects	No	1384	1.05 (0.93–1.18)	0.43
M04A	Anti-gout preparations	No	243	1.11 (0.83–1.49)	0.47
G02B	Contraceptives for topical use	No	2549	0.97 (0.89–1.06)	0.50
N02C	Anti-migraine preparations	No	1656	1.04 (0.93–1.15)	0.50
C09B	ACE inhibitors combinations	No	353	0.93 (0.74–1.18)	0.57
C09D	Angiotensin II antagonists combinations	No	648	1.03 (0.86–1.22)	0.77
C01B	Antiarrhythmics class I and II	No	230	0.97 (0.72–1.30)	0.82
D07X	Corticosteroids other combinations	Yes, treatment of allergy/allergic conjunctivitis	210	1.03 (0.76–1.39)	0.85

ATC = anatomical therapeutic chemical, ACE = angiotensin converting enzyme, ADHD = attention deficit hyperactivity disorder, CI = confidence interval, GORD = gastro-oesophageal reflux disease.
*Significant after correction for multiple testing (FDR corrected).

Appendix Table B
Associations between dry eye symptoms and medication groups (ATC 4th level), corrected for age and sex only

ATC-code	Name	Used in treatment of dry eye or causally related disorders?	n	Odds ratio (95% CI)	P-value
S01XA	Other ophthalmologicals	Yes, treatment of dry eye	552	14.77 (11.50–18.96)	<0.001*
A02BCE	Proton pump inhibitors	No	6571	1.54 (1.46–1.63)	<0.001*
R01AD	Corticosteroids	Yes, treatment of allergy/allergic conjunctivitis	3091	1.42 (1.32–1.53)	<0.001*
R06AX	Other antihistamines for systemic use	Yes, treatment of allergy/allergic conjunctivitis	1967	1.54 (1.41–1.69)	<0.001*
S01GX	Other antiallergics	Yes, treatment of allergy/allergic conjunctivitis	381	2.47 (2.02–3.03)	<0.001*
H03AA	Thyroid hormones	No	2583	1.36 (1.25–1.47)	<0.001*
R03AC	Selective beta-2-adrenoreceptor agonists	Yes, treatment of allergy/allergic conjunctivitis	2547	1.36 (1.25–1.48)	<0.001*
R03AK	Adrenergics in combination with corticosteroids or other drugs, excl. anticholinergics	Yes, treatment of allergy/allergic conjunctivitis	2656	1.34 (1.24–1.45)	<0.001*
R06AE	Piperazine derivatives	Yes, treatment of allergy/allergic conjunctivitis	1386	1.44 (1.29–1.61)	<0.001*
S01ED	Beta blocking agents	No	218	2.44 (1.86–3.20)	<0.001*
A06AD	Osmotically acting laxatives	No	1128	1.48 (1.31–1.67)	<0.001*
A06AC	Bulk forming laxatives	No	718	1.63 (1.40–1.89)	<0.001*
A03AA	Synthetic anticholinergics, esters with tertiary amino group	No	246	2.25 (1.75–2.90)	<0.001*
S01EE	Prostaglandin analogues	No	236	2.18 (1.68–2.83)	<0.001*
N05BA	Benzodiazepine derivatives	No	1365	1.38 (1.24–1.54)	<0.001*
N02BE	Anilides	Yes, treatment for pain symptoms	552	1.64 (1.38–1.94)	<0.001*
N06AX	Other antidepressants	No	887	1.41 (1.23–1.62)	<0.001*
M01AE	Propionic acid derivatives	Yes, treatment for pain symptoms	1221	1.33 (1.18–1.49)	<0.001*
R03BA	Glucocorticoids	Yes, treatment of allergy/allergic conjunctivitis	1689	1.26 (1.14–1.39)	<0.001*
M01AB	Acetic acid derivatives and related substances	Yes, treatment for pain symptoms	1650	1.26 (1.13–1.39)	<0.001*
G04BD	Drugs for urinary frequency and incontinence	No	209	1.84 (1.40–2.43)	<0.001*
B03BA	Vitamin B12 (cyanocobalamin and analogues)	No	500	1.48 (1.23–1.77)	<0.001*
N06BA	Centrally acting sympathomimetics	No	259	1.72 (1.34–2.22)	<0.001*
N06AB	Selective serotonin reuptake inhibitors	No	2438	1.20 (1.10–1.31)	<0.001*
N03AX	Other antiepileptics	No	321	1.61 (1.28–2.01)	<0.001*
N05CD	Benzodiazepine derivatives	No	714	1.34 (1.15–1.57)	<0.001*
B03BB	Folic acid and derivatives	No	542	1.37 (1.15–1.63)	<0.001*
N06AA	Non-selective monoamine reuptake inhibitors	No	864	1.27 (1.11–1.46)	<0.001*
N02AA	Natural opium alkaloids	Yes, treatment for pain symptoms	330	1.45 (1.16–1.82)	0.001*
N05CF	Benzodiazepine related drugs	No	301	1.47 (1.16–1.85)	0.001*
B01AC	Platelet aggregation inhibitors excl. heparin	No	2704	1.15 (1.05–1.26)	0.002*
C07AA	Beta blocking agents, non-selective	No	543	1.32 (1.11–1.58)	0.002*
M01AC	Oxicams	Yes, treatment for pain symptoms	260	1.46 (1.14–1.88)	0.003*
A03FA	Propulsives	No	240	1.45 (1.12–1.88)	0.005*
H02AB	Glucocorticoids	Yes, treatment for autoimmune disorders	382	1.35 (1.09–1.67)	0.006*

(*continued on next page*)

Appendix Table B (*continued*)

ATC-code	Name	Used in treatment of dry eye or causally related disorders?	n	Odds ratio (95% CI)	P-value
M05BA	Bisphonsphonates	No	616	1.26 (1.07–1.49)	0.007*
D07AC	Corticosteroids, potent (group III)	Yes, treatment of allergy/allergic conjunctivitis	652	1.25 (1.06–1.48)	0.008*
R03DC	Leukotriene receptor analogues	Yes, treatment of allergy/allergic conjunctivitis	291	1.39 (1.09–1.76)	0.008*
D07AA	Corticosteroids, weak (group I)	Yes, treatment of allergy/allergic conjunctivitis	251	1.38 (1.06–1.78)	0.015*
D01AC	Imidazole and triazole derivatives	No	373	1.30 (1.05–1.62)	0.017*
N02AX	Other opioids	Yes, treatment for pain symptoms	325	1.32 (1.05–1.65)	0.018*
G03HB	Antiandrogens and oestrogens	No	449	1.25 (1.04–1.52)	0.020*
C01DA	Organic nitrates	No	273	1.36 (1.05–1.76)	0.021*
G03CA	Natural and semisynthetic oestrogens, plain	No	348	1.29 (1.04–1.59)	0.022*
D07AB	Corticosteroids, moderately potent (group II)	Yes, treatment for autoimmune disorders	744	1.20 (1.02–1.40)	0.023*
A12AA	Calcium	No	476	1.21 (1.00–1.46)	0.046
C07AB	Beta blocking agents, selective	No	4327	1.07 (1.00–1.15)	0.048
C03CA	Sulfonamides, plain	No	320	1.26 (1.00–1.60)	0.049
C10AX	Other lipid modifying agents	No	316	1.27 (1.00–1.60)	0.05
C03AA	Thiazides, plain	No	2509	0.92 (0.84–1.01)	0.08
G04CA	Alpha-adrenoreceptor antagonists	No	554	1.19 (0.98–1.45)	0.08
G03AB	Progestogens and oestrogens, sequential preparations	No	546	0.85 (0.71–1.02)	0.08
N07CA	Antivertigo preparations	No	297	1.23 (0.97–1.57)	0.09
B03AA	Iron bivalent, oral preparations	No	346	1.21 (0.97–1.50)	0.09
A02BA	H2-receptor antagonists	No	376	1.19 (0.96–1.48)	0.12
C10AA	HMG CoA reductase inhibitors	No	5221	1.05 (0.99–1.12)	0.12
A10BA	Biguanides	No	1169	1.11 (0.97–1.26)	0.12
L04AX	Other immunosuppressants	Yes, treatment for autoimmune disorders	340	1.19 (0.95–1.49)	0.14
C09AA	ACE inhibitors, plain	No	2984	0.94 (0.87–1.03)	0.19
R03BB	Anticholinergics	Yes, treatment of allergy/allergic conjunctivitis	532	1.13 (0.94–1.36)	0.20
A07EC	Aminosalicylic acid and similar agents	No	348	1.15 (0.91–1.44)	0.24
C08DA	Phenylalkylamine derivatives	No	243	1.17 (0.89–1.53)	0.26
A10BB	Sulfonylureas	No	384	0.88 (0.70–1.12)	0.30
A10AB	Insulins and analogues for injection, fast acting	No	315	1.13 (0.89–1.44)	0.31
N05AH	Diazepines, oxazepines, thiazepines and oxepines	No	250	1.13 (0.87–1.47)	0.37
G02BA	Intrauterine contraceptives	No	2374	0.96 (0.88–1.05)	0.39
C09CA	Angiotensin II antagonists, plain	No	2005	1.04 (0.94–1.15)	0.41
A10AE	Insulins and analogues for injection, long acting	No	257	1.12 (0.85–1.46)	0.42
C08CA	Dihydropyridine derivatives	No	1384	1.05 (0.93–1.18)	0.43
B01AA	Vitamin K antagonists	No	691	1.07 (0.90–1.26)	0.45
N02CC	Selective serotonin (5HT1) agonists	No	1545	1.04 (0.93–1.15)	0.51
C09DA	Angiotensin II antagonists and diuretics	No	623	1.06 (0.89–1.26)	0.54
G03AA	Progestogens and estrogens, fixed combinations	No	5906	0.98 (0.98–1.04)	0.54
G03AC	Progestogens	No	350	0.95 (0.76–1.19)	0.67
C09BA	ACE inhibitors and diuretics	No	345	0.95 (0.75–1.21)	0.68
D07AD	Corticosteroids, very potent (group IV)	Yes, treatment of allergy/allergic conjunctivitis	442	1.00 (0.82–1.23)	0.96

ATC = anatomical therapeutic chemical, ACE = angiotensin converting enzyme, CI = confidence interval, HMG-CoA = hydroxymethylglutaryl-CoA, H2 = histamine-2.
*Significant after correction for multiple testing (FDR corrected).

Appendix Table C
Associations between dry eye symptoms and individual medications (ATC 5th level), corrected for age and sex only*

ATC7	Name	Used in treatment of dry eye or causally related disorders?	n	Odds ratio (95% CI)	P-value
S01XA20	Artificial tears and other indifferent preparations	Yes, treatment of dry eye	550	15.18 (11.79–19.55)	<0.001*
A02BC01	Omeprazole	No	4532	1.49 (1.40–1.59)	<0.001*
R06AX27	Desloratadine	Yes, treatment of allergy/allergic conjunctivitis	1369	1.56 (1.40–1.74)	<0.001*
H03AA01	Levothyroxine sodium	No	2569	1.35 (1.24–1.46)	<0.001*
R03AC02	Salbutamol	Yes, treatment of allergy/allergic conjunctivitis	2109	1.38 (1.26–1.51)	<0.001*
A02BC02	Pantoprazole	No	1113	1.54 (1.36–1.74)	<0.001*
A06AC01	Ispaghula (psyllaseeds)	No	685	1.68 (1.44–1.96)	<0.001*
A03AA04	Mebeverine	No	246	2.25 (1.75–2.90)	<0.001*
R03AK07	Formoterol and budesonide	Yes, treatment of allergy/allergic conjunctivitis	1437	1.39 (1.25–1.55)	<0.001*
A06AD65	Macrogol combinations	No	864	1.50 (1.31–1.72)	<0.001*
R01AD09	Mometasone	Yes, treatment of allergy/allergic conjunctivitis	779	1.53 (1.32–1.77)	<0.001*
S01GX02	Levocabastine	Yes, treatment of allergy/allergic conjunctivitis	213	2.19 (1.67–2.88)	<0.001*
R06AE09	Levocetirizine	Yes, treatment of allergy/allergic conjunctivitis	1032	1.44 (1.26–1.63)	<0.001*
R01AD08	Fluticasone	Yes, treatment of allergy/allergic conjunctivitis	1186	1.38 (1.22–1.56)	<0.001*
A02BC05	Esomeprazole	No	749	1.47 (1.27–1.71)	<0.001*
N02BE01	Paracetamol	Yes, treatment for pain symptoms	454	1.54 (1.28–1.87)	<0.001*
N06AA09	Amitriptyline	No	675	1.41 (1.21–1.65)	<0.001*
M01AE02	Naproxen	Yes, treatment for pain symptoms	605	1.43 (1.21–1.69)	<0.001*
N05BA04	Oxazepam	No	758	1.38 (1.19–1.60)	<0.001*
N06BA04	Methylphenidate	No	219	1.79 (1.36–2.35)	<0.001*
B03BA03	Hydroxocobalamin	No	453	1.47 (1.22–1.77)	<0.001*
R01AD05	Budesonide	Yes, treatment of allergy/allergic conjunctivitis	386	1.52 (1.24–1.87)	<0.001*
M01AB05	Diclofenac	Yes, treatment for pain symptoms	1441	1.25 (1.12–1.40)	<0.001*
R03AK06	Salmeterol and fluticasone	Yes, treatment for pain symptoms	1216	1.25 (1.11–1.42)	<0.001*
B01AC08	Carbasalate calcium	No	1363	1.25 (1.11–1.41)	<0.001*

(*continued on next page*)

Appendix Table C (*continued*)

ATC7	Name	Used in treatment of dry eye or causally related disorders?	n	Odds ratio (95% CI)	P-value
R03BA05	Fluticasone	Yes, treatment of allergy/allergic conjunctivitis	574	1.37 (1.16–1.63)	<0.001*
B03BB01	Folic acid	No	539	1.37 (1.15–1.64)	0.001*
R03BA08	Ciclesonide	Yes, treatment of allergy/allergic conjunctivitis	292	1.50 (1.18–1.90)	0.001*
N02AA59	Codeine combinations excl. psycholeptics	Yes, treatment for pain symptoms	252	1.54 (1.19–1.98)	0.001*
R06AE07	Cetirizine	Yes, treatment of allergy/allergic conjunctivitis	352	1.45 (1.16–1.80)	0.001*
R06AX26	Fexofenadine	Yes, treatment of allergy/allergic conjunctivitis	270	1.51 (1.18–1.93)	0.001*
M01AC06	Meloxicam	Yes, treatment for pain symptoms	235	1.54 (1.18–2.00)	0.001*
N06AX16	Venlafaxine	No	497	1.33 (1.11–1.60)	0.002*
M05BA07	Risedronic acid	No	219	1.49 (1.13–1.96)	0.004*
D01AC08	Ketoconazole	No	230	1.48 (1.13–1.95)	0.005*
R03AC13	Formoterol	Yes, treatment of allergy/allergic conjunctivitis	206	1.50 (1.13–1.99)	0.005*
C07AB07	Bisoprolol	No	844	1.24 (1.07–1.43)	0.005*
N06AB04	Citalopram	No	682	1.25 (1.06–1.46)	0.007*
C07AA05	Propranolol	No	346	1.35 (1.09–1.69)	0.007*
C10AA07	Rosuvastatin	No	831	1.22 (1.05–1.42)	0.008*
N05BA01	Diazepam	No	399	1.30 (1.06–1.60)	0.012*
R01AD12	Fluticasone furoate	Yes, treatment of allergy/allergic conjunctivitis	388	1.30 (1.06–1.61)	0.013*
G03AA09	Desogestrel and ethinylestradiol	No	522	0.79 (0.66–0.96)	0.015*
N06AB03	Fluoxetine	No	240	1.38 (1.06–1.79)	0.015*
D07AA02	Hydrocortisone	Yes, treatment of allergy/allergic conjunctivitis	246	1.37 (1.06–1.78)	0.017*
G03HB01	Cyproterone and oestrogen	No	449	1.25 (1.04–1.52)	0.020*
M01AE01	Ibuprofen	Yes, treatment for pain symptoms	613	1.22 (1.03–1.44)	0.021*
N07CA01	Betahistine	No	237	1.36 (1.04–1.77)	0.024*
L04AX03	Methotrexate	Yes, treatment for autoimmune disorders	228	1.36 (1.03–1.78)	0.028*
A12AA04	Calcium carbonate	No	405	1.25 (1.02–1.53)	0.032*
R01AD01	Beclometasone	Yes, treatment for autoimmune disorders	326	1.26 (1.01–1.59)	0.045
N05CD07	Temazepam	No	507	1.20 (1.00–1.45)	0.047
C09CA06	Candesartan	No	431	1.21 (0.99–1.48)	0.067
C03AA03	Hydrochlorothiazide	No	2507	0.92 (0.84–1.01)	0.08
N02AX02	Tramadol	Yes, treatment for pain symptoms	255	1.26 (0.97–1.63)	0.081
N06AX11	Mirtazapine	No	244	1.26 (0.97–1.64)	0.085
B03AA02	Ferrous fumarate	No	237	1.26 (0.97–1.64)	0.087
D07AB09	Triamcinolone	yes, treatment for autoimmune disorders	585	1.16 (0.97–1.38)	0.11
G03AB03	Levonorgestrel and ethinylestradiol	No	509	0.86 (0.71–1.03)	0.11
A10BA02	Metformin	No	1169	1.11 (0.97–1.26)	0.12
C08CA01	Amlodipine	No	892	1.12 (0.97–1.30)	0.12
A02BA02	Ranitidine	No	348	1.19 (0.95–1.49)	0.13
C09CA01	Losartan	No	623	1.14 (0.96–1.35)	0.13
N06AB05	Paroxetine	No	1068	1.10 (0.96–1.25)	0.16
R03BA01	Beclometasone	Yes, treatment of allergy/allergic conjunctivitis	362	1.17 (0.94–1.45)	0.17
G03AA12	Drospirenone and ethinylestradiol	No	394	1.16 (0.94–1.42)	0.17
C03CA01	Furosemide	No	247	1.20 (0.92–1.57)	0.18
M05BA04	Alendronic acid	No	359	1.16 (0.93–1.45)	0.18
H02AB06	Prednisolone	Yes, treatment for autoimmune disorders	221	1.21 (0.91–1.61)	0.19
C08DA01	Verapamil	No	241	1.19 (0.90–1.56)	0.22
C09AA02	Enalapril	No	1159	0.93 (0.81–1.06)	0.26
G02BA03	Plastic IUD with progestogen	No	2313	0.95 (0.87–1.04)	0.27
C09CA04	Irbesartan	No	496	0.90 (0.73–1.10)	0.30
N03AG01	Valproic acid	No	197	0.85 (0.61–1.17)	0.31
G04CA02	Tamsulosin	No	385	1.13 (0.89–1.43)	0.31
G03AC06	Medroxyprogesterone	No	201	1.15 (0.87–1.53)	0.33
C10AA05	Atorvastatin	No	1101	1.06 (0.93–1.21)	0.38
N02CC04	Rizatriptan	No	436	0.92 (0.75–1.12)	0.40
C09AA03	Lisinopril	No	528	0.92 (0.76–1.12)	0.41
C09AA05	Ramipril	No	242	0.89 (0.66–1.19)	0.42
B01AA07	Acenocoumarol	No	602	1.06 (0.89–1.27)	0.52
C07AB02	Metoprolol	No	2815	1.03 (0.94–1.12)	0.53
C09CA03	Valsartan	No	236	1.09 (0.82–1.44)	0.55
R03BA02	Budesonide	Yes, treatment of allergy/allergic conjunctivitis	479	1.06 (0.87–1.29)	0.56
B01AC06	Acetylsalicylic acid	No	1199	1.03 (0.90–1.17)	0.65
D07AC01	Betamethasone	Yes, treatment of allergy/allergic conjunctivitis	259	1.06 (0.81–1.39)	0.66
C10AA03	Pravastatin	No	317	1.05 (0.82–1.35)	0.67
C09DA04	Irbesartan and diuretics	No	243	1.05 (0.80–1.39)	0.73
N02CC01	Sumatriptan	No	851	1.02 (0.89–1.18)	0.74
C08CA05	Nifedipine	No	323	0.96 (0.75–1.23)	0.77
G03AA07	Levonorgestrel and ethinylestradiol	No	4606	1.01 (0.94–1.08)	0.81
C09AA04	Perindopril	No	863	1.02 (0.88–1.19)	0.81
A10AB05	Insulin aspart	No	201	1.04 (0.76–1.41)	0.82
R03BB04	Tiotropium bromide	Yes, treatment of allergy/allergic conjunctivitis	382	1.02 (0.82–1.28)	0.83
A07EC02	Mesalazine	No	277	1.02 (0.79–1.32)	0.88
D07AD01	Clobetasol	Yes, treatment of allergy/allergic conjunctivitis	439	1.01 (0.83–1.24)	0.90
C07AB03	Atenolol	No	500	1.01 (0.83–1.22)	0.92
C10AA01	Simvastatin	No	2946	1.00 (0.92–1.08)	0.92
B01AC07	Dipyridamole	No	238	1.01 (0.76–1.34)	0.97

ATC = anatomical therapeutic chemical, CI = confidence interval, IUD = intrauterine device.
*Significant after correction for multiple testing (FDR corrected).

Appendix Table D
Independent associations between dry eye symptoms (highly frequent symptoms) and medication use (ATC 3rd, 4th and 5th level), corrected for age, sex, BMI and 48 comorbidities associated with dry eye, using forward stepwise regression models

ATC code	Name	Odds ratio (95% CI)*	P-value
ATC 3rd level			
A02B	Drugs for peptic ulcer and GORD	1.33 (1.19–1.49)	<0.001
S01E	Antiglaucoma preparations and miotics	1.80 (1.26–2.59)	0.001
B03B	Vitamin B12 and folic acid	1.43 (1.11–1.84)	0.006
A06A	Drugs for constipation	1.28 (1.08–1.55)	0.006
N03A	Antiepileptics	1.38 (1.04–1.83)	0.03
ATC 4th level			
A02BC	Proton pump inhibitors	1.35 (1.20–1.51)	<0.001
B03BA	Vitamin B12	1.76 (1.28–2.42)	<0.001
S01EE	Prostaglandin analogues	1.96 (1.27–3.02)	0.002
N03AX	Other antiepileptics	1.69 (1.12–2.54)	0.01
A06AD	Osmotically acting laxatives	1.35 (1.20–1.51)	0.01
N06AX	Other antidepressants	1.34 (1.05–1.71)	0.02
ATC 5th level			
A02BC01	Omeprazole	1.35 (1.19–1.54)	<0.001
B03BA03	Hydroxocobalamin	1.87 (1.35–2.59)	<0.001
B01AC08	Carbasalate calcium	1.46 (1.15–1.85)	0.002
A06AD65	Macrogol	1.47 (1.16–1.87)	0.003
A02BC02	Pantoprazole	1.28 (1.01–1.64)	0.046
N06BA04	Methylphenidate	1.69 (1.01–2.85)	0.048

GORD = gastro-oesophageal reflux disease.

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