



Effects of physical activity/exercise on tear film characteristics and dry eye associated symptoms: A literature review

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ABSTRACT

Purpose: To conduct a review of the literature in order to identify the potential association between physical activity or exercise and the objective signs and/or subjective symptoms of dry-eye disease.

Methods: A review of PubMed and Web of Science databases was performed, according to the PRISMA guidelines. The papers included in the review addressed the relationship of physical activity or exercise with dry-eye associated signs (changes in tear volume, osmolarity or biochemical composition) and/or subjective symptoms. **Results:** A total of 16 papers were included. In eight, the changes in tear film volume, osmolarity and/or biochemical composition were studied after a single, acute bout of aerobic exercise. In another eight, changes in dry-eye associated symptoms were studied in relation to the habitual practice of physical activity or to prescribed exercise programmes. Acute responses of the tear film to exercise included: a) an increase of tear volume, without an increase of the tear break-up time; b) a trend to increase tear osmolarity, although within its physiological range; and c) a reduced concentration of several cytokines, and other molecular markers of inflammation or oxidative stress. Long-term exposure to physical activity or exercise programmes was associated with relief of dry-eye associated symptoms and a trend to increased tear break-up time.

Conclusions: Despite a high heterogeneity in the studied population, study designs and methods, the current body of evidence suggests a potential role for physical activity as a modulatory stimulus for the proper functioning of the tear film and/or the relief of dry-eye symptoms.

1. Introduction

Insufficient physical activity in every domain of daily life, from work to leisure time, is a major feature of contemporary developed societies, with increasing prevalence during the last 20 years [1]. Insufficient physical activity has been linked to an increased risk of mortality [2] as well as several chronic diseases. Therefore, exercise-based interventions are being promoted to reduce the risk of such diseases, to increase the disease-free time and/or to improve the quality-of-life and well-being of healthy adults [3].

However, in contrast to what happens in other tissues/organs of the human organism, the effects of physical activity/exercise on the eye

structure and functioning, either under physiological conditions or in the context of the pathophysiology of ocular diseases, are largely unknown. Dry eye disease (DED) is among the most frequent chronic pathological conditions affecting the eye. Although its prevalence is difficult to establish, it may range between 5 and 50% of the population [4]. A recent longitudinal study has shown that once initiated, DED tends to progress [5]. DED symptoms impair the perceived quality of life of the affected people and in highly symptomatic individuals cause a work-related impact similar to depression [6]. Therefore this pathological condition is considered a true public health issue, for which a wide range of treatments are in development [7,8]. Although several risk factors have been identified, either non-modifiable (such as age or

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biological sex, among others) or modifiable (such as the time of screen use, the use of ocular hypotensive medications, etc.), to the best of our knowledge the specific role of physical activity or exercise on mitigating the development of DED signs and symptoms has not been previously reviewed.

Therefore, a scoping review of the literature aimed to identify previously published works in which the potential association between the level of physical activity and the amelioration of DED signs and symptoms has been performed.

2. Methods

The literature search was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement [9] without any restriction. A search of PubMed and Web of Science databases was undertaken for articles published up to 11th February 2022 that included two categories of terms: a) DED associated terms: dry eye, Schirmer, phenol red thread, blinking, lacrimal apparatus, lacrimal gland, ocular surface, tear film and tearing; and, b) physical activity or exercise associated terms: exercise, physical activity, physical training, lifestyle-sedentary, sedentary and physical inactivity. Within each category, the terms were combined with the Boolean operator OR to obtain two main searches, one related to DED and another with physical activity or exercise. The results of both searches were combined with the Boolean operator AND to obtain the final search. Additional items were obtained from relevant references cited in previous works or through subscription to periodic notifications to recently accepted/published papers. Given the lack of previous knowledge on the potential number of papers, their study designs, effect sizes, etc., the current study was considered a scoping review and therefore was not registered at PROSPERO.

Two reviewers (S.N-L and A.A-M.) independently assessed the studies for eligibility based on their title and abstract. The following inclusion criteria were used: a) human studies that investigated the relationship between physical activity or exercise and tear volume, tear film stability or other dry eye disease associated signs and symptoms; and b) studies written in English or Spanish. Articles including people affected by Sjögren syndrome, meeting abstracts and papers that could not be read at full text were excluded. There were no disagreements among the reviewers in the studies to be included.

The quality of the cross-sectional and observational studies was assessed with the corresponding Study Quality Assessment Tool developed by the National Institutes for Health [10]. The quality of the interventional studies was assessed with the PEDro Scale [11].

The authorization to perform this review was granted from the Committee of Ethics and Integrity in Research of the Universidad Miguel Hernández de Elche (authorization code TFG.GAF.AAM.SNL.211005).

3. Results

After removing duplicates, 239 unique records were subjected to title and abstract reading and 213 of them were excluded. After reading the 26 remaining articles, 11 of them were unanimously excluded and finally the full text of 15 articles was reviewed. An additional relevant paper published after the search date was also included. Fig. 1 summarizes the flow diagram of the search. The overall quality of the included studies was rated as good.

The included articles were distributed in two main categories: a) papers that explored the acute effects of exercise (Table 1, $n = 8$); and b) papers that studied the effects of long-term exposure to physical activity or exercise (Table 2, $n = 8$).

Among the articles that explored the acute responses to exercise,

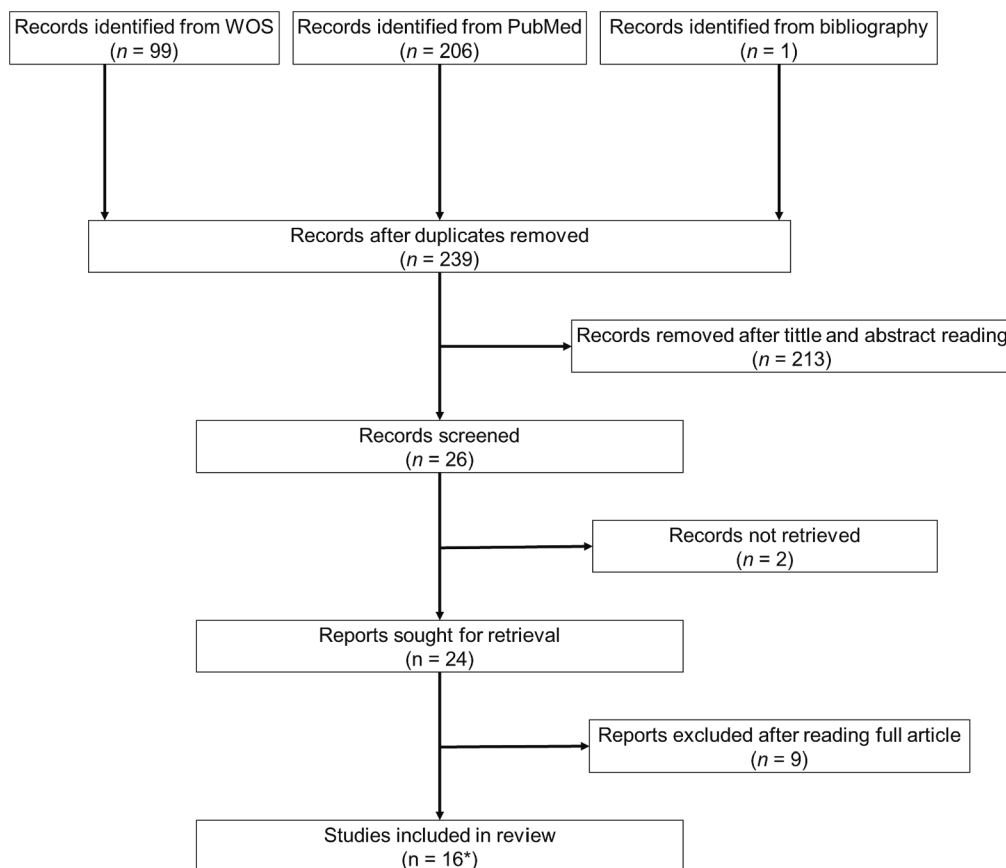


Fig. 1. Flow diagram of the literature search and study selection, according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement [9]. WOS: Web of Science. * An additional reference (Nugyen et al, 2023) [29] was added after the date of the search.

Table 1
Acute effects of physical activity or exercise on tear film signs and symptoms

Author / Year	Study design	Sample	Physical activity or exercise	Signs	Symptoms	Main findings	NIH / PEDro scale
Vera et al, 2017	Quasi-experimental (pre vs. post, without control group)	<ul style="list-style-type: none"> $n = 19$ helicopter pilots 36.58 ± 8.17 years old Males 	<ul style="list-style-type: none"> Treadmill (maximal aerobic exercise) Maximal intensity 3 min warm-up (8 km/h), 1% slope Test set up to 10 km/h and increased 0.25 km/h every 15 s 5 min cold down Indoor 	<ul style="list-style-type: none"> Tear osmolarity (TOsm) 	Ocular Surface Disease Index (OSDI)	<ul style="list-style-type: none"> ↑ Fitness ↓ Tosm = OSDI 	1, 0, 0, 1, 0, 0, 0, 1, 1, 1, 1 = 6
Wylegala et al, 2019	Quasi-experimental (pre vs. post, without control group)	<ul style="list-style-type: none"> $n = 34$ healthy subjects 25.09 ± 1.7 years old 18 male, 16 female 	<ul style="list-style-type: none"> Cycloergometer (incremental aerobic exercise) Low to vigorous intensity 3 min warm-up 5 min test and another consecutive 5 min test at higher intensity Controlled indoor environment 	<ul style="list-style-type: none"> TOsm TBUT Number of blinks per minute 	-	<ul style="list-style-type: none"> After exercise ↑ Tosm During exercise ↑ Tosm in woman than man = TBUT ↓ blinking rate during exercise 	1, 0, 0, 1, 0, 0, 0, 1, 1, 1, 1 = 6
Peart et al, 2020	Quasi-experimental (dry ambient exposure, resting vs. exercising, without control group)	<ul style="list-style-type: none"> $n = 12$ healthy subjects 26.7 ± 5.7 years old 7 male, 5 female 	<ul style="list-style-type: none"> Cycloergometer (continuous aerobic exercise) Vigorous to very hard intensity 5 min warm-up 15 min cycling Artificial indoor low humidity environment 	<ul style="list-style-type: none"> Schirmer test Matrix metalloproteinase-9 (MMP-9) in tear film 	OSDI	<ul style="list-style-type: none"> = Schirmer test = MMP-9 in tear film ↓ OSDI after exercise 	1,1,0,1,0,0,0,1,1,1,1 = 7
Wylegala et al, 2020	Experimental (inhalation vs. non-inhalation of oxygen)	<ul style="list-style-type: none"> $n = 30$ healthy subjects 24.9 ± 1.69 years old Males 	<ul style="list-style-type: none"> Cycloergometer (continuous aerobic exercise) Vigorous intensity 2 min warm-up 2 min cycling, 10 min recovery and another 2 min cycling with inhaling placebo or oxygen Controlled indoor environment 	<ul style="list-style-type: none"> TOsm 	-	<ul style="list-style-type: none"> ↓ TOsm in group that breath oxygen 	1, 0, 0, 1, 1, 0, 0, 1, 1, 1, 1 = 7
Li et al, 2020 Part 1	Quasi-experimental	<ul style="list-style-type: none"> $n = 30$ healthy subjects 23.3 ± 3.6 years old 17 males, 13 females 	<ul style="list-style-type: none"> Treadmill (continuous aerobic exercise) Vigorous intensity 30 min running Controlled indoor environment 	<ul style="list-style-type: none"> Lower Tear Meniscus Area (LTMA) Lower Tear Meniscus Volume (LTMV) 	-	<ul style="list-style-type: none"> ↑ LTMA 10 min after exercise ↑ LTMV 10 min after exercise 	1, 0, 0, 1, 0, 0, 0, 1, 1, 1, 1 = 6
Li et al, 2020 Part 2	Quasi-experimental	<ul style="list-style-type: none"> $n = 13$ healthy subjects 23.6 ± 3.7 years old 8 males, 5 females 	<ul style="list-style-type: none"> Treadmill (continuous aerobic exercise) Vigorous intensity 30 min running Controlled indoor environment 	<ul style="list-style-type: none"> Tears and cytokines collection by capillary micropipette 	-	<ul style="list-style-type: none"> ↓ Inflammatory cytokines after exercise = Inflammatory cytokines to baseline levels after 60 min, except IL-2 	1, 1, 1, 1, 1, 1, 1, 0, 1, 0, 1, 1, 1 = 11
Colorado et al, 2020	Observational	<ul style="list-style-type: none"> $n = 26$ healthy subjects 22 ± 3.7 years old Females 	<ul style="list-style-type: none"> Self-administered questionnaires from two validated questionnaires Exercise frequency 	<ul style="list-style-type: none"> Phenol Red Thread (PRT) TBUT Ocular surface assessment (Effron grading) 	<ul style="list-style-type: none"> Ocular Surface Disease Index (OSDI) Overall Ocular Comfort (OOC) 	<ul style="list-style-type: none"> ↑ Exercise ↑ PRT only in ovulation phase = TBUT = Effron grading = OSDI ↑ OOC at day 21 than day 7 	1, 1, 1, 1, 1, 1, 1, 0, 1, 0, 1, 1, 1 = 11
Abokyi et al, 2022	Experimental (high vs. low cardiorespiratory fitness)	<ul style="list-style-type: none"> $n = 52$ healthy subjects 18-25 years old Both sexes 	<ul style="list-style-type: none"> Treadmill (maximal aerobic exercise) Maximal intensity 10 min warm-up Test set up to 4.02 km/h and increased 	<ul style="list-style-type: none"> PRT TBUT 	-	<ul style="list-style-type: none"> ↑ Fitness ↑ PRT after exercise ↑ Fitness ↑ TBUT before and after exercise than non-fitness subjects 	1, 0, 0, 1, 0, 0, 0, 1, 1, 1, 1 = 6

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Table 1 (continued)

Author / Year	Study design	Sample	Physical activity or exercise	Signs	Symptoms	Main findings	NIH / PEDro scale
Sun et al, 2022	Experimental (healthy subjects vs. DED patients)	<ul style="list-style-type: none"> • $n = 52$ healthy and DED patients • adults, 18–30 years old • Both sexes 	velocity and slope every 3 min <ul style="list-style-type: none"> • Indoor environment similar to outside environment conditions • Jogging (continuous aerobic exercise) • Vigorous intensity • 30 min jogging • Outdoor environment 	<ul style="list-style-type: none"> • Schirmer I test • Keratograph 5M used to measure TBUT • Number of complete blinks and incomplete/total blinks • Tears compositions • Tear meniscus height 	OSDI	<ul style="list-style-type: none"> ↑ Schirmer I test after exercise in DED patients ↓ Schirmer I test after 30 min exercising in DED patients ↑ TBUT after exercise in DED patients ↓ incomplete blinks after 10 min of exercise in DED patients ↑ complete blinks after 10 min of exercise in DED patients ↓ 8-OHdG after exercise in DED patients 	1, 0, 0, 1, 0, 0, 0, 1, 1, 1, 1 = 6

seven followed an experimental or quasi-experimental design, and there was only one with an observational design [12]. Except for the latter, in which the regular physical activity or exercise was studied as one of the lifestyle factors that could affect the clinical assessment of the ocular surface during the menstrual cycle in women, only the acute responses to aerobic exercise were explored. Among them, only one studied responses in DED patients [13], while the remainder compared responses among healthy volunteers with different physical fitness levels (trained vs. untrained). Similarly, the studies with a quasi-experimental design only included healthy volunteers.

Within the papers that explored the effects of long-term physical activity or exercise on DED associated signs and symptoms, only one randomized controlled trial was identified [14], in which the effects of a two-month, daily, unsupervised and polymodal exercise intervention was tested.

Except for one study that was performed in children [15], the rest only included adults of both biological sexes. In most of the papers, the included population consisted of adults between the 2nd and the 6th decade of life, although in a minor number of works, older people (≥ 70 years) were also included. Most of the included studies were carried out in individuals of Asian descent, followed by European and African descent. Longitudinal studies included both men and women, whereas acute interventional studies included mostly men, with few women participating.

Physical activity or exercise was estimated or measured in different ways. In the interventional studies which aimed to analyse the acute responses to exercise, in three papers the exercise consisted of running on a treadmill [16–18] while in the other three publications it was pedalling a *cyclo-ergometer* [19–21]. Most studies were carried out indoors, four with controlled environmental conditions, and another with indoor environmental conditions similar to the outdoor ones [18]. In only one work [13] was the intervention carried out outdoors, i.e. running on a field track. The exercise intensity was measured by electrocardiography and pulmonary gas exchange analysis in two papers [16,21], and indirectly estimated in the remaining articles [13,17–20]. Two interventions consisted of 30 min of submaximal exercise at 60–80 % maximal heart rate- [13,17], whereas only in one did the exercise reach maximal intensity [16]. In one paper exploring the long-term

effects of physical activity or exercise [22], habitual practice was estimated with a validated instrument, the International Physical Activity Questionnaire (IPAQ) [23], whereas *ad hoc*, non-validated instruments were used in the remaining studies.

The DED-associated signs explored included tear volume, tear osmolarity and tear film stability. Assessment of tear volume was carried out with the 5-minute Schirmer test without topical anesthesia [13,14,21,22,24] or the phenol-red thread test [12,18]. In one study, the volume of the lower tear meniscus was measured [17]. Tear osmolarity was measured in three papers [16,19,20]. Tear film stability was measured with the tear break-up time (TBUT) in five papers [12–14,18,22]. Molecular changes of the tear film have been also studied in three studies [13,17,21].

DED-associated symptoms were assessed with different instruments: the Ocular Surface Disease Index (OSDI) was used in two reports [12,25], the Dry Eye Quality of life Score (DEQS) in two reports [14,15], the Symptom Assessment in Dry Eye (SANDE) in one report [21], and other *ad hoc* developed instruments in three reports [22,24,26].

Regarding the acute effect of a single bout of exercise on tear volume, a recent work [18] has shown that a maximal intensity exercise session increased tear volume solely in trained individuals. Additionally, other indicators of tear volume, such as lower tear meniscus volume and area, transiently increased 10 min after performing exercise at an intensity between 60 and 80% of the maximal heart rate, and returned to baseline levels 10 min afterwards in healthy individuals [17]. Similarly, in young individuals diagnosed with DED, a transient increase of tear volume at the end of an exercise session, that returned to baseline within 30 min, has been reported [13]. In contrast, other authors found that the exercise performed by healthy individuals in a controlled dry environment (25 °C, 20% relative humidity) had no effect on tear volume when compared to tear volume at rest, either under the same controlled environmental conditions or under conventional laboratory conditions [21].

Regarding tear film osmolarity, one study found it to increase after a maximal aerobic exercise session [16]. A detailed analysis of this work showed that in well-trained individuals this response was absent, being restricted to individuals with low values of maximal oxygen uptake. The change in tear osmolarity after the maximal exercise bout was

Table 2
Long-term effects of physical activity or exercise on tear film signs and symptoms

Author / Year	Study design	Sample	Physical activity or exercise	Signs	Symptoms	Main findings	NIH / PEDro scale
Kawashima et al, 2014	Cross-sectional	<ul style="list-style-type: none"> • n = 425 office workers (Osaka study) • < 20 – 50 years old • Both sexes 	<ul style="list-style-type: none"> • International Physical Activity Questionnaire - Japanese (IPAQ-J) • High, moderate or low PA 	Japanese DED diagnostic criteria (2006)	<ul style="list-style-type: none"> • Schirmer I test • TBUT • Epithelial damage with fluorescein and lissamine green staining 	<ul style="list-style-type: none"> • Japanese DED diagnostic criteria (2006) Symptom questionnaire • ↑ PA ↓ DED prevalence = Schirmer I test = TBUT = Epithelial damage 	1,1,1,1,0,0,0,1,1,0,1,0,0,1 = 8
Kawashima et al, 2018	Randomized controlled trial	<ul style="list-style-type: none"> • n = 36 office workers • Adults • Both sexes 	<ul style="list-style-type: none"> • Aerobic and resistance exercises • Without prescription of intensity • 2 months, daily • 4 min squats, walk for 20 min, stepping exercises 10 min, bike for 15 min, lightly jog for 10 min or run for 7-8 min 	Japanese criteria for DED diagnosis (2007)	<ul style="list-style-type: none"> • Schirmer I test • TBUT with fluorescein and lissamine green staining • DEQS 	<ul style="list-style-type: none"> • ↑ PA ↓ number of DED diagnoses = Schirmer I test = TBUT • ↑ PA ↓ DEQS 	1,1,1,1,0,1,1,1,1,1,1 = 10
Sano et al, 2018	Quasi-experimental (pre vs. post, without control group)	<ul style="list-style-type: none"> • n = 11 office workers (Japan) • 31-64 years old • Both sexes 	<ul style="list-style-type: none"> • Resistance exercises • Without prescription of intensity • 10 weeks, 3 days/week • 5 types of core resistance exercises • Indoor environment 	-	<ul style="list-style-type: none"> • Women's Health Study Questionnaire (Schaumberg Questionnaire) • DEQS 	<ul style="list-style-type: none"> • ↑ PA ↓ DEQS 	1,0,0,1,0,0,0,0,1,1,0,0 = 4
Cheng et al, 2019	Cross-sectional	<ul style="list-style-type: none"> • n = 915 office workers • Adults • Both sexes 	<ul style="list-style-type: none"> • Their own elaboration questionnaire • Frequency per month and week • 30 min were considered exercising 	-	<ul style="list-style-type: none"> • Their own elaboration and self-administered (categorical) 	<ul style="list-style-type: none"> • ↑ PA ↓ DED symptoms 	1,1,1,0,0,0,0,1,0,0,0,1,1,0 = 6
Hanyuda et al, 2020	Cross-sectional	<ul style="list-style-type: none"> • n = 102582 (Subjects from Japan Public Health Centre-based) • 40-74 years old • Both sexes 	<ul style="list-style-type: none"> • Their own elaboration and validated questionnaire • Moderate to vigorous intensities in MET's • Frequency of PA: <ul style="list-style-type: none"> ■ < 1 time/month ■ 1-3 times/month ■ 1-2 times/week ■ 3-4 times/week ■ Every day • Duration of PA: <ul style="list-style-type: none"> ■ < 30 min ■ 30-59 min ■ 1-2 h ■ 2-3 h ■ 3-4 h ■ ≥ 4 h 	-	<ul style="list-style-type: none"> • Women's Health Study Questionnaire (Schaumberg Questionnaire) 	<ul style="list-style-type: none"> • ↑ PA ↓ DED symptoms 	1,1,1,1,1,1,1,0,1,0,0,0,0,1,1 = 9
Choi et al, 2021	Cross-sectional	<ul style="list-style-type: none"> • n = 475 South Korean • Adults • Both sexes 	<ul style="list-style-type: none"> • Their own elaboration questionnaire • Intensity were not calculated • Frequency of PA: <ul style="list-style-type: none"> ■ < 1 time/week ■ 1-2 times/week 	-	<ul style="list-style-type: none"> • Ocular Surface Disease Index (OSDI) 	<ul style="list-style-type: none"> • ↑ frequency of PA = OSDI 	1,1,1,1,0,0,0,1,1,0,1,1,1,0 = 9

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Table 2 (continued)

Author / Year	Study design	Sample	Physical activity or exercise	Signs	Symptoms	Main findings	NIH / PEDro scale
Mineshita et al, 2021	Cross-sectional	<ul style="list-style-type: none"> • $n = 7419$ children • 6 – 12 years old • Both sexes 	<ul style="list-style-type: none"> ■ 3-4 times/week ■ > 4 times/week • A item from the questionnaire, OMS Health Behaviour in School Aged Children (HBSC) • Moderate to vigorous intensities • Frequency of PA: <ul style="list-style-type: none"> ■ 1 time/week ■ 2 times/week ■ 3 times/week ■ 4 times/week ■ 5 times/week ■ 6 times/week ■ 7 times/week • Duration of PA: <ul style="list-style-type: none"> ■ ≥ 60 min 	-	Questions based in Dry Eye Related Quality of Life Score (DEQS)	↓ PA ↑ use of visual display terminals Use of visual display terminals before sleep ↑ DED	1,1,1,1,0,0,0, 1,0,0,0,0,1 = 6
Nugyen et al, 2023	Cross-sectional	<ul style="list-style-type: none"> • $n = 48418$ • 18 – 96 years old • Both sexes 	<ul style="list-style-type: none"> • Sedentary behaviour (Marshall Sitting Questionnaire) • Short questionnaire to asses health-enhancing physical activity (Dutch National Institute of Public Health and the Environment) 	Women's Health Study dry eye questionnaire (WHS-defined DED)		Higher sedentary time increased the risk of DED, specially in subjects below the physical activity or exercise recommendations of the WHO	1,1,1,1,1,0, 1,0,0,0,1,1 = 9

negatively correlated to maximal oxygen uptake. Similarly, an intervention consisting of two consecutive exercise intensities showed that tear film osmolarity is increased after a first session (5 min at an intensity between 30 and 50% of the heart rate reserve, i.e., a low to moderate intensity exercise), regardless of whether subjects had their eyes open or closed [19]. Tear film osmolarity remained elevated after a second session of exercise (5 min at an intensity between 50 and 70% of the heart rate reserve, i.e., at vigorous intensity). The osmolarity increase was more pronounced in women than in men, and was partly affected by the blinking rate [19]. In another paper where two repetitions of exercise at 70% of heart rate reserve were performed only by men, tear film osmolarity increased after the exercise protocol and this response was partly blocked by the administration of inhaled 95–99.5% oxygen between the two exercise steps [20].

Tear film stability, estimated by the TBUT, increased after a maximal exercise session in both, trained and non-trained individuals, although values were significantly higher in athletes, both at baseline and after exercise [18]. Similarly, in individuals affected by DED, exercise prolonged TBUT [13]. Nevertheless, the absence of changes in TBUT after exercise has been also reported [19].

The concentration of several cytokines, enzymes, oxidation markers and mucins in tears and its changes in response to acute maximal exercise have been studied in a few works. Among a panel of 15 cytokines, interferon- γ , tumour necrosis factor- α , interleukin (IL)-1 β , IL-4, IL-5, IL-10, IL12P70, IL-13, IL-15, IL-17A, IL-21 and IL-27 decreased 20 min after a single session of maximal intensity exercise in healthy individuals, whereas other chemokines such as CCL/MIP-3 α decreased for longer times (60 min) or were not affected by exercise, such as IL-2 [17]. The effects of exercise on IL-6 concentration seems to depend on the

phenotype, because in healthy individuals it decreased 20 min after exercise [17], whilst in people affected by DED its concentrations was unaffected 30 min after exercise [13]. The enzyme matrix metalloproteinase 9 (MMP-9), a key biological marker of DED, has also been quantified in two papers. Tear levels of MMP-9 increase in healthy individuals when exposed to a desiccating environment, but the increase was smaller when participants exercised to exhaustion [21]. In contrast, in people affected by DED, MMP-9 concentration was unaffected by a similar session of maximal exercise [13]. In DED subjects, tear concentration of lactoferrin and mucin 5 subtype AC (MUC5AC) did not change with exercise [13], but no data have been reported yet in healthy individuals. Interestingly, exercise decreased the tear concentration of the oxidative marker 8-hydroxy-2'-deoxyguanosine (8-OHdG), while the concentration of (O-acyl)- ω -hydroxy fatty acids, which is closely related to tear film stability, did not change.

Regarding the effects of exercise on subjective DED symptoms, exposure of healthy individuals to a desiccating environment increased their frequency and severity. This increase of symptoms was abolished after the individuals performed a session of maximal intensity exercise [21].

Another set of papers analysed the long-term effects of physical activity or exercise on tear production and tear stability. They were distributed in two categories: a) interventional studies; and b) association studies.

Two long-term interventional studies were found, a randomized clinical trial (RCT) [14] and a quasi-experimental design study [27]. Even considering both studies together, the effects of long-term exposure to exercise as an intervention have been tested in a very limited number of subjects ($n = 28$) and therefore it is very difficult to draw

definitive conclusions.

In the quasi-experimental study, a cognitive behavioural therapy-based exercise program that consisted of an initial psychological intervention followed by 10 weeks of abdominal core strength training (performed 3 days a week, at home, following a workbook, with the practical guidance of a health exercise instructor) was undertaken by sedentary office workers (31–64 years) of both biological sexes [27]. After the intervention, the mean DEQS score decreased, although in a few individuals it was unchanged.

In the RCT, a multi-component intervention (combining diet, exercise and encouragement of positive-thinking) was implemented for three months in young, sedentary office workers of both biological sexes [14]. The exercise program adhered to the 2006 exercise guidelines of the Ministry of Health, Labour and Welfare of Japan, and consisted in performing one of these activities daily: squats for 4 min, walking for 20 min, stepping exercises for 10 min, biking for 15 min, lightly jogging for 10 min, or running for 7–8 min. The diet intervention was aimed to reduce the carbohydrate intake, as well as balancing the fish and fresh vegetables intake, thanks to an agreement with the company's cafeteria. Data analysis was performed in individuals that executed $\geq 60\%$ of the intervention. After the intervention, the experimental group showed significantly lower DEQS scores than the control group, although TBUT and tear volume showed no differences between groups. Within the DEQS items, the experimental group showed a reduction in the «painful or sore eyes» and «ocular fatigue» descriptors. The authors attributed the mismatch between DED signs and symptoms to a possible association of DED symptomatology with depression.

In addition to the interventional studies, a series of cross-sectional studies have found potential associations of DED signs or symptoms with reduced habitual physical activity. The first study in which physical activity was associated to DED was performed in Japan and named the «Osaka Study» [22]. Its results have been also summarized and updated recently [24]. In a cross-sectional survey including nearly 425 adult office workers of both biological sexes, the Osaka Study measured physical activity with the Japanese version of the IPAQ, tear volume, TBUT and dry-eye associated symptoms using an *ad hoc* questionnaire [24]. After distributing the participants into two groups, DED and non-DED, they found that non-DED participants tended to score higher in the IPAQ, with a significant higher weekly energy expenditure. TBUT was shorter in sedentary individuals than in physically active participants, although tear volume was similar in both groups.

In a study performed in 915 Chinese adult internet workers of both biological sexes (more than 50% of them younger than 30 years old) the association of habitual physical activity with DED was also suggested [28]. Although the methods reported to estimate habitual physical activity and DED were not explicitly validated, a significant reduction of the eye-discomfort associated symptoms (such as reduced vision) was found among those who declared exercise 3 or more times per week, in comparison with participants reporting lower, habitual, physical activity.

The largest cross-sectional study to date (102,582 adult participants, 47,346 men and 55,236 women, 40–74 years) that associated habitual physical activity with DED was also conducted in a Japanese population [26]. Data were obtained from the ongoing, cohort JPHC-NEXT Study, in which DED and physical activity were reported through self-administered questionnaires, complemented with telephone interviews. After categorizing by gender, participants were classified into quartiles of total leisure-time physical activity, estimated in metabolic equivalent hour per day (METs-hour/day). A reduction in the prevalence of DED was found within the increased leisure-time total physical activity group, for both men and women. The inverse association was found for the total daily sitting time.

In contrast with previous works, a more recent cross-sectional study in 475 adults of both biological sexes of a single rural area, recruited from the cohort of the Korean Study of Environmental Eye Disease, has reported an absence of effect of habitual physical activity on DED-

associated signs [25]. Although in this study DED diagnosis was determined with the OSDI, the habitual physical activity was estimated with a non-validated questionnaire, and the subjects were distributed based on their declared weekly frequency of exercise practice.

The latest work [29], a cross-sectional data exploitation of a cohort study in the north of the Netherlands, including data from 48,418 adults, has linked sedentary behaviour (i.e., the daily time spent sitting) with an increased risk of experiencing DED. For comparisons, DED cases were distributed among highly symptomatic vs. clinical diagnosis. After correcting for several variables (including 48 comorbidities associated with DED), and separating the individuals in two groups (those under the physical activity or exercise recommendations of WHO and those meeting these recommendations), the authors found that the higher risk of experiencing DED, specially highly symptomatic DED, that was associated to the daily sitting time, was abolished in the participants that followed the WHO recommendations of physical activity or exercise.

4. Conclusions

This scoping review of the literature aimed to synthesize the current knowledge on the potential association between physical activity or exercise and DED. It was found that since the first observation of a potential association, provided by the Osaka Study [22], the scientific interest in this topic has been increasing over time. The more recent works, which include experimental or quasi-experimental designs, randomized controlled trials, or exploitation of large datasets, provide more convincing evidence of a positive association between physical activity or exercise and tear volume and osmolarity, tear film stability, and the alleviation of DED symptoms. Despite this, the literature covering this topic is still scarce and heterogeneous in terms of study design, studied population or measurement methods, so current conclusions cannot be regarded as definitive.

From the available literature some findings seem to arise. Independently of the presence or absence of dry eye and of the level of physical fitness of the individual, many works agree that after performing a short bout of high to maximal intensity aerobic exercise: a) tear volume increases; b) tear osmolarity increases; and c) TBUT does not change or is prolonged. These responses have been only observed acutely after a single exercise bout. The duration of the response and whether it is maintained after repeated bouts of exercise need to be further studied.

The increased tear volume and tear film osmolarity seem to be somewhat contradictory and need to be much more clearly explained in future studies. A possible explanation could be that the TearLab® instrument used in the reviewed works has a large variability (10.5 to 15 mOsm·l⁻¹ [30,31], even in resting individuals. The reported changes of tear film osmolarity after exercise are within the range of the variability of this instrument in all the published papers, and within the normal range of tear osmolarity in healthy subjects [32]. In addition, only one measurement of tear film osmolarity was taken per individual and time-point. Given the variability of the system it has been suggested that at least three consecutive measurements should be taken and the average value used for comparisons [30]. Therefore, based on the current literature, the increase in tear film osmolarity after a single bout of maximal or near maximal aerobic exercise should be interpreted cautiously. Since the increased tear volume and osmolarity were reported in different and independent studies, future studies could try to measure them in the same sample.

Although the absolute value of the osmolarity change may simply reflect the variability of the measurement system, it is interesting that all the papers suggest an increasing trend after the exercise bout. This is observed even at low to moderate exercise intensity of short duration, and seems to be independent of tear evaporation, since it occurred either when the individuals had their eyes open or closed during exertion [19]. A potential link between osmolarity and oxygen bioavailability is suggested by the fact that after supplemental oxygen administration [20] or in individuals with high maximal oxygen uptake [16] the increase of

tear film osmolarity in response to high or maximal intensity exercise was of lower magnitude. The smaller change in tear film osmolarity in individuals with high maximal oxygen uptake fits well with the observation of an increased tear volume in trained individuals after an exercise bout [18], and suggests the potential involvement of structures with oxygen chemosensitivity in the modulation of this response.

The currently prevailing view is that during exercise of increasing intensity, an initial sharp reduction of the parasympathetic activity occurs which is followed by the progressive activation of the sympathetic nervous system. This view has been recently challenged, as a high degree activity of the parasympathetic division seems to be still present when exercising at moderate to high intensity [33]. Interestingly, the acinar cells of the lacrimal gland have cholinergic and adrenergic receptors, and both seem to independently stimulate lacrimal gland blood flow on the one hand, and the secretion of proteins, water and electrolytes on the other [34,35]. Therefore, the concurrent activity of both autonomic divisions on the lacrimal gland could be influencing the increased tear volume and/or its different composition after exercise.

Regarding the studies in which the long-term effect of exercise was studied, they rely mostly on the relief of DED associated symptoms and in some, increased TBUT was also found. Therefore, it seems difficult to establish a causal relationship between the improvement of DED signs caused by the exercise and the reported reduction of DED associated symptoms. Other independent factors, such as the reduced time of screen exposure due to the time that the individual dedicated to the exercise sessions could be also involved. In experimental animal models several central and peripheral mechanisms have been identified as potential mediators of exercise-induced analgesia [36]. Some of them may be also involved in the reduction of the pain sensations that DED patients experience when performing physical activity or exercise. Additionally, it is interesting to note that although the autonomic control of Meibomian gland secretion is not fully understood [35], the rat Meibomian gland displays parasympathetic innervation [37,38] and cultured human Meibomian cells express cholinergic receptors [39] whose stimulation may influence intracellular calcium dynamics and cell proliferation. Habitual physical activity or exercise produces a long-term adaptation of the autonomic nervous system, increasing the so-called "parasympathetic tone". Therefore, it can be hypothesised that under a higher, basal, tonic activity of the parasympathetic division of the autonomic nervous system due to an habitual practice of physical activity or exercise [33], both the lacrimal gland secretion and the physiological functioning of the Meibomian gland should be improved.

In summary, the current literature strongly suggests a potential role for physical activity as a modulatory stimulus for the proper functioning of the tear film and the prevention or alleviation of DED signs and symptoms, even though further studies are needed to clearly establish a causal relationship. In the light of the current knowledge on this topic future works should reduce the heterogeneity of the study designs. For instance, since the prevalence of DED is influenced by factors such as sex or age [4,40,41] study samples should be more representative of the population diagnosed with DED. In addition, they should further explore the mechanisms underlying the association between physical activity and dry eye, and develop interventions based on the current international recommendations on physical activity and exercise.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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