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The physical and mental burden of dry eye disease: A large population-based study investigating the relationship with health-related quality of life and its determinants

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ABSTRACT

Purpose: This large cross-sectional population-based study investigated the relationship between dry eye disease (DED) and health-related quality of life (HR-QoL).
Methods: Dry eye and HR-QoL were assessed in 78,165 participants (19–94 yrs, 59.2% female) from the Dutch population-based Lifelines cohort, using the WHS and the SF36 questionnaire, respectively. Logistic regression was used to assess the relationship between DED and below median Physical Component Summary (PCS) and Mental Component Summary (MCS) score, corrected for age, sex, education, BMI, and 52 comorbidities.
Results: Overall, 8.9% of participants had DED. Participants with DED had an increased risk of low PCS (OR 1.54 (95% CI 1.46–1.62)) and MCS scores (OR 1.39 (95% CI 1.32–1.46)), corrected for age and sex. This risk remained significant after correction for comorbidities ($P < 0.0005$). Increasing DED symptom frequency was associated with decreasing HR-QoL ($P < 0.0005$). Undiagnosed DED subjects had a significantly increased risk of low mental HR-QoL with increasing dry eye symptoms compared to diagnosed subjects ($P < 0.0005$). Compared to allergic conjunctivitis, glaucoma, macular degeneration and retinal detachment, DED showed the highest risk of low HR-QoL. Compared to other common systemic and chronic disorders, such as depression, rheumatoid arthritis, and COPD, DED was distinctive by having a substantial reduction in both PCS and MCS.
Conclusion: DED is associated with substantial reductions in both physical and mental HR-QoL, also after correction for associated comorbidities. Not having a diagnosis is associated with worse mental HR-QoL in subjects with severe DED. Our results underline the importance of recognizing dry eye as a serious disorder.

1. Introduction

Dry eye disease (DED) is a multifactorial disease that affects the ocular surface and tear film [1]. DED is a common condition worldwide, with prevalence estimates ranging from 5 to 50%, depending on the definition used and population studied [1]. Patients report symptoms such as dryness, itching, grittiness, pain, light sensitivity, and blurry vision that can have a severe impact on patients' lives [1]. Furthermore, DED is associated with substantial direct and indirect costs, making DED an important public health problem [1]. Health-related quality of life (HR-QoL) is a multi-dimensional measure that includes domains related to physical, mental, social, and emotional functioning in the context of health and disease [2]. HR-QoL has become an important measure of the impact of disease and to assess treatment efficacy [3], including that of dry eye [4,5].

Several population-based studies on DED and HR-QoL suggest that

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DED has an adverse effect on HR-QoL, affecting physical and potentially psychological well-being [1,6–13]. However, these studies were either limited by small sample size and/or did not investigate the role of severity levels of dry eye. Moreover, they did not take into account many of the currently known comorbidities of dry eye that could confound a true association, such as autoimmune conditions and psychiatric disease which have been shown to substantially reduce HR-QoL as well [14,15]. As the severity of DED can range from a mere nuisance to severely debilitating, and DED is associated with numerous systemic disorders, it is vital to take these determinants into account when assessing HR-QoL of dry eye.

Furthermore, the role of age and sex on the effect of DED on HR-QoL is not fully known. Only a few studies have investigated the role of sex, finding DED to affect HR-QoL more in women than in men. These studies, however, did not account for different severity levels of dry eye, with women generally having more severe dry eye [16,17]. Also, it is unknown whether a presence of a clinical diagnosis of DED affects the relationship between DED and HR-QoL. Undiagnosed DED may provide a greater burden to dry eye subjects than diagnosed disease, due to greater uncertainty, no or small prospects of treatment and improvement, and lack of recognition. We therefore hypothesized that the absence of a DED diagnosis by a clinician would be associated with a reduced HR-QoL.

Hence, the purpose of this large population-based study was to clarify the relationship between DED and all domains of HR-QoL. We tested interactions of this relationship with age, sex, and the presence of a DED diagnosis, and investigated the role of symptom severity on HR-QoL. Importantly, we took into account and corrected for numerous possible confounding comorbidities of dry eye [15].

2. Methods

2.1. Lifelines cohort and participants

Lifelines is a multi-disciplinary prospective population-based cohort study examining the health and health-related behaviors of 167,729 persons living in northern Netherlands. It employs a broad range of investigative procedures in assessing the biomedical, socio-demographic, behavioral, physical, and psychological factors that contribute to the health and disease of the general population, with a special focus on multi-morbidity and complex genetics [18]. Participants, mainly of European ancestry, were included via general practitioners or self-enrollment between 2006 and 2013 and will be followed for at least 30 years. The cohort has been shown to be broadly representative of the adult population of the North of the Netherlands, and the recruitment strategy had minor effect on the level of representativeness [19]. The cohort is described in detail elsewhere [20]. 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.

We needed to include at least 36,986 participants to be able to detect an odds ratio of 1.1 of having reduced quality of life in dry eye subjects, with a power of 80%, an alpha of 0.05, and an estimated prevalence of

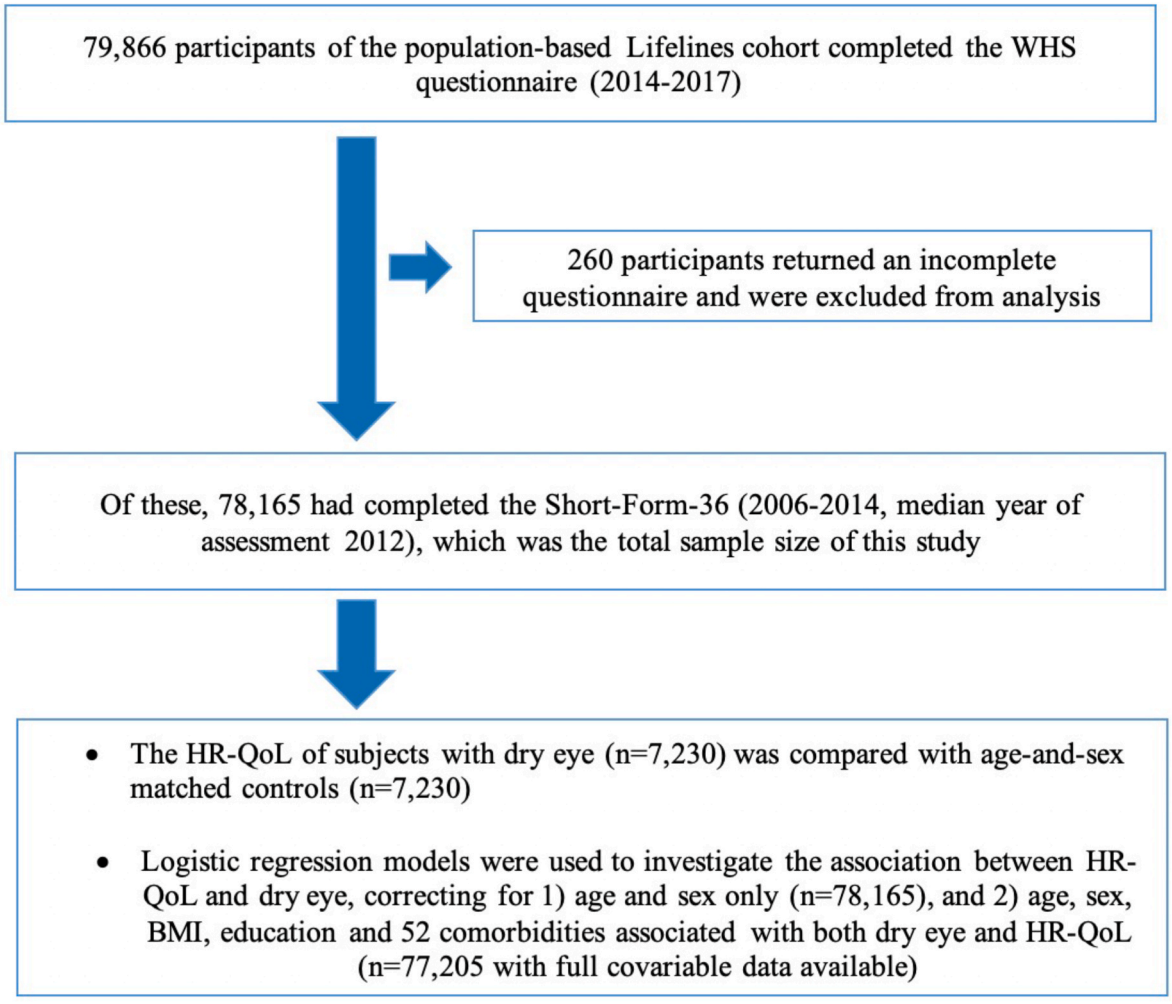

Fig. 1. Overview of study.

dry eye of 10% [15]. For our second outcome variable, a more severe degree of dry eye, we needed to include 44,216 participants to be able to detect an odds ratio of 1.2 of having reduced quality of life in dry eye subjects with a power of 80%, an alpha of 0.05, and an estimated prevalence of highly symptomatic dry eye of 2% [15]. Therefore, we aimed to include at least 44,216 participants for this study. An overview of the study is illustrated in Fig. 1.

2.2. Assessment of dry eye

No gold standard for a diagnosis of DED exists that is easily implemented in large population-based studies [21]. In this study, DED was assessed between 2014 and 2018 with the Women's Health Study (WHS) dry eye questionnaire [20]. This short 3-item questionnaire is the most widely used questionnaire to assess dry eye in population-based studies [1]. It has been validated against a standardized clinical exam [22] and showed similar sensitivity and specificity as a 16-item instrument [22, 23]. The WHS 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 questions had the possible answers: 0 never, 1 sometimes, 2 often, or 3 constantly. The third question inquiries 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'. A subject is considered to have dry eye if there is the presence of both dryness and irritation either 'constantly' or 'often', and/or report having a previous clinical diagnosis of DED [22]. This definition was used as the primary outcome variable in our analysis and is further referred to as 'dry eye (WHS)'. Subjects with dry eye are referred to as 'subjects with dry eye' or 'dry eye subjects' As a secondary outcome variable we also assessed 'highly symptomatic dry eye', which was defined as both dryness and irritation either 'constantly' or 'often' [22].

2.3. Assessment of health-related quality of life (HR-QoL)

The SF36 questionnaire was used to measured HR-QoL between 2006 and 2014, with the median year of measurement being 2012. SF36 is the most frequently used and widely recognized tool for assessing HR-QoL [24]. The questionnaire is used in many settings, including clinical practice, health policy evaluation, and general population surveys [25]. SF36 covers eight domains: physical functioning (PF), role limitations caused by physical health problems (RP), bodily pain (BP), general health perceptions (GH), energy/fatigue (vitality-VT), social functioning (SF), role limitations caused by emotional problems (RE), and mental health (MH) [24]. The eight domain scores range from 0 to 100, with higher scores indicating better HR-QoL. These scores were aggregated into two summary scores: the physical component summary (PCS) and the mental component summary (MCS), that attest physical and mental HR-QoL, respectively. PCS and MCS were calculated by standard algorithms that weigh the eight domains differently. This is illustrated by the PCS algorithm below (limited to two decimal places) [26].

$$PCS = 50 + AGG_{PHYS} \times 10$$

$$AGG_{PHYS} = (PF_Z \times 0.42) + (RP_Z \times 0.35) + (BP_Z \times 0.32) + (GH_Z \times 0.25) + (VT_Z \times 0.22) + (SF_Z \times -0.01) + (RE_Z \times -0.19) + (MH_Z \times -0.22)$$

As can be seen, the summary scores are generated by multiplying each SF-36 domain's z-score by the factor score coefficient and summing the eight products. Notably, the domains related to mental quality of life (mental health, role emotional, and social functioning) contribute negatively to the PCS, and vice versa domains related to physical quality of life lower MCS score. The algorithms thereby ensure that PCS and MCS are not correlated to each other, so that they measure different aspects of quality of life. The PCS and MCS have sufficient discriminant validity to identify clinically meaningful differences between samples [24]. Each score is calibrated to have a mean value of 50 and a standard deviation of 10 in the US general population [26]. SF36 has been translated and validated for use among the Dutch-speaking residents of the Netherlands [27]. In this study, a below median PCS and MCS score was regarded as a low physical and mental quality of life, respectively.

2.4. Assessment of possible confounding factors

All participants completed questionnaires at baseline (2006–2014) and follow-up visit (2014–2017) and were at both of these visits asked about the presence of a broad range of disorders. At baseline, participants were asked: "Could you indicate which of the following disorders you have or have had?". In addition, subjects were asked to report any other disorders that they have or have had, using free text. At the follow-up assessment, using the same questions, participants were asked to report any additional disorders that had presented since the previous assessment. Based on this, 118 dichotomous variables were created covering a broad range of the most common conditions and traits. Of these, 55 were independently associated with dry eye, see Vehof et al. [15]. These disorders were tested for an association with HR-QoL ($P < 0.20$), which led to a final set of 52 comorbidities that were corrected for in our analyses. These disorders were: contact lens use, macular degeneration, glaucoma/ocular hypertension, allergic conjunctivitis, Bell's palsy, laser refractive surgery, eye surgery (any other), rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, thyroid disease, Graves' disease, Crohn's disease, sarcoidosis, depression, "burnout", autistic disorder, chronic fatigue syndrome, carpal tunnel syndrome, spasticity, migraine, asthma, eczema, hay fever, allergy (any), acne, psoriasis, anemia, diabetes, hypertension, atherosclerosis, arrhythmia, liver cirrhosis, chronic cystitis, stomach ulcer, osteoporosis, incontinency, sinusitis, irritable bowel syndrome, fibromyalgia, intervertebral disc herniation, repetitive strain injury, back pain, osteoarthritis, sleep apnea, vitamin B12 deficiency, low blood pressure, costochondral junction syndrome, gall stones, eating disorder, ADHD and COPD. Other variables corrected for in this study were age, sex, BMI, and educational level (completion of higher vocational or university education diploma or not).

2.5. Statistics

Descriptive statistics were used to describe the study population characteristics. We used logistic regression models to assess the relationship between low quality of life (PCS lower than median and MCS lower than median, dependent variables) and dry eye (both dry eye (WHS) and highly symptomatic dry eye, independent variables). Results were corrected for (i) age and sex, and (ii) age, sex, BMI, education level, and the 52 comorbidities associated with DED and HR-QoL. This was regarded as the main analysis. In addition, we compared the mean scores of the eight domains in dry eye compared to age- and sex matched controls (1:1). A Mann-Whitney *U* test was used to compare between groups. Next, we examined the effect of dry eye symptom severity on HR-QoL by calculating odds ratio of having low HR-QoL for every dry eye symptom frequency level compared to 'never' symptoms.

Further, we repeated our main analysis while stratifying by sex, by

age groups (20–40 yrs, 40–60 yrs, 60+ yrs), and by the presence of a clinical DED diagnosis. To examine any significant effect of age, sex, or diagnosis on the relationship between dry eye and HR-QoL, the interaction terms 'age*dry eye', and 'sex*dry eye', and 'clinical diagnosis of dry eye* dry eye ordinal symptom score' were tested for significance by adding them in the respective multivariable models in addition to the individual variables of these interaction terms.

As a sensitivity analysis, we performed the same tests as our analyses above, but with the outcome variable lowest quartile of HR-QoL (PCS and MCS), instead of below median.

To better understand the relative impact of DED on HR-QoL compared to other diseases, we calculated odds ratios of having low PCS and MCS for other eye diseases (a history of retinal detachment surgery, allergic conjunctivitis using eye drops, macular degeneration with self-reported visual impairment, glaucoma using eye drops, and glaucoma that needed surgery), and other chronic systemic disorders (migraine, irritable bowel syndrome, COPD, obstructive sleep apnea syndrome, depression, rheumatoid arthritis, and fibromyalgia), corrected for age and sex only.

All analyses were cross-sectional. A p-value of below 0.05 was regarded as statistically significant for all the analyses above.

3. Results

Table 1 describes the characteristics of the study population (n = 78,165). A total of 8.9% of participants had dry eye, based on the WHS questionnaire. Highly symptomatic dry eye was found in 1.8% of participants. The mean PCS and MCS scores in our cohort were 53.0 and 51.2, respectively. The number of subjects for which information on all demographics and possible comorbidities was complete was 77,205.

Table 1
Characteristics of the study population.

	All participants (n = 78,165)
Age, years (range)	50.1 (19–94)
Female sex	59.2%
BMI (mean (kg/m^2), SD)	26.1 (4.3)
Income above 3000 euros per month	32.6%
Income between 2000 and 3000 euros per month	29.8%
Income below 2000 euros per month	27.6%
Higher vocational or university diploma	32.4%
HR-QoL (Short-form 36)	
- Physical Component Summary, (mean, SD)	53.0 (7.3)
- Mental Component Summary, (mean, SD)	51.2 (8.3)
Dry eye	
- Highly symptomatic dry eye[a]	1.8%
- Clinical diagnosis of dry eye	8.0%
- WHS definition dry eye[b]	8.9%
Prevalence of at ≥1 comorbidity[c]	90.3%
Participants with complete information on all demographics and possible comorbidities	77,205

BMI: Body mass index, HR: Health-related quality of life, SD: Standard deviation, WHS: Women's Health Study.

[a] Both dryness and irritation either 'constantly' or 'often'.

[b] Both dryness and irritation either 'constantly' or 'often', and/or a previous clinical diagnosis of DED.

[c] Contact lens use, macular degeneration, glaucoma/ocular hypertension, allergic conjunctivitis, Bell's palsy, laser refractive surgery, eye surgery (any other), rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, thyroid disease, Graves' disease, Crohn's disease, sarcoidosis, depression, "burnout", autistic disorder, chronic fatigue syndrome, carpal tunnel syndrome, spasticity, migraine, asthma, eczema, hay fever, allergy (any), acne, psoriasis, anemia, diabetes, hypertension, atherosclerosis, arrhythmia, liver cirrhosis, chronic cystitis, stomach ulcer, osteoporosis, incontinency, sinusitis, irritable bowel syndrome, fibromyalgia, intervertebral disc herniation, repetitive strain injury, back pain, osteoarthritis, sleep apnea, vitamin B12 deficiency, low blood pressure, costochondral junction syndrome, gall stones, eating disorder, ADHD and COPD.

3.1. The relation between dry eye and HR-QoL: main analysis

The relationship between dry eye and HR-QoL is presented in Table 2. This table first describes the prevalence of having low (below median) physical and mental quality of life, as measured by the PCS and MCS, in subjects without dry eye and subjects with dry eye. Moreover, it presents the odds ratios of having low PCS and MCS for dry eye subjects. The odds ratios (ORs) corrected for age and sex illustrate how severe HR-QoL is affected in dry eye subjects; the ORs corrected for age, sex, BMI, education, and 52 comorbidities illustrate how severe dry eye itself is affecting HR-QoL, because this model corrects for the HR-QoL-lowering effects of these comorbid conditions [15]. Appendix Table 1 provides further details on the prevalence and ORs of low HR-QoL in all eight domains of the SF36.

Dry eye subjects have a higher prevalence of low HR-QoL on all eight domains of SF36, and both summary scores MCS and PCS. Low physical HR-QoL was found in 62% of dry eye subjects, compared to 49% in subjects without dry eye (PCS OR 1.54 (95% CI 1.46–1.62) P < 0.0005, corrected for age and sex). Similarly, low mental HR-QoL was found in 58% of dry eye subjects, compared to 49% of subjects without dry eye (MCS OR 1.39 (95% CI 1.32–1.46) P < 0.0005, corrected for age and sex). Moreover, in subjects with highly symptomatic dry eye, the prevalence of low PCS and MCS was as high as 71% and 68%, respectively. Subjects with highly symptomatic dry eye were more than twice as likely to have a low physical and mental quality of life, compared to subjects without dry eye. After additional correction for BMI, education, and 52 comorbidities, the odds ratios decreased, but remained substantially and significantly increased compared to subjects without dry eye. These findings suggest a serious negative impact of dry eye on HR-QoL.

Fig. 2 depicts the mean scores of the eight domains of HR-QoL in subjects with highly symptomatic dry eye, subjects with dry eye (WHS definition), and in age- and sex-matched controls. A completely filled octagon would represent a perfect quality of life in all domains. As can be seen, HR-QoL is reduced in every domain in people with dry eye and further decreased in subjects with highly symptomatic dry eye. The corresponding numeric values of PCS, MCS, and all eight domains can be found in Appendix Table 2. The mean PCS score was 48.1 (SD 10.0) in subjects with highly symptomatic dry eye and 50.6 (SD 8.9) in subjects with dry eye (WHS). Both scores were significantly worse than that of age-and-sex matched controls, who had a PCS of 52.6 (SD 7.5) (P < 0.0005 for both groups). Similarly, the mean MCS score was 47.3 (SD 10.3) in subjects with highly symptomatic dry eye and 49.7 (SD 9.2) in subjects with dry eye (WHS), both significantly lower than that of controls (51.1 (SD 8.4)) (P < 0.0005 for both groups).

3.2. The relation between dry eye symptom severity and HR-QoL

Table 3 shows the odds ratios of low quality of life in those with sometimes, often, and constant dryness symptoms compared to asymptomatic participants. The odds ratios of having a low PCS increased gradually with symptom frequency. Subjects with 'constant' symptoms of dryness of the eyes were three times more likely to have a low PCS score (OR 3.06 (95% CI 2.26–4.14)) than those without symptoms, whereas subjects with 'often' symptoms had double the risk of a low PCS score (OR 2.08 (95% CI 1.91–2.26)). This stepwise increase in the prevalence of low HR-QoL with increasing symptom frequency was less apparent for MCS.

3.3. The role of age and sex on the relation between dry eye and HR-QoL

The association between dry eye and HR-QoL, stratified by age groups and sex, is shown in Table 4. In subjects without dry eye, women scored lower on HR-QoL than men, and increasing age was associated with lower physical quality of life and higher mental quality of life. HR-QoL is strongly affected by dry eye in every age group and in both males and females. There was no apparent effect of age or sex on the

Table 2
The relationship between dry eye and health-related quality of life.

SF36	Prevalence of below median score in subjects with no dry eye (WHS) (n = 72,428)	Prevalence of below median score in subjects with dry eye (WHS), (n = 7,230)	Prevalence of below median score in subjects with highly symptomatic dry eye (n = 1,512)	Dry eye (WHS)				Highly symptomatic dry eye			
				Corrected for age and sex only		Corrected for all[a]		Corrected for age and sex only		Corrected for all[a]	
				OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
PCS	49%	62%	71%	1.54 (1.46–1.62)	<0.0005	1.22 (1.15–1.29)	<0.0005	2.29 (2.04–2.58)	<0.0005	1.53 (1.34–1.74)	<0.0005
MCS	49%	58%	68%	1.39 (1.32–1.46)	<0.0005	1.22 (1.16–1.29)	<0.0005	2.07 (1.85–2.32)	<0.0005	1.64 (1.45–1.85)	<0.0005

PCS: Physical component summary, MCS: Mental component summary, OR: odds ratio, CI: confidence interval.
[a] Corrected for age, sex, Body mass index, education, and 52 comorbidities. 77,205 subjects were included in analysis with all comorbidities.

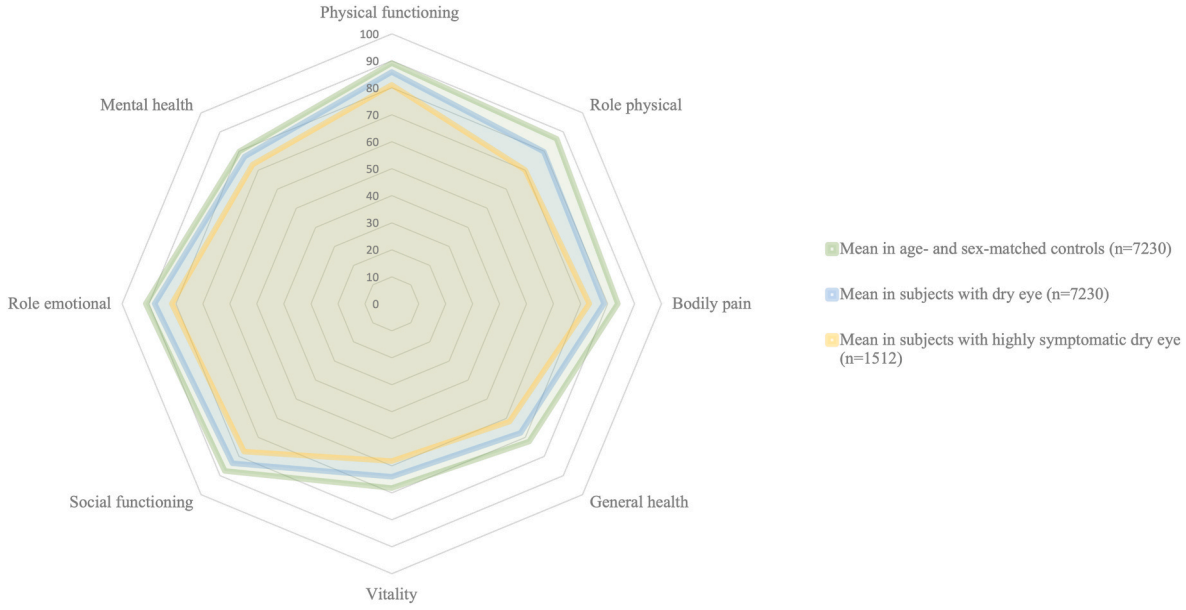

Fig. 2. Mean scores of the eight domains of health-related quality of life in subjects with dry eye (Women's health study definition), in subjects with highly symptomatic dry eye, and in age- and sex-matched controls.

Table 3
The association between frequency of dryness symptoms and health related quality of life.

	PCS		MCS	
	ORs (95% CI) corrected for age and sex	ORs (95% CI) corrected for all[a]	ORs (95% CI) corrected for age and sex	ORs (95% CI) corrected for all[a]
Never	Reference	Reference	Reference	Reference
Sometimes (n = 24420)	1.26 (1.22–1.30) P < 0.0005	1.21 (1.17–1.26), P < 0.0005	1.41 (1.36–1.45), P < 0.0005	1.37 (1.32–1.42), P < 0.0005
Often (n = 2677)	2.08 (1.91–2.26) P < 0.0005	1.57 (1.43–1.72), P < 0.0005	1.97 (1.81–2.15), P < 0.0005	1.67 (1.53–1.83), P < 0.0005
Constant (n = 251)	3.06 (2.26–4.14) P < 0.0005	1.88 (1.34–2.63), P < 0.0005	1.73 (1.32–2.25), P < 0.0005	1.36 (1.02–1.82), P = 0.035

PCS: Physical Component Summary, MCS: Mental Component Summary, ORs: odds ratios, CI: 95% confidence intervals.
[a] Corrected for all: corrected for age, sex, Body mass index, education and 52 comorbidities.

association between dry eye (WHS) and HR-QoL (interaction term age*dry eye and sex*dry eye, all P > 0.05). However, in subjects with highly symptomatic dry eye, higher age was found to decrease the association between dry eye and PCS (interaction term age*highly symptomatic dry eye: PCS P = 0.01, MCS P = 0.74). Furthermore, males with highly symptomatic dry eye were more likely to have a low PCS than women with the same disease burden, while for MCS this increased risk in men was less apparent (interaction term sex*highly symptomatic dry eye: PCS P = 0.01, MCS P = 0.09).

3.4. The role of a clinical diagnosis on the relation between dry eye and HR-QoL

The relation between low health-related quality of life and symptom severity stratified by the presence of a clinical diagnosis of DED is shown in Fig. 3. Undiagnosed subjects had a markedly sharper increase in the prevalence of low mental quality of life with increasing symptoms than those with a presence of a dry eye diagnosis. Indeed, the interaction term 'clinical diagnosis of dry eye*dryness frequency' was significant for MCS (P = 0.005). There was no significant difference between subjects with and without a clinical diagnosis in PCS scores (interaction term 'clinical diagnosis of dry eye*dry eye ordinal symptom score' PCS P = 0.42).

Table 4
The association between dry eye and health-related quality of life, stratified for age groups and sex.

		Subjects without dry eye		Dry eye (WHS)			Comparison of dry eye subjects (WHS) to subjects without dry eye		Highly symptomatic dry eye			Comparison of dry eye subjects with highly symptoms to subjects without dry eye	
Age	N	Prevalence of low PCS	Prevalence of low MCS	N (%)	Prevalence of low PCS	Prevalence of low MCS	OR of low PCS (CI, P-value)	OR of low MCS (CI, P-value)	N (%)	Prevalence of low PCS	Prevalence of low MCS	OR of low PCS (CI, P-value)	OR of low MCS (CI, P-value)
20–40	16,445	39%	58%	1174 (7.1%)	47%	67%	1.20 (1.05–1.38), P = 0.02	1.26 (1.10–1.45), P = 0.001	222 (1.4%)	61%	78%	1.87 (1.39–2.53), P < 0.0005	1.92 (1.37–2.70), P < 0.0005
40–60	45,603	49%	50%	3820 (8.4%)	60%	61%	1.22 (1.13–1.32), P < 0.0005	1.25 (1.16–1.34), P < 0.0005	830 (1.8%)	71%	69%	1.58 (1.34–1.88), P < 0.0005	1.53 (1.30–1.80), P < 0.0005
60+	16,113	60%	38%	2022 (12.6%)	74%	47%	1.29 (1.14–1.45) P < 0.0005	1.12(1.01–1.25), P = 0.03	407 (2.5%)	78%	59%	1.22 (0.93–1.59), P = 0.16	1.72 (1.38–2.14), P < 0.0005
Sex													
Male	31891	47%	43%	1569 (4.9%)	59%	51%	1.36 (1.21–1.52), P < 0.0005	1.26 (1.13–1.41), P < 0.0005	1183 (0.3%)	70%	64%	2.20 (1.65–2.93), P < 0.0005	1.85 (1.42–2.41), P < 0.0005
Female	46274	51%	54%	5448 (11.8%)	63%	60%	1.19 (1.11–1.27), P < 0.0005	1.21 (1.14–1.29), P < 0.0005	276 (1.5%)	72%	69%	1.40 (1.21–1.62), P < 0.0005	1.59 (1.39–1.81), P < 0.0005

3.5. Sensitivity analysis

As a sensitivity analysis, we also investigated lowest quartile of HR-QoL as an outcome variable instead of below median HR-QoL. All results were broadly similar to the main analysis above, with no alterations in statistical significance of any of the results discussed above (data not shown).

3.6. HR-QoL in dry eye compared to other systemic and eye diseases

Fig. 4 shows the risk of low HR-QoL in different eye diseases (Fig. 4.1) and different chronic systemic disorders (Fig. 4.2) on HR-QoL. The risk of low PCS and MCS is higher for highly symptomatic dry eye than for any of the other eye diseases investigated. This comparison included conditions macular degeneration, glaucoma, allergic conjunctivitis, and retinal detachment (Fig. 4.1). Fig. 4.2 shows that highly symptomatic dry eye is associated with a risk of low HR-QoL non-inferior to that of other serious chronic diseases. For example, the risk of low physical quality of life is similar to that of COPD and IBS. Strikingly, the risk of low MCS is higher for DED than for all other chronic systemic diseases investigated, except depression. While the other chronic conditions primarily affected either mental or physical quality of life, highly symptomatic dry eye stands out by substantially reducing both physical and mental quality of life.

4. Discussion

This large, population-based study aimed to clarify the relationship between dry eye and health-related quality of life (HR-QoL). Dry eye was found to be associated with substantial reductions in all domains of HR-QoL measured by the SF36. This reduction is partly explained by comorbidities of dry eye such as chronic pain disorders, rheumatologic, autoimmune, and psychiatric disorders. However, after correcting for these comorbidities, dry eye was still significantly associated with both reduced physical and mental quality of life, suggesting a serious impact of dry eye on HR-QoL. Younger age and male sex were associated with a greater impact of highly symptomatic dry eye on physical quality of life. Interestingly, undiagnosed subjects with highly symptomatic dry eye were more likely to have a low mental quality of life than diagnosed subjects with the same symptom burden.

So far, only one large population-based study investigated the relationship between dry eye and HR-QoL. In this study with 3275 subjects in the United States from 2014, Paulsen et al. found that dry eye is associated with low quality of life. Dry eye subjects had reduced MCS and PCS scores, also when controlling for age, sex, education, and a number of common conditions (cardiovascular disease, diabetes, severe headaches or migraines, arthritis, cancer, hypertension, asthma, thyroid disease, diabetic retinopathy, age-related macular degeneration, retinal detachment, cataract, and glaucoma) [6]. The definition of dry eye used for this study was 'at least moderately bothersome symptoms present at minimum sometimes and/or treated with eye drops', and not a validated dry eye questionnaire, such as the WHS used in the current study. Our highly powered study is the first of its kind conducted in a European population. It further adds that all eight domains of quality of life are substantially reduced in subjects with dry eye. We assessed 118 possible confounding comorbidities and corrected for 52 associated with both HR-QoL and dry eye. Dry eye remained significantly associated with low quality of life even after correcting for all associated conditions that could confound the relationship. This adds evidence to a causal relation between dry eye and low HR-QoL.

This is the first study to demonstrate conclusively that dry eye is associated with reduced *mental* health-related quality of life by using validated questionnaires. A review article of literature up to and including 2013 concluded that DED caused a substantially reduced physical QoL but only demonstrated a "potentially" negative impact of DED on psychological function and QoL [9]. However, most studies

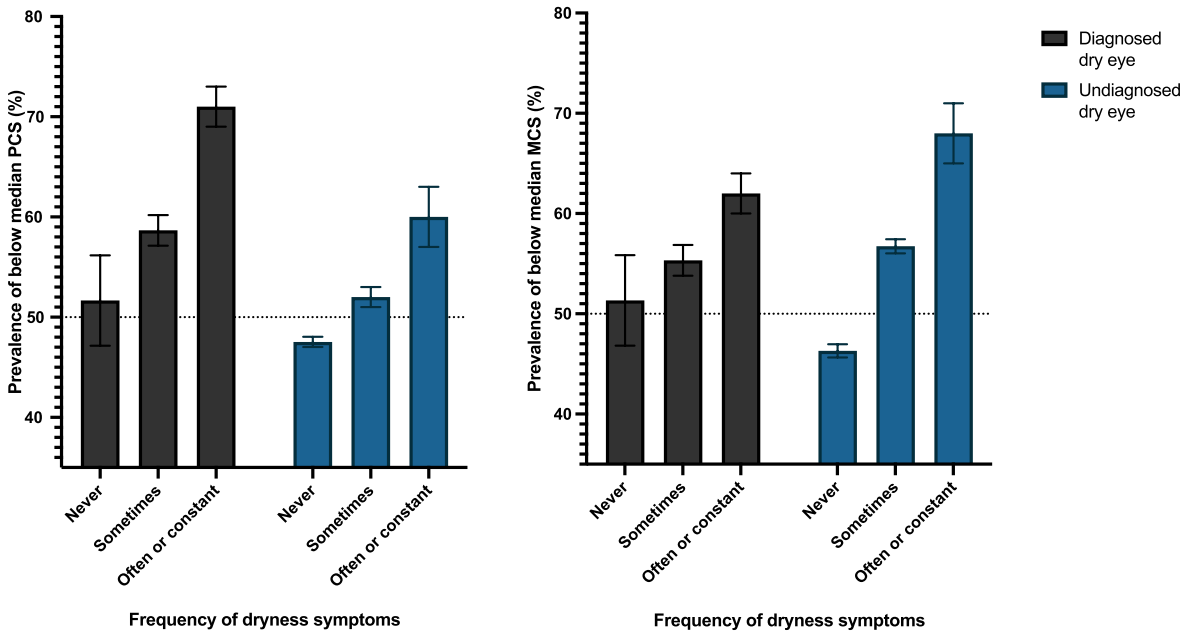

Fig. 3. Prevalence of low health related quality of life (PCS and MCS) for different dry eye symptom frequency levels in subjects with and subjects without a clinical diagnosis of dry eye.

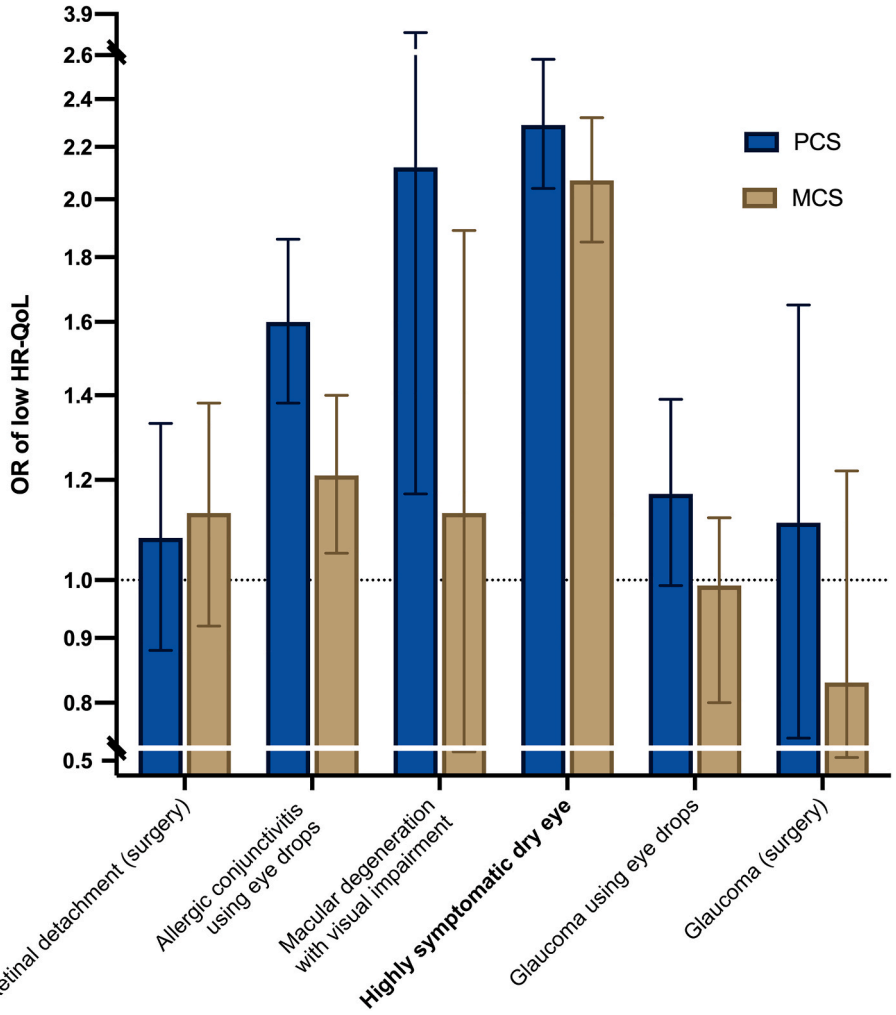

Fig. 4. Odds ratios of having low physical and mental component summary scores for several i) eye disorders, and ii) chronic systemic disorders, compared to highly symptomatic dry eye, corrected for age and sex.

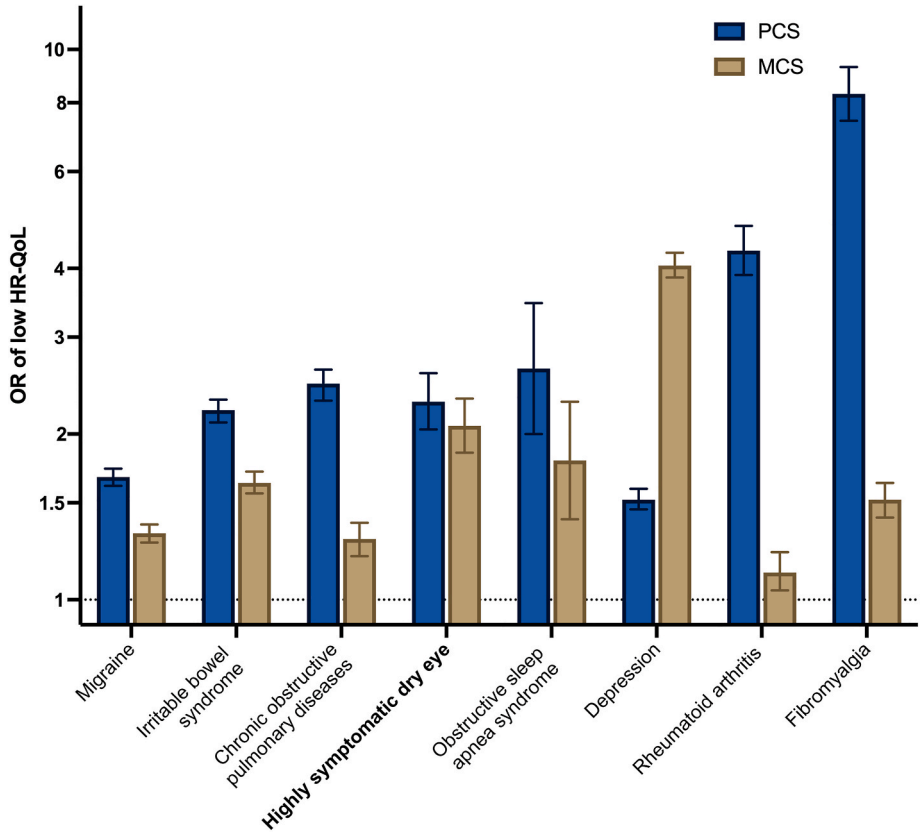

Fig. 4. (*continued*).

reviewed were underpowered with fewer than 100 subjects with dry eye, and none included more than 200 subjects with dry eye. One study included 130 non-Sjögren's dry eye, 32 Sjögren's syndrome dry eye patients, and 48 healthy controls, and found dry eye to reduce all domains of SF36 apart from mental health [7]. However, this study only reported the outcomes of the separate domains, not the MCS score [7]. We found that subjects with highly symptomatic dry eye have more than twice the risk of having a low mental HR-QoL score (MCS) compared to controls. This increased risk was still largely present after correcting for comorbidities, which suggests that dry eye itself has a negative impact on mental quality of life. However, we cannot exclude the possibility that having a low mental quality of life worsens dry eye symptomology. For instance, the well-known association between depression and dry eye is thought to be bidirectional [28]. Despite accounting for conditions such as depression, it is possible that low mental quality of life from other causes that were not accounted for may similarly exacerbate dry eye symptoms. Either way, our findings suggest that psychological support should be given a larger focus in dry eye consultations. Current consultations by clinicians largely focus on evaluating signs and symptoms of dry eye only. Future studies should investigate how and to what extent psychological support, such as cognitive behavioral therapy, could improve HR-QoL and dry eye symptomatology in dry eye patients.

Interestingly, the point estimate of the odds ratio of having a low mental quality of life was higher in those with 'often' symptoms, compared to those with 'constant' symptoms. It may be that subjects with constant symptoms seek help and use artificial tears more than subjects with inconstant symptoms. Indeed, the subjects with constant symptoms were found to use artificial tears far more frequently than those with often symptoms in our cohort (73% versus 41%, respectively). It might also point to that the unpredictability of having often but not constant symptoms induces a psychological burden at least as severe as that of constant symptoms. Coping mechanisms, including thoughts and emotions, have been shown to influence dry eye symptoms [29]. It may be that subjects with constant symptoms of dry eye develop better coping mechanisms than those with inconstant symptoms. However, due to the cross-sectional nature of this study, we cannot state any causal relationship. Also, the relationship may be confounded by factors not taken into account, such as seeking medical care or treatment for dry eye.

Schaumberg et al. found DED to have a greater negative impact on quality of life in women than in men, in a study of 1581 females and 581 males [16,17]. The study found women with DED were less likely than men with DED to report feeling calm and peaceful or having a lot of energy, and more likely to report feeling depressed. However, the men and women were selected from different populations, which could have confounded results. Moreover, these findings might have been confounded by dry eye symptom severity levels which were not accounted for. Women have been found to have more severe dry eye than men, and thus their quality of life might therefore be more affected [30,31]. The current study adds comparison between the sexes while investigating highly symptomatic dry eye only. Interestingly, our results show that male sex is associated with a greater risk of low quality of life in subjects with highly symptomatic dry eye. This may be the result of sex-differences in actions made when dry eye symptoms are present. Women seek medical care more than men [32] and open up more about their dry eye symptoms [33], leading to opportunities for earlier diagnosis and treatment of DED. Also, women are found to use conventional DED therapies, such as artificial tears, more than men [17]. Indeed, in every age group of this cohort, women used more ocular lubricants for dry eye than men, also relatively when you take into account symptoms of dry eye [15]. Given all this, it appears men open up less about their dry eye symptoms, treat their dry eye more poorly, and are paying for it by a diminished quality of life. Future longitudinal studies are warranted to see if the reduced HR-QoL in men reflects their well-documented reluctance to access medical care and therefore possibly less than adequate treatment, and if introduction of improved treatment regimens

increases their HR-QoL.

It is very difficult to define a clinically important difference in HR-QoL score. As an example, a person with a traumatic corneal erosion is likely to have a much greater reduction of HR-QoL than a person with dry eye. However, the corneal erosion is likely to heal within a few days by itself or with relatively simple treatment. Dry eye, on the other hand, may last a lifetime and has no curative treatment. Thus, one could argue that the latter represents a greater overall loss of HR-QoL. The measure of HR-QoL does not take into account the chronicity of a disease, and therefore absolute cut-off values for 'low HR-QoL' have been discarded [24]. We believe the substantial increase in risk of low quality of life in dry eye subjects found in this study are representing a meaningful reduction of HR-QoL, as was also shown by the comparison with – and similar impact to that of – other serious disorders (Fig. 2). This substantial burden is even more explicit when accounting for the chronicity of DED.

This is the first study that assessed the role of a formal clinical diagnosis on the association between dry eye and HR-QoL. Our results show that subjects with highly symptomatic dry eye without a prior diagnosis of dry eye by a clinician had worse mental HR-QoL compared to those with a diagnosis of dry eye. This could imply that receiving a formal diagnosis is important in improving the quality of life of people who experience severe dry eye. Subjects without a diagnosis may struggle with the uncertainty of experiencing symptomology they cannot define or reason. In addition, dry eye can severely affect productivity and social life, and subjects without a diagnosis may lack the understanding, social credence, and work-related facilitation required to uphold their quality of life. As recognized by the TFOS European ambassador meeting, dry eye goes often undiagnosed and is an under-recognized disorder in many European countries [34]. More and improved information to the general public, accentuating dry eye as a recognized clinical disorder, is required.

Past studies have found that patients with mild and severe dry eye experience a reduction in quality of life comparable to patients with mild psoriasis and moderate-to-severe angina, respectively [1,35]. Our study added that subjects with highly symptomatic dry eye had a greater reduction in quality of life than patients with other eye disorders including glaucoma requiring surgery, allergic conjunctivitis needing eye drops, and a history of retinal detachment. Noteworthy, subjects with highly symptomatic dry eye experience a substantial reduction in *both* mental and physical quality of life, which is uncommon for most chronic disorders. Compared to patients with rheumatoid arthritis, COPD and migraine, for example, highly symptomatic dry eye subjects have much greater risks of low mental quality of life. This study, therefore, clearly shows that dry eye is a serious disease with a severe impact on both physical and mental quality of life, and stresses that timely referral, diagnosis, and/or treatment of subjects with dry eye is essential.

This study has several limitations. First, as dry eye and HR-QoL were assessed cross-sectionally, the current study cannot state causality of any findings. This is relevant, as low quality of life may also contribute to the experience of dry eye symptoms. Second, HR-QoL and dry eye were assessed at different time points, which could impact the associations found in our cross-sectional analyses and lower the power to find a true association. A third limitation of this study is that the frequency of dry eye symptoms does not give a complete picture of dry eye symptom severity. There may be substantial intra-group variations in the severity or dryness at every frequency level. Also, objective measures of dry eye severity were not assessed. Additional objective measures could have provided a greater insight into what factors or subtypes of dry eye contribute most to the observed reductions in HR-QoL (e.g. aqueous tear deficiency or meibomian gland dysfunction). However, this is not easily implemented in large epidemiological studies. Furthermore, detailed information about visual disturbances in the subjects with dry eye would have allowed the current study to investigate if and to what extent reductions in HR-QoL were mediated by reductions in vision quality. Lastly, when correcting for numerous comorbidities, we might have overcorrected and thus underestimated the true effect of dry eye on QoL. For instance, when correcting for depression in assessing the impact of dry eye on MCS, we eliminate any effect of dry eye mediated depression. This study's strengths include an unprecedented sample size that allowed us to gain new and deeper insights using different strata of dry eye subjects and to account for a large number of possible confounding comorbidities. More than 100 possible confounding comorbidities and conditions were assessed and taking into account for this study. Finally, the extensive data on other medical conditions in the study participants allowed for novel comparison between HR-QoL in dry eye versus other eye diseases and chronic systemic diseases, which shows the clinical relevance of our findings.

5. Conclusion

In conclusion, dry eye was associated with a substantial reduction in both physical and mental quality of life. Quality of life decreased sharply with increasing symptoms of dry eye. Younger age, male sex, and undiagnosed dry eye was tied to lower HR-QoL in subjects with highly symptomatic dry eye. Clinicians and the general public should be better informed about dry eye's impact on physical and mental HR-QoL, and it should be emphasized that dry eye is a serious disorder that requires timely diagnosis and treatment. Future studies are warranted to investigate how and to what extent psychological support could improve HR-QoL and dry eye symptomatology in dry eye patients.

Declaration of competing interest

No conflicting relationship exists for any author.

PCS: Physical Component Summary, MCS: Mental Component Summary, ORs: odds ratios, WHS: Women's Health Study, CI: 95% confidence interval. Odds ratios were corrected for age, sex (in age group analyses only), Body mass index, education, and 52 comorbidities. 77,205 subjects were included in analysis with all comorbidities.

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Appendix

Appendix Table 1

The relationship between dry eye and all eight domains of health-related quality of life

SF36	Prevalence of below median score in subjects without dry eye (WHS) (n = 72,428)	Prevalence of below median score subjects with dry eye (WHS) (n = 7,230)	Prevalence of below median score in subjects with highly symptomatic dry eye (n = 1,512)	Dry eye (WHS)				Highly symptomatic dry eye			
				Corrected for age and sex only		Corrected for all*		Corrected for age and sex only		Corrected for all*	
				OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Physical Functioning (PF)	58%	70%	80%	1.45 (1.37–1.54)	<0.0005	1.23 (1.16–1.31)	<0.0005	2.38 (2.09–2.72)	<0.0005	1.65 (1.43–1.91)	<0.0005
Role physical (RP)	20%	31%	42%	1.70 (1.61–1.79)	<0.0005	1.22 (1.15–1.30)	<0.0005	2.65 (2.38–2.95)	<0.0005	1.56 (1.38–1.76)	<0.0005
Bodily pain (BP)	53%	66%	75%	1.58 (1.50–1.66)	<0.0005	1.22 (1.15–1.30)	<0.0005	2.30 (2.04–2.59)	<0.0005	1.50 (1.32–1.72)	<0.0005
General health (GH)	46%	57%	69%	1.51 (1.44–1.59)	<0.0005	1.20 (1.13–1.27)	<0.0005	2.43 (2.17–2.72)	<0.0005	1.62 (1.44–1.84)	<0.0005
Vitality (VT)	53%	64%	75%	1.51 (1.43–1.59)	<0.0005	1.25 (1.18–1.32)	<0.0005	2.49 (2.20–2.80)	<0.0005	1.76 (1.55–2.01)	<0.0005
Social functioning (SF)	42%	54%	66%	1.50 (1.43–1.58)	<0.0005	1.20 (1.14–1.27)	<0.0005	2.33 (2.09–2.60)	<0.0005	1.58 (1.40–1.78)	<0.0005
Role emotional (RE)	12%	18%	24%	1.49 (1.40–1.60)	<0.0005	1.17 (1.09–1.27)	<0.0005	2.18 (1.93–2.46)	<0.0005	1.42 (1.24–1.64)	<0.0005
Mental health (MH)	46%	56%	67%	1.43 (1.36–1.50)	<0.0005	1.21 (1.15–1.28)	<0.0005	2.21 (1.97–2.46)	<0.0005	1.64 (1.45–1.85)	<0.0005

WHS: Women's Health Study, OR: Odds ratio, CI: confidence interval.
*Corrected for age, sex, Body mass index, education, and 52 comorbidities. 77,205 subjects were included in analysis with all comorbidities.
The low prevalence of below median scores on the domains Role Physical and Role Emotional are due to the fact that the majority of subjects had a perfect score on these domains.

Appendix Table 2

Mean scores of all eight domains of health-related quality of life in controls, subjects with dry eye (Women's health study), and subjects with highly symptomatic dry eye

SF36 summary scores and domains	Mean (SD) in age and sex-matched controls	Mean (SD) in subjects with dry eye (WHS)	Mean (SD) in subjects with highly symptomatic dry eye
PCS	52.6 (7.5)	50.6 (8.9) °	48.1 (10.0) °
MCS	51.1 (8.4)	49.7 (9.2) °	47.3 (10.3) °
Physical Functioning	89.2 (14.9)	85.9 (17.5) °	81.1 (20.1) °
Role physical	86.4 (29.6)	79.7 (34.9) °	70.0 (40.4) °
Bodily Pain	83.8 (19.0)	78.7 (21.0) °	73.3 (22.6) °
General Health	72.1 (16.4)	67.6 (18.2) °	61.8 (19.7) °
Vitality	68.3 (16.7)	64.1 (17.7) °	58.3 (18.7) °
Social Functioning	87.6 (17.9)	83.6 (20.2) °	77.5 (23.1) °
Role emotional	91.2 (24.9)	87.9 (28.9) °	81.6 (35.3) °
Mental Health	79.8 (13.7)	77.1 (14.6) °	73.0 (16.2) °

PCS: Physical Component Summary, MCS: Mental Component Summary, SF36: Short Form 36, SD: standard deviation, WHS: Women's Health Study.
° significantly lower than controls ($P < 0.0005$).

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