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Use of digital displays and ocular surface alterations

TESIS DOCTORAL

Presentada por:
Cristian Talens Estarelles

Dirigida por:
Santiago García Lázaro
Alejandro Cerviño Expósito

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USE OF DIGITAL DISPLAYS AND OCULAR SURFACE ALTERATIONS

Memoria presentada por
CRISTIAN TALENS ESTARELLES
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DECLARACIÓN

Ninguna parte de este trabajo ha sido presentada para optar a ningún otro grado ni titulación, ni en esta ni en otra universidad o institución educativa o de investigación.

El Dr. Santiago García Lázaro, Profesor Titular de la Universidad de Valencia y el Prof. Alejandro Cerviño Expósito, Catedrático de la Universidad de Valencia

CERTIFICAN que la presente memoria “Use of digital displays and ocular surface alterations” resume el trabajo de investigación de D. Cristian Talens Estarelles, bajo su dirección y supervisión, y constituye su Tesis Doctoral para optar al Grado de Doctor en Optometría y Ciencias de la Visión.

Y para que así conste, y en cumplimiento de la legislación vigente, firman el presente certificado en Valencia, a mayo de dos mil veintitrés.

Fdo. Santiago García Lázaro Fdo. Alejandro Cerviño Expósito

A l'abuelita i l'abuelito,

per escriure les pàgines més boniques de la meua vida

"*And medicine, law, business, engineering, these are noble pursuits and necessary to sustain life. But poetry, beauty, romance, love, these are what we stay alive for. To quote from Whitman, "O me! O life! of the questions of these recurring; ... Of myself forever reproaching myself; Of eyes that vainly crave the light, of the objects mean, of the struggle ever renew'd; ... What good amid these, O me, O life?* Answer. *That you are here – that life exists, and identity; that the powerful play goes on, and you may contribute a verse. That the powerful play *goes on* and you may contribute a verse. What will your verse be?*"

N.H. Kleinbaum, Dead Poets Society

Walt Whitman, O me! O life!

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Resumen

Aunque nuestra comprensión de los efectos del uso de dispositivos electrónicos sobre la superficie ocular ha aumentado considerablemente desde el inicio de siglo, varias preguntas importantes siguen sin respuesta. Asimismo, los avances tecnológicos y la aparición de nuevas formas de dispositivos digitales hacen necesaria una investigación continua. Esta tesis doctoral presenta un total de 12 estudios independientes los cuales constituyen los pilares de este trabajo (Capítulos 4-15).

En primer lugar, el **Capítulo 4** tuvo como objetivo evaluar la asociación entre los factores de riesgo de la enfermedad de ojo seco (EOS) y el síndrome visual informático (SVI). Se llevó a cabo una encuesta *online* anónima en 851 estudiantes universitarios. Los participantes se clasificaron en dos grupos, en función de si padecían SVI (n = 628) o no (n = 222). Los resultados de este capítulo revelaron que varios factores de riesgo y condiciones de salud relacionados con el ojo seco están asociados con el SVI, por lo que las preguntas relacionadas con los factores de riesgo de la EOS pueden ser especialmente relevantes en pacientes que usan dispositivos electrónicos por períodos prolongados.

Las anomalías del parpadeo constituyen uno de los principales mecanismos causantes de las alteraciones de la superficie ocular asociadas al SVI. Así pues, el objetivo del **Capítulo 5** fue evaluar las diferencias en la cinemática del parpadeo durante la lectura con diferentes dispositivos electrónicos y una condición control sin dispositivo. Treinta y dos sujetos jóvenes fueron incluidos en este estudio. Se grabó el parpadeo de los participantes mientras leían en un ordenador portátil, una tableta, un libro electrónico (e-book), un teléfono móvil y durante una tarea control sin dispositivo. A juzgar por los resultados, la cinemática de parpadeo varía considerablemente entre los dispositivos y con respecto a una tarea de baja demanda cognitiva sin dispositivo. Estas diferencias probablemente se deban a la diferente forma en que se posicionan y usan las pantallas y a la demanda cognitiva de la tarea.

En la actualidad existen diferentes tipos de dispositivos electrónicos y las diferencias en su naturaleza y en la forma en que se utilizan pueden condicionar su impacto sobre la superficie ocular. Teniendo en cuenta los resultados del Capítulo 5, el **Capítulo 6** tuvo como objetivo comparar el impacto de dispositivos anteriores sobre la superficie ocular y la película lagrimal de 31 individuos jóvenes. El impacto más bajo se obtuvo con el teléfono móvil y el e-book, probablemente debido a un ángulo de mirada más bajo asociado con el uso del teléfono móvil y a las propiedades ópticas mejoradas del e-book. La instilación de lágrima artificial no mostró una mejora estadística en las

variables de superficie ocular y película lagrimal para el mismo dispositivo, aunque atenuó los efectos del uso de la pantalla.

Por otro lado, la identificación de individuos con predisposición a alteraciones de la superficie ocular con el uso de los dispositivos electrónicos puede proporcionar al especialista una ventaja considerable en el manejo de la condición. El **Capítulo 7** tuvo como objetivo identificar qué parámetros de la superficie ocular y la película lagrimal son predictores del impacto del uso del ordenador sobre la superficie ocular. Para ello, se evaluó la superficie ocular de 82 estudiantes universitarios antes y después de leer con un ordenador durante 30 minutos. Los resultados mostraron que los participantes con mayores síntomas de ojo seco tenían más probabilidades de experimentar un mayor aumento de los síntomas con el uso del ordenador, mientras que un tiempo de ruptura lagrimal más largo y un mayor aumento del enrojecimiento conjuntival estaban asociados a una mayor reducción de la estabilidad lagrimal.

Hoy en día los especialistas tienen una variedad de estrategias de manejo disponibles para prevenir o reducir los efectos del uso de dispositivos digitales sobre la superficie ocular. El **Capítulo 8** tuvo como objetivo evaluar y comparar la efectividad de cuatro estrategias principales de manejo (instilación inicial de lágrima artificial, descanso breve, uso de un filtro de luz azul y control de parpadeo) para prevenir los efectos del uso de pantallas digitales sobre la superficie ocular, en una muestra de 47 individuos jóvenes. Los resultados de este capítulo evidenciaron que la instilación de lágrima artificial y el control del parpadeo son las mejores estrategias de manejo para prevenir los efectos del uso de pantallas digitales sobre la superficie ocular, mientras que el uso de un filtro de luz azul no ofrece beneficios apreciables.

El uso de lentes de contacto es ampliamente reconocido como uno de los principales factores de riesgo para la EOS y, en consecuencia, para el SVI. Por ende, el **Capítulo 9** tuvo como objetivo evaluar los posibles efectos sumatorios del uso de dispositivos electrónicos (ordenador y teléfono móvil) por periodos cortos y de lentes de contacto sobre la superficie ocular y la película lagrimal en una muestra de 34 adultos jóvenes. Los hallazgos de este capítulo indicaron que el uso de lentes de contacto no tiene efectos sumatorios sobre los signos y síntomas de ojo seco cuando se usan dispositivos digitales por períodos cortos y que la instilación de lágrima artificial es una estrategia eficaz para reducir el impacto del uso de dispositivos electrónicos en usuarios de lentes de contacto.

Del mismo modo, el ojo seco se clasifica como el efecto adverso más común de la queratomileusis in situ asistida por láser (LASIK, del inglés *laser in-situ keratomileusis*), teniendo esta técnica la mayor incidencia y gravedad de EOS posoperatoria de todos los procedimientos queratorefractivos. El objetivo del **Capítulo 10** fue evaluar el impacto del uso del ordenador por periodos cortos sobre la superficie ocular en personas intervenidas de LASIK, a fin de determinar si los pacientes post-LASIK tienen un mayor riesgo de ojo seco asociado al uso de dispositivos digitales. Se evaluaron los síntomas de ojo seco y la superficie ocular de 18 individuos jóvenes intervenidos de LASIK miópico y 18 controles, antes y después de realizar una tarea de 30 minutos utilizando un ordenador con y sin instilación inicial de lágrima artificial. En definitiva, el aumento de los síntomas de ojo seco y los síntomas de SVI reportados durante la tarea con el ordenador fueron similares entre ambos grupos de estudio. Los síntomas estuvieron acompañados por un empeoramiento significativo de los signos de ojo seco en el grupo LASIK. Por otro lado, la instilación de lágrima artificial fue eficaz para prevenir el empeoramiento de los signos y síntomas del ojo seco en ambos grupos poblacionales.

El objetivo del **Capítulo 11** fue evaluar la relación entre los síntomas oculares y la sensibilidad corneal a estímulos mecánicos y fríos en 52 usuarios frecuentes de ordenador, tras haberse reportado que períodos repetidos de estimulación de la superficie ocular por inestabilidad lagrimal pueden alterar la excitabilidad de los receptores corneales y su capacidad de respuesta a estímulos nuevos. Los umbrales de sensibilidad mecánica y al frío de la córnea central se determinaron en un ojo aleatoriamente seleccionado de cada participante utilizando el UNSW LJA (del inglés *University of New South Wales Liquid Jet Aesthesiometer*). Los usuarios de ordenador sintomáticos mostraron umbrales de sensibilidad al frío más bajos en comparación con los usuarios asintomáticos, lo que sugiere alteraciones en la función sensorial de la córnea en usuarios de ordenador con SVI. Asimismo, mayores síntomas de SVI, particularmente síntomas relacionados con el ojo seco, se asociaron con umbrales de excitación más bajos (hipersensibilidad) de las neuronas corneales a estímulos fríos.

Teniendo en cuenta estos hallazgos, el **Capítulo 12** tuvo como objetivo evaluar los posibles efectos del uso del ordenador durante periodos cortos sobre la sensibilidad de la córnea y analizar las asociaciones con posibles factores determinantes en una muestra similar de sujetos jóvenes. Las medidas de sensibilidad se tomaron antes y después de trabajar con un ordenador de sobremesa durante 1 hora en una tarea de libre

elección. En base a los resultados de este capítulo, el uso del ordenador durante un periodo de una hora no tuvo ningún efecto sobre la sensibilidad de la córnea central a estímulos mecánicos y fríos. Además, los síntomas oculares y las variables demográficas no se asociaron con los cambios en la sensibilidad con el uso del ordenador.

Debido al cambio significativo en el índice de refracción del aire a la película lagrimal, las anomalías en la película lagrimal pueden afectar notablemente a la calidad visual. Con esta premisa en mente, el objetivo del **Capítulo 13** fue evaluar y comparar exhaustivamente los cambios en la función visual y la calidad óptica y de la película lagrimal en un grupo de trabajadores que usaban el ordenador como herramienta de trabajo (n = 40) y un grupo de trabajadores sin ordenador (n = 40) a lo largo de una jornada laboral normal. Según los resultados de este capítulo, aunque la agudeza visual se mantuvo sin cambios, varios aspectos de la función y la calidad visual disminuyeron durante un día de uso del ordenador. Estos cambios estuvieron acompañados de una mayor sintomatología de ojo seco y alteraciones de la película lagrimal, las cuales probablemente jugaron un papel fundamental.

El SVI está muy influenciado por la demanda visual y la duración de la tarea. A los usuarios frecuentes de dispositivos digitales a menudo se les recomienda seguir la regla 20-20-20 (apartar la mirada de la pantalla durante al menos 20 s a un objeto distante situado a una distancia de al menos 20 pies tras 20 minutos de trabajo continuo), aunque con evidencia científica limitada. El objetivo del **Capítulo 14** fue evaluar los beneficios visuales de tomar descansos regulares basados en esta popular regla de ergonomía visual. Para ello, se descargó en los ordenadores portátiles de 29 usuarios de ordenador sintomáticos un software informático (*eyeblink,* https://www.blinkingmatters.com/), modificado por el desarrollador para este estudio, que utilizaba la cámara web del ordenador para evaluar los descansos del usuario, la mirada y el parpadeo, y el cual emitía recordatorios personalizados de descansos basados en la regla 20-20-20. El SVI, la visión binocular y la superficie ocular se evaluaron antes y después de seguir la regla durante dos semanas y una semana tras su interrupción. Los resultados de este capítulo indicaron que la regla 20-20-20 es una estrategia eficaz para reducir los síntomas de SVI y ojo seco, aunque dos semanas no fueron suficientes para mejorar considerablemente la visión binocular o los signos de ojo seco.

Por último, teniendo en cuenta los cambios globales en la educación y en los patrones de uso de la tecnología que surgieron tras el brote de coronavirus (COVID-19), el **Capítulo 15** tuvo como objetivo evaluar los posibles efectos de cambiar a un formato

de educación *online* sobre los síntomas de ojo seco y los factores de riesgo de la EOS. Para ello se llevó a cabo una encuesta *online*, transversal y anónima en 812 estudiantes universitarios. En general, asistir a clases *online* se asoció de forma independiente con tener síntomas de ojo seco. A pesar de una menor prevalencia de factores de riesgo de EOS, un mayor uso del ordenador estuvo detrás de la mayor sequedad ocular reportada por los estudiantes *online*.

Abstract

Although our understanding of the effects of digital display use on the ocular surface has increased considerably since the turn of the century, several major questions remain unanswered. Likewise, technological advances and the appearance of new forms of digital displays demand continuous research. This thesis presents a total of 12 independent studies that constitute the chapters of this work (Chapters 4-15).

In the first place, **Chapter 4** aimed to explore the association between digital eye strain (DES) and dry eye-related lifestyle and demographic factors. For this purpose, an anonymous online survey was carried out on 851 university students. Participants were classified into DES (n = 628) or non-DES (n = 222). The results of this chapter revealed that several dry eye-related risk factors and health conditions are associated with DES. Therefore, clinicians should acknowledge the relevance of triaging questions and dry eye disease (DED) risk factors when dealing with patients who view screens for extended periods.

Blinking abnormalities make up one of the main DES-inducing mechanisms. Accordingly, the aim of **Chapter 5** was to assess the differences in blinking kinematics between reading on different digital displays and a non-device control condition. Thirty-two young individuals were included in this study. The blinks of the participants were recorded while reading on a laptop computer, tablet, electronic reader (e-reader), and smartphone and in a non-device control condition. Judging by the results, blinking kinematics seem to vary considerably between displays and with respect to a non-device, low-demanding control condition. These differences could probably be attributed to differences in the way the displays are set up and used and the cognitive demand of the task at hand.

Nowadays, numerous new kinds of digital displays have been developed and the differences in their nature and the ways in which they are set up and used may condition their impact on the ocular surface. Bearing in mind the results of Chapter 5, **Chapter 6** aimed to compare the impact of the aforementioned digital displays on the ocular surface and tear film of 31 young individuals. According to the findings of this chapter, the lowest impact was obtained with the smartphone and the e-reader, probably due to a lower gaze angle associated with smartphone use and to the enhanced optical properties of the e-reader. The instillation of artificial tears did not show a statistical improvement in ocular surface and tear film variables for the same device, although it attenuated the effects of display use.

On a different note, effective identification of individuals with a predisposition to the disruption of their ocular surface following display use can provide the practitioner with a considerable advantage in managing the condition. **Chapter 7** aimed to identify which ocular surface and tear film characteristics are relevant predictors of the impact of computer use on dry eye signs and symptoms. For the purpose, the ocular surface of 82 undergraduate students was assessed at baseline and after they had read on a computer for 30 minutes. According to the results of this chapter, participants with greater dry eye symptoms were more likely to experience a greater increase in symptomatology following computer use, while a longer tear break-up time and a greater increase in conjunctival redness with computer use were associated with a greater reduction in tear stability.

Nowadays, clinicians have a range of management strategies available to reduce or prevent the effects of digital display use on the ocular surface. **Chapter 8** aimed to assess and compare the effectiveness of four main management strategies (instillation of artificial tears, taking a brief break, using a blue light screen filter, and blink control) for preventing the short-term effects of digital display use on dry eyes, in a sample of 47 young individuals. The results of this chapter showed that the instillation of artificial tears and blink control were the best management strategies for preventing short-term effects of digital display use on dry eyes, while using a blue light filter did not offer any benefits.

Contact lens (CL) wear is widely recognised as one of the main risk factors for DED and consequently for DES. Accordingly, **Chapter 9** aimed to evaluate the potential additive effects of short-term display use (computer and smartphone) and CL wear, in addition to the benefits of artificial tear instillation, on the ocular surface and tear film in a sample of 34 young volunteers. The findings of this chapter showed that CL wear has no additive effects on signs and symptoms of dry eye when using digital devices for short periods and that the instillation of artificial tears is an effective strategy for reducing the impact of display use in CL wearers.

Similarly, dry eye is categorized as the most common adverse effect of laser in situ keratomileusis (LASIK) surgery, with this technique having the highest incidence and severity of postoperative DED of all kerato-refractive procedures. The aim of **Chapter 10** was to assess the impact of short-term computer use on the ocular surface of individuals after LASIK in order to determine whether post-LASIK patients are at an increased risk of digital display-induced dry eye. The dry eye symptoms and ocular surface of 18 post-myopic LASIK, young individuals and 18 controls were evaluated

before and after performing a 30-minute task on a computer with and without initial instillation of artificial tears. Overall, the increase in symptoms of dry eye and the symptoms of DES reported during the computer task were comparable between both study groups. Symptoms were accompanied by a significant worsening of dry eye signs in the LASIK group. In parallel, the instillation of artificial tears was effective in preventing the worsening of dry eye signs and symptoms in all cases.

Repeated periods of ocular surface stimulation by tear film instability may alter the excitability of corneal receptors and their responsiveness to new stimuli. Accordingly, the aim of **Chapter 11** was to evaluate the relationship between ocular symptoms and corneal sensitivity to mechanical and cold stimuli in 52 frequent computer users. Mechanical and cold sensation thresholds were determined at the central cornea of the randomly selected eye of each participant using the University of New South Wales Liquid Jet Aesthesiometer (UNSW LJA, UNSW, Sydney, Australia). Symptomatic computer users exhibited lower cold sensation thresholds compared to asymptomatic users, which suggests alterations in the corneal sensory function among computer users with DES. Likewise, greater symptoms of DES, particularly dry eye related symptoms, were associated with lowered excitation thresholds (hypersensitivity) of the corneal neurons to corneal cooling.

Considering these findings, **Chapter 12** aimed to evaluate the potential effects of short-term computer use on the sensitivity of the cornea to various stimuli and analyse associations with possible determinants in a similar sample of subjects. Sensitivity measurements were taken before and after working on a desktop computer for 1 hour in a freely chosen task. The results of this chapter indicate that short-term computer use had no effect on the sensitivity of the central cornea to mechanical and cold stimuli. Additionally, ocular symptoms and demographic variables were not associated with the changes in sensitivity following computer use.

Due to the significant refractive index change from air to tear film, abnormalities to the tear film can impact visual quality in a significant way. Based on this premise, the aim of **Chapter 13** was to thoroughly assess and compare the changes in visual function and optical and tear film quality in a group of computer workers (n = 40) and a group of non-computer workers (n = 40) throughout a normal working day. According to the results of this chapter, while visual acuity remained unchanged, several aspects of visual function and quality of vision declined over a day of intense computer use.

DES is highly influenced by the visual demand and the duration of a given task. Based on this principle, frequent screen users are often advised to follow the 20-20-20 rule (look away from the screen for at least 20 s to a distant scene at least 20 feet away after every 20 minutes of continuous work), although with limited evidence. Accordingly, the aim of **Chapter 14** was to evaluate the visual benefits of taking regular breaks based on this popular rule of visual ergonomics. To test the study hypothesis, bespoke computer software (eyeblink, https://www.blinkingmatters.com/), modified for the study by the developer, which employs the laptop webcam to assess user breaks, eye gaze and blinking, and which emits personalized reminders of breaks based on the 20-20-20 rule, was downloaded onto the laptops of 29 symptomatic computer users. DES, binocular vision and dry eye were assessed before and after two weeks of using the reminders and one week after the discontinuation of the strategy. The results of this chapter indicate that the 20-20-20 rule is an effective strategy for reducing DES and dry eye symptoms, although 2 weeks was not enough to considerably improve binocular vision or dry eye signs.

Finally, considering the global changes in education and technology use patterns following the coronavirus (COVID-19) outbreak, the last study presented in this work, and described in detail in **Chapter 15**, aimed to assess the potential effects of switching to an online lecture format on dry eye symptoms and DED risk factors. For this purpose, an anonymous cross-sectional online survey was carried out on 812 university students. Largely, attending online lectures was independently associated with having dry eye symptoms. Despite a lower prevalence of DED risk factors, higher computer use is probably the reason behind the greater ocular dryness reported by online students.

Acronyms and symbols

°	Degrees
°C	Degrees Celsius
ΔD	Prism dioptres
arc sec	Seconds of arc
cd/m^2	Candela per square metre
cm	Centimetres
cpd	Cycles per degree
cpm	Cycles per minute
D	Dioptres
Dk/t	Oxygen transmissibility
fps	Frames per second
Hz	Hertz
m	Metres
mg	Milligrams
mm	Millimetres
mOsm/L	Milliosmoles per litre
ms	Milliseconds
n	Sample size
nl	nanolitres
pH	Potential hydrogen
ppi	Pixels per inch
r	Pearson correlation coefficient
R^2	Coefficient of determination
s	Seconds
Sβ	Standardized beta coefficient
α	Significance level
β	Probability of type II error
β	Unstandardized beta coefficient
µl	Microlitres
µm	Micrometres
ρ	Spearman correlation coefficient

ANOVA	Analysis of variance
App	Application

CDVA	Corrected distance visual acuity
CNVA	Corrected near visual acuity
BCOR	Back central optic radius
BFCI	Best-fit circle irregularity
BFCI-SD	Standard deviation of best-fit circle irregularity
BFCR	Best-fit circle radius
CEORLab	Clinical and Experimental Optometry Research Laboratory
CI	Confidence interval
CL	Contact lens
CLDEQ-8	8-item Contact Lens Dry Eye Questionnaire
COVID-19	Coronavirus disease
CSF	Contrast sensitivity function
CVS	Computer vision syndrome
CVS-Q	Computer Vision Syndrome Questionnaire
DED	Dry eye disease
DEQ-5	5-item Dry Eye Questionnaire
DES	Digital eye strain
E-ink	Electronic ink
E-reader	Electronic reader
ETDRS	Early treatment diabetic retinopathy study
FACT	Functional acuity contrast test
FBUT	Fluorescein break-up time
HOA	Higher-order aberration
HSVET	High-speed visual eye-tracker
IOSS	Instant Ocular Symptoms Survey
IQR	Interquartile range
LASIK	Laser in situ keratomileusis
LCD	Liquid crystal display
LDA	Light Disturbance Analyzer
LDI	Light disturbance index
LED	Light emitting diode
LFU	Lacrimal functional unit
LJA	Liquid Jet Aesthesiometer
LLT	Lipid layer thickness

LOA	Lower-order aberration
LWE	Lid wiper epitheliopathy
MGD	Meibomian gland dysfunction
MUC5AC	Tear mucin 5AC
NIBUT	Non-invasive break-up time
NIKBUT	Non-invasive keratograph break-up time
NPC	Near point of convergence
OCI	Ocular Comfort Index
OR	Odds ratio
OSDI	Ocular Surface Disease Index
PBS	Phosphate buffered saline
QoV	Quality of Vision questionnaire
RAF	Royal air force rule
rANOVA	Repeated-measures analysis of variance
RMS	Root mean square
ROS	Reactive oxygen species
Rx	Refraction
SANDE I	Symptom Assessment in Dry Eye version 1
SANDE II	Symptom Assessment in Dry Eye version 2
SD	Standard deviation
SE	Standard error
TBUT	Tear break-up time
TFOS DEWS	Tear Film and Ocular Surface Society International Dry Eye Workshop
TFSQ	Tear film surface quality
TMH	Tear meniscus heigh
TRPM8	Transient receptor potential melastatin 8
TRPV1	Transient receptor potential vanilloid 1
UNESCO	United Nations Educational, Scientific and Cultural Organization
UNSW	University of New South Wales

List of figures

List of tables

1.

Introduction

1.1 Digital eye strain and dry eye

The use of digital displays is ubiquitous and has become a common and essential practice in our everyday life, with people using these devices in every aspect of their professional and private life. In 1995 there were 16 million internet users in the world (0.4% of the population), while nowadays there are as many as 5385 million (67.9% of the population) (Internet World Stats, 2023). These numbers tend to peak among young people, with 95% of young Europeans using the internet daily and spending almost 6 hours a day on average on screens (Eurostat, 2022). New forms of digital displays, such as laptops, smartphones, tablets or electronic readers (e-readers), have emerged, and the use of digital screens is no longer restricted to desktop computers.

This tremendous change in work and life conditions over the last decades has been accompanied by an increase in health-related complaints which have been collectively termed "computer vision syndrome" (CVS) or more recently "digital eye strain" (DES) (American Optometric Association, 2023). Two main and distinct categories have been determined for DES, based on the type of sensation and perceived location: internal and external (Portello et al., 2012; Sheedy et al., 2003a). Internal symptoms are related to refractive, accommodative, or vergence anomalies and include strain, eye ache, headache behind the eyes, diplopia, and blur. External symptoms are related to dry eye and encompass eye burning, irritation, tearing, tired eyes, foreign body sensation, and eye discomfort, and are often encountered in otherwise healthy individuals (Coles-Brennan et al., 2019).

Substantial research points to greater dry eye symptoms in digital display users compared to non-users (Uchino et al., 2013). Many studies also advise of the relationship between the use of digital screens and tear film and ocular surface abnormalities (Choi et al., 2018; Ribelles et al., 2015; Yazici et al., 2015). For instance, fluorescein break-up time (FBUT), non-invasive break-up time (NIBUT), and tear meniscus height (TMH) have been shown to be significantly lower in digital display users and decrease with the duration of device use (Choi et al., 2018; Ribelles et al., 2015; Yazici et al., 2015). Similarly, oxidative stress markers in the tear film (Choi et al., 2018), inflammatory mediators (Ribelles et al., 2015) and tear osmolarity (Yazici et al., 2015) have been shown to be altered in computer users. Not surprisingly, digital display use is considered a contributing factor to dry eye disease (DED) (Stapleton et al., 2017). According to a recent meta-analysis, the overall prevalence of DED in computer users is probably around 49.5%

and ranges from 9.5% to 87.5% (Courtin et al., 2016). This prevalence appears to be higher than that of the general population, which, as indicated by the Tear Film and Ocular Surface Society International Dry Eye Workshop (TFOS DEWS) II epidemiology report, is found to range between 5 and 50% at various ages (Stapleton et al., 2017).

The impact of computer use on the ocular surface has been primarily attributed to sustained gazing, which leads to decreased blink rate and amplitude (i.e., an increase in incomplete blinking) (Portello et al., 2013), and increased ocular surface exposure associated with high visualization angles (Ranasinghe et al., 2016; Tsubota & Nakamori, 1993), ultimately leading to tear film instability and evaporation (Pansell et al., 2007; Tsubota, 1995).

1.2 Symptom-inducing factors

1.2.1 Blinking abnormalities

1.2.1.1 Reduced blink rate

Blinking is essential for maintaining ocular surface integrity, tear film stability and clarity of vision (Cruz et al., 2011). Blinking keeps the eye surface humid and hydrated, favours the drainage of tears, helps in the expression of lipids from the meibomian glands and spreads tear lipids through the precorneal film (Doane, 1981; Holly, 1980; Korb et al., 1994). Therefore, a reduced blink rate will contribute to the disruption of the tear film and a reduction of its quality and quantity, along with an increase in corneal stress, leading to dry eye symptoms (Blehm et al., 2005).

A reduced blink rate during computer use is consistently reported in the literature (Freudenthaler et al., 2003; Patel et al., 1991; Schlote et al., 2004; Tsubota & Nakamori, 1993; Wong, 2002). Tsubota and Nakamori (1993) evaluated the blinking of 104 office workers and found a mean blink rate of 22 blinks/min while relaxed, 10 blinks/min while reading a book and 7 blinks/min while reading on a computer. Similarly, Patel et al. (1991) found a substantial reduction in the mean blink rate between the time before and during computer use (18.4 vs 3.6 blinks/min, respectively).

In many of these studies, however, test conditions were not kept constant and varied not only in the method of presentation but also in task format. It has been shown that the blink rate is affected by factors such as poor visual image (like reduced contrast and decreased font size) (Gowrisankaran et al., 2007) or increased cognitive and visual

task demand (Cardona et al., 2011; Himebaugh et al., 2009). These may arise from the need for a longer fixation duration so as to increase the time to acquire visual information (Cardona et al., 2011; Portello et al., 2013). It has been suggested that the poorer image quality of digital screens compared to printed text might be responsible for the differences in the blink rate (Chu et al., 2011). Eyelid squinting improves visual acuity and decreases retinal illumination in glare conditions (Sheedy et al., 2003b). Sheedy et al. (2005) noted that voluntary squinting significantly reduced the blink rate by an average of 50% or more, with greater squinting causing greater reductions. Therefore, a poorer image quality of electronic text compared to print and possible glare from the device screen may be behind the adversely affected blink rate reported in these studies (Portello et al., 2013).

Chu et al. (2014) compared the blink rate of 25 individuals who performed a continuous, 20-minute reading task on a desktop computer or in print, with the text matched for size and contrast and with a similar luminance and viewing angle. The authors concluded that there was no greater reduction in the blink rate during computer use compared to print and that previous differences were likely due to differences in cognitive demand. One year later, Rosenfield et al. (2015) confirmed this hypothesis and proposed that, given the technological improvements in digital displays over the past years, dry eye symptoms which users continue to experience today are more likely due to factors such as incomplete blinking or increased corneal exposure than a decline in the blink rate.

Nakamura et al. (2010) evaluated whether reduced blinking during digital display use had a direct, deleterious impact on lacrimal gland function in rats. The authors concluded that not only was there an excessive evaporative loss of tears during computer use, caused by abnormal blinking, but also a possible hypofunction of the lacrimal gland, which led to a reduced tear secretion in chronic display users. Kamoi et al. (2012) found no infiltration of immune cells in the lacrimal glands of computer users and suggested that dry eye associated with digital screens is likely due to a disorder in tear secretion, rather than impaired tear production. Similarly, Su et al. (2006) found that the prevalence of tear secretion dysfunction, assessed through the Schirmer test, was approximately 40% in a sample of office workers, and that dysfunction increased with the working time.

When it comes to handheld devices research is still limited. Choi et al. (2018) and Argilés et al. (2015) hypothesized that reading from smaller screens possibly worsens the spontaneous blink rate, as it requires lower saccade amplitude and no need for combined blinking. Nevertheless, Benedetto et al. (2013) found a significantly lower blink rate

when reading for 1 hour from a tablet compared to print, despite a similar setup including distance, page and font size, as well as the number of words per page.

1.2.1.2 Incomplete blinking

Although a reduced blink rate might not be as relevant with contemporary digital displays, individuals continue to suffer from ocular surface dryness following their use. According to recent research, incomplete blinking may be a more pertinent issue (Chu et al., 2014; Portello et al., 2013; Rosenfield et al., 2015). Partial blinking alters the distribution of mucin over the ocular surface, causes poor maintenance of lipid layer integrity and reduces tear film thickness in the inferior cornea, which is, therefore, more prone to tear evaporation and break-up problems (McMonnies, 2007). Additionally, blinking abnormalities affect the drainage of tears, leading to low tear clearance from the ocular surface, and the accumulation of inflammatory mediators in the conjunctival sac (Tsubota, 1998).

Portello et al. (2013) found a positive correlation between the total symptom score and the percentage of incomplete blinks while reading on a desktop computer. In parallel, several authors have reported a higher proportion of incomplete blinks in individuals who read on an electronic platform compared to hardcopy text (Chu et al., 2010; Nakamura et al., 2010).

Regarding handheld devices, Golebiowski et al. (2020) found an increase in the number of incomplete blinks during smartphone use: 6 versus 15 incomplete blinks at 1-minute and 15-minutes of device use, respectively. Also, a greater proportion of incomplete blinks has been reported while reading on a tablet (14.5%) compared to print (5%) (Argilés et al., 2015).

Harrison et al. (2008) mentioned that incomplete blinks may occur so as to not interrupt concentration. This links with McMonnies' suggestion that partial blinking may represent an attempt to inhibit spontaneous blinking during visually demanding tasks (McMonnies, 2007). Cardona et al. (2011) observed a negative influence of cognitive demand on blink amplitude in individuals playing a computer game. Nevertheless, greater symptomatology and a higher percentage of incomplete blinks have been reported during computer use (7.02%) compared to reading from printed paper (4.33%) with matched visual demand (Chu et al., 2014). It is relevant to mention that most studies comparing different devices or formats were not masked (i.e., participants knew which device they

were performing the task with). Therefore, subjective responses to questionnaires may have been influenced by format preference or bias based on prior experiences or preconceptions.

Alterations in tear composition and distribution as well as break-up problems resulting from abnormal blinking could further alter the blinking pattern by decreasing the maximum blink interval (i.e., maximum time the eyes can stay open without blinking) (Inomata et al., 2018), and by causing compensatory blinking (Nielsen et al., 2008). Nielsen et al. (2008) reported a compensatory burst of blinks during the shifts between periods of high and low visual and cognitive demand in computer users performing two different tasks in a simulated office environment. The authors attributed this phenomenon to compensation for the oppression of blinking and complete eyelid closure during the more demanding task – a wetting process, which could be viewed as a marker of ocular surface disturbance.

Table 1.1 summarizes the literature relevant to the impact of digital display use on blinking.

Table 1.1. Summary of the literature on the effects of digital display use on blinking.

Reference	Sample	Task	Duration and distance	Main findings
(Patel et al., 1991)	n = 16 17-31 years	Playing a computer game vs conversation.	10 min, not provided	• Lower BR with the computer.
(Tsubota & Nakamori, 1993)	n = 104 20-69 years	Relaxed conditions vs reading a book vs viewing text on computer.	Not provided	• Lower BR with the computer vs reading and relaxed. • Lower BR with reading vs relaxed.
(Freudenthaler et al., 2003)	n = 51 18-53 years	Computer use (arrangement of words in alphabetical order) vs conversation.	10 min, 40 cm	• Lower BR with the computer.
(Schlote et al., 2004)	n = 30 18-67 years. Patients with DED	Computer use (arrangement of words in alphabetical order and reading) vs conversation.	30 min, 40 cm	• Lower BR with computer.
(Himebaugh et al., 2009)	n = 32 22-73 years Healthy and DED patients	Looking straight ahead vs watching a movie vs playing a video game vs identifying changing letters on a computer.	3 min, not provided	• Lower BR while playing the computer game and identifying changing letters on the computer (high-concentration tasks). • No differences in BA among tasks. • No differences in BR or BA between DED and control.
(Chu et al., 2010)	n = 24	Reading aloud from a computer vs reading aloud from printed text. Matched text characteristics.	20 min, 50 cm	• No significant difference in BR between tasks.
(Cardona et al., 2011)	n = 25 21-28 years	Viewing distance target (baseline) vs playing a slow-paced computer game vs playing a fast-paced computer game.	20 min, 50 cm	• Lower BR with the computer. • Lower BR with the fast-paced game vs the slow-paced game. • Lower BA with the computer. • Higher % incomplete blinks with computer.

(Chu et al., 2014)	n = 25 22-28 years	Reading aloud from a computer vs reading aloud from print. Matched text characteristics.	20 min, 50 cm	• No significant difference in BR between tasks. • Higher % incomplete blinks with computer.
(Rosenfield et al., 2015)	n = 16 16-17 years	Reading aloud from a tablet vs reading aloud from print / high cognitive demand task vs low cognitive demand task. Matched text characteristics.	10 min, 30 cm	• No change in BR caused by method of presentation. • Lower BR with high-cognitive demand.
(Argilés et al., 2015)	n = 50 18-74 years	Viewing distance target (baseline) vs reading on a tablet (book position) vs reading on a computer vs reading printed text (pasted on computer) vs reading printed text (book position).	6 min, 40-60 cm	• Lower BR with the tablet, computer and printed text vs viewing distant target. • Higher BR with the tablet vs printed text (down gaze). • Lower BR with printed text (book position) vs printed text (pasted on the computer). • Higher % incomplete blinks with the tablet and the computer vs printed text.
(Golebiowski et al., 2020)	n = 12 18-23 years	Reading on a smartphone.	60 min, 30-34 cm	• Increase in incomplete blinks/minute over time. • No significant change in BR over time.

BA = Blink amplitude; BR = Blink rate; DED = Dry eye disease.

1.2.2 Gaze angle

A pertinent issue in digital display-induced dry eye is the specific gaze angle adopted while using the device. Greater gaze angles result in a wider palpebral fissure which, in turn, leads to increased instability of the tear film because of the thinning of the mucin and lipid layers (Pansell et al., 2007), and to a greater ocular surface area being exposed to the effects of tear film evaporation and desiccation (Tsubota, 1995). Computer screens, mainly desktop displays, are usually held at higher gaze angles compared to hardcopy text.

Tsubota and Nakamori (1993), obtained an average exposed ocular surface area of 1.2 cm^2 when reading a book and 2.3 cm^2 when working on a computer. Years later, these authors studied the effects of exposed surface area on tear dynamics and confirmed that tear evaporation increased proportionally with ocular surface area, not only per eye but also per area unit, being 3.4 and 2.5 times greater when looking up and ahead than when looking down (Tsubota, 1995). Likewise, Ranasinghe et al. (2016) found that the angle of gaze to the monitor was significantly higher in computer workers with DES or severe DES than in those without DES or mild DES, respectively.

Unlike computers, handheld devices are typically held at closer distances and below eye level. Therefore, it is expected that individual differences in the way that the digital displays are set up and used may account for differences in their effects on the ocular surface. Nielsen et al. (2008) investigated how the ocular surface area was affected by a high versus low position of the monitor. The authors observed a significant decrease in ocular surface area when lowering the gaze angle by 25°.

A relationship between gaze angle and the blink rate is suspected. A lower blink rate has been observed when reading printed text in downgaze (Benedetto et al., 2013; Koslowe et al., 2011). Nielsen et al. (2008) found that lowering the gaze angle of the monitor by 25° decreased the blink rate significantly. Consequently, the effect of a lower blink rate while using digital displays in downgaze is difficult to predict. It is hypothesized that the reduction in the blink rate may be a direct consequence of the reduction in the exposed ocular surface area (Nakamori et al., 1997). Thus, a low position of the monitor may still be preferable (Nielsen et al., 2008). The extent to which the decrease in the blink rate matches the decrease in exposed ocular surface area is still unknown.

1.2.3 Meibomian gland dysfunction

Proper blinking plays an important role in maintaining the lipid layer through meibomian gland lipid expression (Korb et al., 1994). Delivery of the oils which constitute the lipid layer of the tear film occurs in part by the expression of small aliquots from the meibomian glands with each blink (Bron et al., 2017). Abnormal blinking may alter meibomian gland secretion, leading in the long run to chronic changes in the gland, which may eventually cause inflammation, gland obstruction and a further reduction of the outflow of meibum (Wan et al., 2016). According to Blehm et al. (2005), blinking abnormalities, such as a reduced blink rate and incomplete eyelid closure associated with digital display use, may lead to a high incidence of meibomian gland dysfunction (MGD) in computer users.

Wang et al. (2018), for instance, found that participants who exhibited incomplete blinking had greater levels of meibomian gland dropout, along with lower tear film lipid layer thickness (LLT), tear film stability and expressed meibum quality, which predisposed them to the development of evaporative dry eye. Wu et al. (2014) explored meibomian gland function in a group of long (> 4 hours/day) and short (< 4 hours/day) time digital display workers. The results revealed a positive correlation between the time spent using the display and lid margin abnormalities, meibomian gland dropout and altered meibum expression. Finally, lid margin abnormalities associated with MGD can also result in inefficient tear film spreading, which may further contribute to dry eye signs and symptoms in digital display users.

Overall, MGD associated with display use may add up to abnormal blinking and boost tear instability and evaporation, ultimately leading to an increase in inflammatory cytokines, osmolarity and reduced mucin secretion (Fenga et al., 2014; Ribelles et al., 2015; Uchino et al., 2014), which may further exacerbate dryness by initiating the closed loop of inflammatory vicious circle of DED (Baudouin et al., 2013; Bron et al., 2017). Digital display-induced ocular surface inflammation, MGD and DED, along with the consequent chemical and mechanical stimulation of the cornea, will simultaneously lead to eye redness, particularly prevalent among digital display users (Alabi & Simpson, 2019; Downie et al., 2016).

1.3 Tear film and ocular surface

1.3.1 Tear volume

Several studies have reported a reduction in tear film volume after digital display use (Cardona et al., 2011; Choi et al., 2018; Nakamura et al., 2010; Ribelles et al., 2015; Su et al., 2006; Yazici et al., 2015). Yazici et al. (2015) evaluated changes in Schirmer test results in young computer workers over a 9-hour working day. The results revealed a significant decrease in tear volume following computer use, with an approximate 9% reduction in Schirmer at the end of the day. Similarly, a decreased TMH was found after playing a computer game for only 20 minutes (Cardona et al., 2011). As for long-term computer use, a large-scale epidemiological study, involving 1025 digital display users, found a significantly lower Schirmer score in those who used the computer for more than 2 hours per day, or for more than 4 years (Nakamura et al., 2010).

As for handheld devices, no difference in TMH was found after reading on a smartphone for 60 minutes (Golebiowski et al., 2020). Similarly, Maducdoc et al. (2017) and Prabhasawat et al. (2019) found no differences in tear volume (Schirmer test and TMH, respectively) after reading on a tablet, compared to reading in print.

Overall, computer use seems to cause a reduction in tear volume. Conversely, handheld devices might alter tear film volume to a lesser extent, although more research is needed in specifically designed studies to draw conclusions.

1.3.2 Tear stability

Reduced tear stability in computer users is commonly acknowledged (Cardona et al., 2011; Hirota et al., 2013; Uchino et al., 2013; Wu et al., 2014; Yazici et al., 2015). Uchino et al. (2013) investigated tear function in 672 office workers and found an average FBUT of 4 s, with 78.6% of participants having an FBUT shorter than 5 s. Tear stability has been shown to decrease with the duration of computer use (Hirota et al., 2013; Wu et al., 2014; Yazici et al., 2015). A considerably shorter FBUT has been found in individuals using the computer for more than 4 hours per day (4.92 s), in comparison to those with less than 4 hours of daily use (6.71 s) (Wu et al., 2014). Hirota et al. (2013) found a decrease in mean NIBUT after playing a computer game for 30 minutes compared to baseline. Conversely, other studies did not find a correlation between time spent in front of a computer and tear stability (Fenga et al., 2008; Nakamura et al., 2010).

Reduced tear stability has been observed even after a few minutes of computer use (Cardona et al., 2011; Hirota et al., 2013). For instance, Cardona et al. (2011) found a significant decrease in FBUT and NIBUT in participants who played on the computer for as little as 20 minutes, for both fast-paced and slow-paced gameplay. The authors, who additionally evaluated tear volume, suggested that tear film stability may be more influenced by dynamic visual tasks than volume.

An overall trend towards reduced tear stability following the use of digital screens is also seen when it comes to the use of handheld devices (Choi et al., 2018; Kim et al., 2017; Moon et al., 2016; Prabhasawat et al., 2019). Choi et al. (2018) found a significantly shorter non-invasive keratograph break-up time (NIKBUT) and FBUT at 4 hours of smartphone use, compared to baseline. Moon et al. (2016) found that FBUT improved significantly in a sample of 916 children after cessation of smartphone use over 4 weeks. Similarly, Kim et al. (2017) observed a reduction in FBUT in participants who used a tablet for 1 hour (either watching a movie or playing a computer game), and Prabhasawat et al. (2019) found reduced FBUT and NIBUT values in individuals who read on a tablet for as little as 20 minutes. Nonetheless, no difference in NIBUT or LLT was observed after reading on a smartphone for 60 minutes (Golebiowski et al., 2020).

1.3.3 Tear composition

The use of digital displays has also been associated with alterations in the composition of the tear film (Choi et al., 2018; Fenga et al., 2014; Ribelles et al., 2015; Uchino et al., 2014; Yazici et al., 2015). Osmolarity is considered the most reliable marker of DED severity, acting as a global indicator of ocular surface impairment and inflammation (Lemp et al., 2011). Increased osmolarity was reported in a group of 51 computer users at the end of a 9-hour working day (Yazici et al., 2015). Additionally, osmolarity was negatively correlated with the duration of computer use and with FBUT and Schirmer scores. The authors stated that reduced tear volume and increased tear evaporation were responsible for the increase in tear osmolarity (Yazici et al., 2015). Likewise, Fenga et al. (2014) reported an inverse correlation between tear osmolarity and FBUT, and a direct correlation with corneal stain, ocular surface dysfunction and MGD in 64 computer workers.

Ribelles et al. (2015) found a significantly higher level of interleukins-1β and -6 in computer users as compared to non-computer users, which reflected a relevant

inflammatory background in individuals using this display. As expected, these pro-inflammatory mediators correlated with clinical DED parameters.

Chronic inflammation and elevated tear osmolarity cause damage to the ocular surface, including loss of goblet cells in the conjunctiva or stem cells in the limbus (Yamaguchi, 2018). Mucins dissolved in tears are produced by goblet cells and play an important role in epithelial surface protection, by increasing epithelium wettability and helping it to retain fluids (Hori, 2018). Uchino et al. (2014) found that mean tear mucin 5AC (MUC5AC) concentration was lower in computer users who worked for longer hours (> 7 hours), compared with those who worked less (< 5 hours), and in symptomatic participants than in asymptomatic ones.

Oxidative stress is considered a possible inciting factor in the generation of ocular surface inflammation. Choi et al. (2018) measured oxidative stress markers in the tear film of 80 volunteers, before and after smartphone and computer use. The authors found an increase in hexanoyl lysine concentration after 4 hours of smartphone use, compared with baseline and 1-hour use. Additionally, the authors assessed oxidative stress by measuring reactive oxygen species (ROS) in the conjunctival epithelium and found an increase in ROS production after using the smartphone and the computer. The scientists concluded that smartphone use could induce an oxidative stress response and cellular apoptosis at the ocular surface (Choi et al., 2018).

1.3.4 Ocular surface staining

Vital staining can be used to indicate corneo-conjunctival epithelial damage. An increased prevalence of corneal staining was observed in a large sample of young office workers who used the computer for an average of 7.9 hours a day (Uchino et al., 2013). Another study found significantly greater corneal staining scores in a group of computer workers compared with controls (Doguizi et al., 2019). Similarly, an increase in corneal staining has been found to correlate with the time of daily computer use (Wu et al., 2014). In this regard, a significant association between the degree of incomplete blinking and the grade of corneal staining has been demonstrated (Collins et al., 2006; Harrison et al., 2008). Consequently, ocular surface staining may arise from tear thinning and reduced goblet cell mucin in the exposed area, leading to exposure keratopathy (McMonnies, 2007).

Several investigations have revealed that there is no effect of digital display use on ocular surface staining (Fenga et al., 2008; Kawashima et al., 2015; Kojima et al., 2011; Prabhasawat et al., 2019; Yazici et al., 2015; Yokoi et al., 2015). Kojima et al. (2011), for instance, found no difference in vital staining (fluorescein and rose bengal) scores between participants who worked on the computer for less than 4 hours per day and those who worked for longer periods. Likewise, no differences in corneal and conjunctival staining scores were found after reading for 20 minutes on a tablet or in print (Prabhasawat et al., 2019). However, since only young and middle-aged individuals participated in these studies, the results may not apply to older individuals.

All things considered, ocular surface staining has been suggested to lack discriminatory power and act as a sign of severe disease rather than mild-to-moderate disorder (Sullivan et al., 2010; Wolffsohn et al., 2017). According to the literature, staining may be absent in up to 40-50% of mild to moderate DED patients (Lemp et al., 2011; Sullivan et al., 2012), which may explain discrepancies in results among studies.

1.3.5 Conjunctival redness

As aforementioned, conjunctival redness may arise as a consequence of induced ocular surface inflammation, MGD and ocular surface dryness following digital display use (Downie et al., 2016). Conjunctival redness has been shown to occur as a response to chemical and mechanical stimulation of the cornea (Alabi & Simpson, 2019), which may further explain the increased prevalence of eye redness in individuals with DES-related dry eye.

Choi et al. (2019), for example, found an increase in conjunctival bulbar redness after a 15-minute computer reading task, as well as a significant effect of task duration on this parameter. Tauste et al. (2018) found that bulbar redness was the most prevalent abnormality of the ocular surface in office workers, ahead of corneal staining, and that the risk for conjunctival limbal redness was higher for those who used the computer for more than 4 hours per day. Regarding handheld devices, longer daily smartphone usage and higher lifetime smartphone exposure, have been associated with a higher likelihood of suffering from eye redness (Kim et al., 2016).

Table 1.2 summarizes the literature relevant to the impact of digital displays on the tear film and ocular surface.

Table 1.2. Summary of the literature on the effects of digital display use on the tear film and ocular surface.

Reference	Sample	Task	Duration and distance	Tear volume	Tear stability	Tear composition	Ocular surface
(Patel et al., 1991)	n = 16 17-31 years	Playing a computer game.	10 min, not provided	—	• No change in NIBUT.	—	—
(Su et al., 2006)	n = 319 24.2 ± 3.8 years	Ocular examination of operators working with LCDs.	13.6 ± 5.7 months of employment, not provided.	40.1 % prevalence of tear secretion dysfunction (Schirmer test score ≤ 5mm).	—	—	—
(Fenga et al., 2008)	n = 70 31-56 years	Computer workers with and without MGD.	3.9 ± 1.7 h/day, not provided	• Lower Schirmer in workers with MGD.	• No differences in FBUT between workers with and without MGD.	—	• Higher conjunctival signs in workers with MGD. • No differences in corneal staining between workers with and without MGD.
(Nakamura et al., 2010)	n = 1025 35.6 ± 10.1 years	A survey of office computer workers.	5.1 ± 2.7 h/day of computer use / 8.2 ± 5.7 computer working years, not provided.	• Lower Schirmer with working years (≥ 4 years) and computer daily using time (≥ 2 h).	• No effect of computer use duration on FBUT.	—	—
(Cardona et al., 2011)	n = 25 21-28 years	Viewing distance target (baseline) vs playing a slow-	20 min, 50 cm	• Lower TMH following computer use.	• Shorter FBUT and NIBUT following computer use.	—	—

		paced computer game vs playing a fast-paced computer game.		• No differences in phenol red test among tasks.	• Shorter FBUT and NIBUT after a fast game vs a slow game. • Lower LLT following computer use.		
(Kojima et al., 2011)	n = 171 28-73 years	Short-term computer workers vs long-term computer workers.	≤ 4 h/day (short-term) / > 4 h/day (long-term), not provided	• Lower TMH in long-term computer workers. • No differences in Schirmer between groups.	• No differences in FBUT between groups.	—	• No differences in corneal or conjunctival staining between groups.
(Hirota et al., 2013)	n = 11 19-32 years	Playing a computer game.	60 min, 40 cm	—	• Reduced NIBUT after 30 and 60 min.	—	—
(Yazici et al., 2015)	n = 77 20-50 years	Computer users vs non-computer users.	6.9 ± 2.7 h (working day), not provided	• Reduced Schirmer in computer users after the working day.	• Reduced FBUT in computer users after the working day.	• Increased osmolarity in computer users after working day.	—
(Wu et al., 2014)	n = 53 20-52 years	Short-term computer workers vs long-term computer workers.	≤ 4 h/day (short-term) / > 4 h/day (long-term), not provided	• No difference in Schirmer between groups.	• Shorter FBUT in long-term workers. • Lower meibum expression in long-term workers.	—	• Greater corneal staining in long-term workers. • Greater lid margin abnormalities in long-term workers.
(Uchino et al., 2014)	n = 96 22-60 years	Short vs intermediate vs long-term computer workers.	< 5 h/day (short) / 5-7 h/day (intermediate) / > 7 h/day	—	—	• Reduced MUC5AC concentration in long-term computer workers.	—

			(long), not provided				
(Ribelles et al., 2015)	n = 148 40-65 years	Computer users vs non-computer users.	—	• Lower Schirmer in computer users.	—	• Higher IL-1β and IL6 levels in older patients and in computer users.	—
(Maducdoc et al., 2017)	n = 44 21-31 years	Reading from a tablet vs reading from print.	60 min, 37.9 ± 5.1 cm (print) / 38.1 ± 5.6 cm (tablet)	• No changes in Schirmer after reading from either the tablet or print. • No differences in Schirmer between tasks.	—	—	—
(Kim et al., 2017)	n = 59 22-64 years	Watching a movie or playing a game on a tablet.	60 min, 40 cm	—	• Reduced FBUT after tablet use.	—	—
(Choi et al., 2018)	n = 80 21-26 years	Playing a game on smartphone vs playing a game on computer.	4 h, not provided	• No changes in Schirmer and TMH after smartphone or computer use.	• Reduced FBUT after 4 h smartphone use. • Reduced NIKBUT after 1 h and 4 h smartphone use.	• Increased HEL concentration after 4 h smartphone use. • Increased ROS levels after 1 h and 4 h smartphone and computer use.	
(Golebiowski et al., 2020)	n = 12 18-23 years	Reading from a smartphone.	60 min, 30-34 cm	• No changes in TMH.	• No changes in lipid layer appearance. • No changes in NIBUT.	—	—

(Prabhasawat et al., 2019)	n = 30 24-55 years	Reading from a tablet vs reading from print.	20 min, 30 cm	• No changes in TMH after reading from the tablet or print. • No differences in TMH between tasks.	• Reduced FBUT and NIBUT after reading from the tablet or print. • No differences in FBUT and NIBUT between tasks.	—	• No changes in corneal and conjunctival staining after reading from the tablet or print. • No differences in corneal and conjunctival staining between tasks.
(Doguizi et al., 2019)	n = 102 38.9 ± 5.5 years in computer users / 37.8 ± 5.8 years in control.	Vocational computer users (> 6 h/day) vs control (< 1 h/day).	—	• Lower Schirmer in computer users. • Reduced TMH and TMA in computer users.	• Shorter FBUT in computer users.	—	• Higher staining score in computer users. • No differences in MGD score between computer users and control.

FBUT = Fluorescein break-up time; h/day = hours per day; HEL = Hexanoyl lysine; IL = Interleukins; LCD = Liquid crystal display; LLT = Lipid layer thickness; MGD = Meibomian gland dysfunction; MUC5AC = Tear mucin 5AC; NIBUT = Non-invasive break-up time; NIKBUT = Non-invasive keratograph break-up time; TMA = Tear meniscus area; TMH = Tear meniscus height; ROS = Reactive oxygen species.

1.4 Visual function

DED leads to tear film instability and hyperosmolarity, inflammation of the ocular surface and, ultimately, visual disturbance (Craig et al., 2017), which has been shown to significantly impact patients' quality of life (Benítez-del-Castillo et al., 2017). The tear film is the first surface that light encounters before entering the eye and, given the significant index change from air to tear film, the precorneal tear film has the greatest dioptric power of any optical interface of the eye (Albarrán et al., 1997). Consequently, alterations in the composition, distribution and homogeneity of the tear film may lead to notable changes in the visual function (Benito et al., 2011). Studies indicate a reduction in visual acuity and contrast sensitivity, and an increase in glare disability in individuals with DED (Goto et al., 2002; Puell et al., 2006; Ridder et al., 2011).

The tear film undergoes disruptions following a blink, leading to its break-up (Albarrán et al., 1997). After a blink, the progressive irregularity in the thickness of the tear film over the ocular surface worsens its optical quality more and more (Liu et al., 2010). When the tear film breaks up, the cornea is exposed. Unlike the tear film, the cornea has a naturally irregular surface caused by the presence of numerous microvilli. Therefore, in the absence of the tear film, the quality of the image formed is poor. Goto et al. (2002), for instance, found that visual acuity decreased significantly from 1.18 to 0.34 (decimal notation) in non-Sjögren's syndrome dry eye individuals after they gazed for 10-20 s without blinking. Likewise, contrast sensitivity and higher-order optical aberrations (HOAs) have been shown to significantly decrease and increase, respectively, when blinking is suppressed (Liu et al., 2010).

Visual disturbances, such as blur or glare, are common visual symptoms in digital display users. According to a survey involving 520 New York office workers, up to 36% reported having blurred vision while using the computer and 24.1% declared suffering from sensitivity to bright lights during computer use (Portello et al., 2012). In all cases, the symptom score increased with the number of hours of computer use. Considering the aforementioned, it is expected that at least part of these symptoms are attributable to alterations in the tear film associated with digital display use.

It is relevant to bear in mind that alterations of the visual function during display use tend to be mostly associated with alterations in the mechanism of accommodation and vergence, which are beyond the scope of this work. Portello et al. (2012) found that blurred vision during computer use was mostly correlated with accommodation rather

than dry eye (0.38 for dry eye vs 0.72 for accommodation), while sensitivity to bright lights was mostly correlated with dry eye (0.62 for dry eye vs 0.32 for accommodation).

Overall, there is a lack of research on the effects of digital display use on visual function. Investigation is needed to understand the effects of digital technology on vision across all ages so as to establish guidelines for its usage.

1.5 Risk factors

1.5.1 Contact lens wear

Contact lens (CL) wear is recognized as one of the main risk factors for DED (Stapleton et al., 2017). According to the literature, DED appears to be up to 4 times more prevalent in CL wearers (Paulsen et al., 2014; Tan et al., 2015; Viso et al., 2009). The use of CLs leads to a thinner and irregular lipid layer with deficient tear spreading and wettability (Yokoi et al., 2008), tear film instability (Santodomingo-Rubido et al., 2006), increased tear evaporation and osmolarity (Hori, 2018), lower basal tear turnover rate (Santodomingo-Rubido et al., 2006), decreased tear volume (Chen et al., 2011; Del Águila-Carrasco et al., 2015) and reduced levels of MUC5AC (Berry et al., 2008). Additionally, the structure and function of the meibomian glands can also be affected by CL wear (Alghamdi et al., 2016).

Several studies indicate an increase in the prevalence of dry eye symptoms in CL wearing computer workers (Aakre & Doughty, 2007; González-Méijome et al., 2007; Kojima et al., 2011; Ranasinghe et al., 2016; Tauste et al., 2016, 2018; M. Uchino et al., 2008, 2011). For instance, Gonzalez-Meijome et al. (2007) found that soft CL wearers who worked on digital displays for longer periods were more likely to develop symptoms such as eye burning and scratchiness than non-CL wearers. The combination of long-term digital display work and CL wear was found to synergistically exacerbate dry eye symptoms.

Tauste et al. (2016) found that workers who wore CLs and used the computer for more than 6 hours per day were more likely to suffer from DES than non-CL wearers working on the computer for the same amount of time. The authors found a trend towards a greater problem in those who wear conventional hydrogel, and especially silicone hydrogel, CLs compared with rigid gas permeable users. These results were attributed to possible ineffective cleaning of the monthly replaced hydrogel and silicone hydrogel lenses with multipurpose lens care solutions, which lead to superficial deposits, and to

the high elastic modulus and hydrophobic surfaces, with a tendency to accumulate lipid deposits, of the silicone hydrogel lenses. Years later, the same authors carried out a similar experiment and analysed the differences in the appearance of the ocular surface of CL and non-CL digital display workers, with different lens materials (Tauste et al., 2018). The study revealed that digital display workers who wore CLs were more likely to suffer from bulbar, limbal and lid redness and lid roughness. Additionally, conventional hydrogel wearers had the highest prevalence of ocular surface abnormalities, while rigid gas permeable CL wearers had the lowest. The authors attributed these findings in part to the lower permeability of conventional hydrogel lenses, as opposed to the higher permeability of silicone hydrogel lenses, which limits the passage of oxygen to the cornea and favours corneal and conjunctival vascular response (Tauste et al., 2018).

As for tear function, a reduced TMH was obtained in long-term CL wearing computer workers, in comparison with short-term workers who did not wear CLs (Kojima et al., 2011). Nevertheless, no differences between groups were found in Schirmer, FBUT and fluorescein or rose bengal staining. Likewise, no differences in Schirmer, FBUT and fluorescein staining have been found between CL and non-CL wearing computer workers, although there could be an underestimation in FBUT and Schirmer as a result of the study design (Tauste et al., 2018).

CL wear has been shown to increase the blink rate, even in fully adapted wearers (Jansen et al., 2010). Although one of the most pertinent issues associated with digital display use is a reduced blink rate, it should be noted that CL wearers may be up to 12 times more likely than emmetropes to report dry eye symptoms (Nichols et al., 2005). Conversely, blink amplitude did show a reduction in CL wearers who were playing a video game (Jansen et al., 2010). Partial blinking leads to tear film evaporation and break-up problems and the precipitation of deposits on the lens surface (McMonnies, 2007), which decreases lens wettability and leads to enhanced symptoms of dryness and discomfort (Zhao et al., 2010).

Table 1.3 summarizes the literature relevant to the impact of CL wear on the tear film, ocular surface and blinking in digital display users.

Table 1.3. Summary of the literature on the effects of contact lens wear on the tear film, ocular surface and blinking in digital display users.

Reference	Sample	Purpose	Main findings
(González-Méijome et al., 2007)	n = 334 18-61 years	Evaluate dryness symptoms in CL and non-CL wearing computer users.	• Higher scratchiness in CL wearers. • Higher prevalence of reported symptoms at the end of the day in CL wearers. • Higher scratchiness in female vs male CL-wearers. • Higher burning sensation with longer computer work in CL wearers. • Increase in scratchiness symptoms in CL wearers with air conditioning and heating units exposure.
(Uchino et al., 2008)	n = 4393 22-60 years	Determine the prevalence of DED risk factors in computer workers.	• Higher prevalence of DED in CL wearers computer workers. • Higher prevalence of severe DED symptoms in CL wearers computer workers.
(Jansen et al., 2010)	n = 15 18-30 years	Examine blink parameters and tear stability while listening to music or playing a computer game with and without CLs.	• Lower BR and BA with the computer vs listening to music without CLs. • Lower BA with the computer vs listening to music with CLs. • No change in BR between tasks with CLs. • Higher AB when using the computer with CLs. • Higher % of blinks preceded by AB when using the computer with CLs. • Increased ocular irritation with CLs.
(Kojima et al., 2011)	n = 171 28-73 years	Evaluate the effects of CL wear on ocular surface and tear film.	• Lower TMH in CL wearers. • Higher dry eye symptomatology and severity in CL wearers.

			• Higher symptom aggravation from exposure to air conditioners in CL wearers. • No differences in FBUT, Schirmer and staining between CL and non-CL wearers.
(Ranasinghe et al., 2016)	n = 2210 18-60 years	Describe the prevalence of DES associated factors.	• Higher prevalence of DED in CL vs non-CL wearers. • Use of CLs second most significant risk factor for DES.
(Tauste et al., 2016)	n = 426 47.3 ± 8.9 years	Analyse of the relationship between DES and CL use in computer workers.	• Higher DES prevalence in CL wearers. • Higher risk of DES in CL wearers using the computer > 6 h/day. • Trend to higher DES prevalence in SH and CH CL wearers vs RGP CL wearers.
(Tauste et al., 2018)	n = 236 26-67 years	Study the differences in ocular surface and tear film of CL vs non- CL wearers computer workers.	• Higher risk of ocular surface abnormalities in CL vs non-CL wearers. • Higher prevalence and / or risk of ocular surface abnormalities with CH and SH CLs vs RGP CLs (CH > SH > RGP). • No differences in prevalence or risks of FBUT and Schirmer abnormalities between CL and non-CL wearers. • Higher risk of redness in CL wearers with > 4 h/day computer exposure.

AB = Area of tear film break-up; BA = Blink amplitude; BR = Blink rate; CH = Conventional hydrogel; CL = Contact lens; DED = Dry eye disease; DES = Digital eye strain; FBUT = Fluorescein break-up time; h/day = hours per day; RGP = Rigid gas permeable; SH = Silicone hydrogel; TMH = Tear meniscus height.

1.5.2 Age and sex

Age is categorized as a consistent risk factor for DED (Stapleton et al., 2017). The meta-analyses carried out by the TFOS DEWS II confirmed that symptomatic disease and signs of DED increase with age (Stapleton et al., 2017). Ranasinghe et al. (2016) evaluated the prevalence of DES in a group of 250 computer office workers and found that the prevalence significantly increased with age. These results are particularly relevant considering that internet adoption among seniors has risen steadily over the last decades (Ramón-Jerónimo et al., 2013).

Digital display use is particularly frequent among young people. Rahman and Sanip (2011) found that younger age (< 27 years) resulted in higher odds of DES than older age (> 33 years) and attributed these findings to the negative correlation found between age and duration of computer use. Kim et al. (2016) studied the association between smartphone use and ocular health in a group of 715 adolescents, with a mean age of 15 years, and found that lifetime exposure to smartphones increased the risk of ocular symptoms including dryness. The authors advised that special caution should be taken by adolescents, given their increased time of exposure to digital displays.

Regarding younger age groups, digital display use in children is strongly associated with paediatric DED (Moon et al., 2014, 2016). For instance, a decrease in FBUT and an increase in dry eye symptoms have been obtained following longer daily smartphone use in children aged 7-12 years (Moon et al., 2016). Additionally, this study found that the odds of having DED were 13 times higher in children who used a smartphone for more than 3 hours per day (Moon et al., 2016).

Female sex is widely accepted as a risk factor for the development of DED (Stapleton et al., 2017). Differences in DED rates between women and men, however, tend to become significant only with increasing age (Stapleton et al., 2017). Schaumberg et al. (2013), observed that women were, on average, 6 years younger when diagnosed with DED compared to men. In their study, women also reported a significantly greater impact of DED on everyday activities, including working on a computer (Schaumberg et al., 2013). Research has revealed an abnormally low Schirmer test and reduced spontaneous blink frequency in older women (53-65 years) working on computers, compared to younger ones (40-52 years) (Ribelles et al., 2015). Elevated levels of interleukins-1β and -6 were also found following greater computer use and were more common in older participants (Ribelles et al., 2015).

1.5.3 Environmental conditions

Studies reveal a strong association between low relative humidity environments and the prevalence of DED (Wolkoff, 2008). Tear evaporation rate, LLT, ocular comfort, and tear film stability and production are adversely affected by low relative humidity (Abusharha & Pearce, 2013; Madden et al., 2013). Low relative humidity exposure of the ocular surface may cause conjunctival goblet cell cornification and alter the delivery of mucins which make up the tear film (Corrales et al., 2011). High horizontal or downward air velocity, caused by the use of ventilation fans or air conditioning settings, can also increase tear film evaporation leading to exposure keratitis and epithelial damage (Koh et al., 2012).

Moreover, elevated room temperature has been found to adversely affect tear film quality (Abusharha et al., 2016). Mendell et al. (2002) found that lowering room temperature by 1 °C (within 22-26 °C) decreased dry eye symptoms by 19%. Cold thermoreceptors in the cornea regulate the basal flow of tears (Belmonte & Gallar, 2011). Consequently, warmer office environments will reduce basal tear secretion. Lower temperatures stimulate thermo-sensitive cold fibres in the cornea which will initiate reflex blinking (Collins et al., 2009). Hence, higher temperatures will lower the blink rate and promote dryness. Likewise, increased temperatures have been associated with a less stable tear film lipid layer (Bron et al., 2004).

Furthermore, airborne chemicals produced by building materials and products can cause eye irritation and oxidative stress (Kjaergaard et al., 1992). However, measurements in office environments show concentration levels are not high enough to trigger symptoms of irritation (Wolkoff, 2013).

Finally, improper lighting conditions, with unequal luminance between the digital display and its background, glare from windows or overhead lights and reflections from the display screen, can cause discomfort and disability glare (Hultgren & Knave, 1974). Glare and reflections from the screen reduce contrast, leading to poorer image quality (Thomson, 1998). This is particularly relevant, as the reduced image quality of the electronic screen has been associated with a reduction in the blink rate (Chu et al., 2011). In parallel, glare may cause the contraction of the orbicularis oculi muscle in order to decrease retinal illumination and improve vision (Sheedy et al., 2003b), leading to squinting and further reducing blink frequency (Sheedy et al., 2005).

1.6 Management strategies

Artificial tears constitute one of the main management strategies for digital display-induced dry eye. According to several investigations, lubricating eye drops may be effective in counteracting the effects of digital display use on the ocular surface (Acosta et al., 1999; Blehm et al., 2005; Coles-Brennan et al., 2019; Guillon et al., 2004; Tribley et al., 2011). High-viscosity eye drops (elastoviscous solution) have been shown to regulate the interblink interval and relieve ocular symptoms during digital display use more effectively than regular balanced salt solutions (Acosta et al., 1999). Also, the instillation of artificial tears has been shown to reduce symptoms of dryness in regular CL wearing computer users, although symptoms may not be fully eliminated (Guillon et al., 2004).

Another treatment option includes dietary supplementation with omega-3 fatty acids (Bhargava et al., 2015, 2016; Thakur et al., 2016). In a randomized, double-blind study with 478 symptomatic, regular computer users, the daily supplementation of two 180 mg capsules of omega-3 fatty acids for two months significantly alleviated dry eye symptoms, decreased tear evaporation rate and improved Nelson grade (cellular morphology and goblet cell density) in individuals with DES-associated dry eye (Bhargava et al., 2015).

As for the impact of digital display use on blinking, blink training may be a helpful management strategy for symptomatic digital display users. Portello and Rosenfield (2010) found that increasing the blink rate during computer reading by means of a metronome, to produce a blink every 4 s, did not reduce symptoms significantly. According to recent findings, incomplete blinking may be a more pertinent issue than the blink rate (Chu et al., 2014; Rosenfield et al., 2015). However, it should be noted that participants in both studies were required to read aloud, and this may have represented a subtle stimulus to blink. Overall, blink exercises focused on increasing the completeness of blinks during display use are expected to be more appropriate, although they may hinder task performance (Cardona et al., 2011; Harrison et al., 2008; Portello & Rosenfield, 2010).

Screen filters, such as anti-glare filters, act as neutral density filters which can be useful in reducing screen reflections and improving contrast (Sheedy, 1992; Thomson, 1998). The better image quality of the display screen and the reduced glare can decrease squinting (Sheedy et al., 2003b) and alter blinking to a lesser extent (Miyake-Kashima et

al., 2005). Other filters, such as mesh or polarizing filters, may also be appropriate (Thomson, 1998). According to studies, the use of screen filters is associated with a reduced incidence of dry eye in digital display users (Ranasinghe et al., 2016; Shantakumari et al., 2014).

In parallel, it has been suggested that blue light emitted by digital screens is a contributing factor to DES (Isono et al., 2013). Nonetheless, to date, there is no consensus on the effectiveness of blue-filtering lenses for the management of symptoms during digital display use (Cheng et al., 2014; Lin et al., 2017; Palavets & Rosenfield, 2019). Cheng et al. (2014) showed no improvement in Schirmer test values in a group of dry eye and non-dry eye individuals after wearing low, medium and high-density blue light filters. Participants with dry eye reported more comfort with all filters, although no difference was found in the control group. Lin et al. (2017) found that wearing high-blocking spectacles led to fewer feelings of itchy eyes in patients compared to no-blocking and low-blocking spectacles. Nevertheless, the study sample was considerably small, and, despite the efforts of the researchers, complete masking was not possible (i.e., participants could suspect which glasses they were wearing). Palavets and Rosenfield (2019) recently found that a filter which eliminated 99% of the blue light emitted from a tablet was not more effective than an equivalent neutral density filter in reducing DES symptoms, including dryness. All things considered, there is limited evidence to support the proposal that blue light emitted by digital displays can cause eyestrain.

Finally, ergonomic considerations while using digital displays could be critical for the management of DES (Coles-Brennan et al., 2019; Rosenfield, 2011). Adequate blinking may be suppressed to maximize the acquisition of information in visually demanding tasks. Therefore, good text legibility, including contrast, text size, line spacing, etc. will reduce cognitive and visual task demand and improve blinking, causing less dry eye signs and symptoms (Cardona et al., 2011; Chu et al., 2011; Gowrisankaran et al., 2007; Himebaugh et al., 2009; Portello et al., 2013; Tsubota & Nakamori, 1993). Likewise, appropriate lighting, achieved with a uniform distribution of luminance in the visual field (Wolkoff, 2013), and careful positioning of the display, avoiding screen reflections and glare from the window or overhead lights, will prevent squinting (Sheedy et al., 2005) and blinking abnormalities (Miyake-Kashima et al., 2005). Regarding illumination, researchers recommend for the brightness of the screen to match the immediate surroundings in order to avoid glare that either these surroundings or the display itself may generate (Shantakumari et al., 2014; Thomson, 1998). Furthermore,

lowering the monitor will reduce ocular surface exposure (Nielsen et al., 2008) and thus reduce tear film instability (Pansell et al., 2007) and evaporation (Tsubota, 1995).

DES is highly influenced by the visual demand and the duration of a given task. As previously addressed, longer periods of screen visualization have been associated with greater tear film and ocular surface abnormalities (Choi et al., 2018; Doguizi et al., 2019; Hirota et al., 2013; Moon et al., 2016; Nakamura et al., 2010; Tauste et al., 2016, 2018; Uchino et al., 2014; Wu et al., 2014; Yazici et al., 2015). Therefore, taking regular breaks is generally considered a good management strategy (Agarwal et al., 2013; Blehm et al., 2005; Coles-Brennan et al., 2019; Ramón-Jerónimo et al., 2013; Shantakumari et al., 2014). Lastly, adequate work environments with appropriate room temperature (20-23 °C), ambient humidity, and no direct horizontal or upper air from ventilation fans, will help maintain a normal eye blink frequency and minimize alterations of the tear film (Wolkoff, 2005; Wolkoff et al., 2006).

DES represents in most cases a reversible condition which tends to improve with the sole interruption of display use. Recent research revealed a significant improvement in both subjective symptoms and objective signs (punctate epithelial erosion and FBUT) of dry eye in a large sample of children after cessation of smartphone use for 4 weeks (Moon et al., 2016). Remarkably, the DED rate in the DED group decreased from 100% to 0% after smartphone cessation, although the actual prevalence of DED in this study may have been affected by using adult-targeted diagnostic criteria. Despite these results, it should be noted that long-term digital display use is considered a predisposing factor to DED, which in its most severe condition can lead to permanent damage to the ocular surface.

Table 1.4 summarizes the main strategies for the management of digital display-induced dry eye.

Table 1.4. Main strategies for the management of dry eye associated with digital display use.

Management strategy	References	Potential benefits and results
Artificial tears	(Acosta et al., 1999; Blehm et al., 2005; Coles-Brennan et al., 2019; Guillon et al., 2004; Tribley et al., 2011)	• Regularization of the IBI. • Reduction of dry eye symptoms. • Better results with high viscosity eyedrops.
Omega-3 fatty acids supplementation	(Bhargava et al., 2015, 2016; Thakur et al., 2016)	• Alleviation of dry eye symptoms. • Reduction of tear fil evaporation rate. • Improvement of cellular morphology and goblet cell density.
Blink training	(Chu et al., 2014; Portello et al., 2013; Rosenfield et al., 2015)	• Lack of available literature. • Training of BA expected to be more beneficial than BR.
Anti-reflection screen filters	(Miyake-Kashima et al., 2005; Ranasinghe et al., 2016; Shantakumari et al., 2014; Thomson, 1998)	• Increase of BR and BA. • Reduction of dry eye symptoms. • Reduction of DED incidence.
Blue-light blocking filters	(Cheng et al., 2014; Isono H et al., 2013; Lin et al., 2017; Palavets & Rosenfield, 2019)	• Possible reduction of dry eye symptoms. • No consensus. • No difference with neutral density filters. • Lack of available literature.
Ergonomic practices ○ *Optimum text legibility and quality.* ○ *Appropriate lighting and screen positioning.* ○ *Lower monitor height.*	(Agarwal et al., 2013; Cardona et al., 2011; Chu et al., 2011; Coles-Brennan et al., 2019; Gowrisankaran et al., 2007; Himebaugh et al., 2009; Miyake-Kashima et al., 2005; Nielsen et al., 2008; Pansell et al., 2007; Portello et al., 2013; Thomson, 1998; Tsubota, 1995; Tsubota & Nakamori, 1993)	• Increase of BR and BA. • Improvement of tear film stability. • Reduction of exposed ocular surface area. • Reduction of tear film evaporation. • Reduction of dry eye symptoms.
Regular breaks	(Agarwal et al, 2013; Blehm et al., 2005; Coles-Brennan et al., 2019; Ramón-Jerónimo et al., 2013; Shantakumari et al., 2014)	• Reduction of tear film abnormalities. • Reduction of dry eye symptoms.

Work environments ○ *Appropriate room temperature and humidity.* ○ *Avoidance of direct air to the eyes.*	(Abusharha et al., 2016; Bron et al., 2004; M. Collins et al., 2009; Mendell et al., 2002; Wolkoff, 2005; Wolkoff et al., 2006)	• Increase of BR. • Improvement of tear film stability. • Reduction of tear film evaporation. • Reduction of ocular surface desiccation. • Reduction of dry eye symptoms.

BA = Blink amplitude; BR = Blink rate; DED = Dry eye disease; IBI = Inter-blink interval.

1.7 Conclusions

Abnormal blinking, including a reduced blink rate and incomplete eyelid closure during computer use is considered one of the main mechanisms of digital display-induced dry eye. Possible glare from the device screen and poor image quality of electronic text are probably the reasons for the change in the blink rate observed in digital display users. Nevertheless, given recent technological improvements, incomplete blinking, caused by increased cognitive and task demand, might be a more pertinent issue today. Other dry eye-inducing factors include increased ocular surface exposure associated with high visualization angles at which computers are usually held and MGD prompted by abnormal blinking in long-term display users.

Studies indicate a reduction in tear volume, a noticeable decrease in tear stability and alterations in tear film composition, including increased osmolarity levels, inflammatory cytokines, oxidative stress markers and reduced mucin secretion in computer users. Conjunctival redness is frequently found in display users, whereas vital staining of the ocular surface may be a sign of a mild-to-moderate disorder. The impact on the tear film and ocular surface may be less significant following the use of handheld devices compared with computer use, although more research is needed in specifically designed studies. Signs and symptoms of ocular surface dryness are globally accepted to be dose-dependent and to increase with the task duration. Risk factors such as CL wear, advanced age, female sex, inadequate lighting, and high-temperature and low-humidity environmental conditions could contribute to a higher prevalence and severity of dry eye in digital display users. Figure 1.1 shows the process by which digital displays and associated factors give rise to ocular surface alterations, ultimately leading to DED.

Finally, the management strategy should follow a multidirectional approach, with various treatments being applied in conjunction. These may include the use of high-viscosity lubricating eyedrops, omega-3 fatty acids dietary supplementation, blink exercises focused on increasing blink amplitude, the use of screen filters, improving the work environment, optimizing screen position, and taking regular breaks.

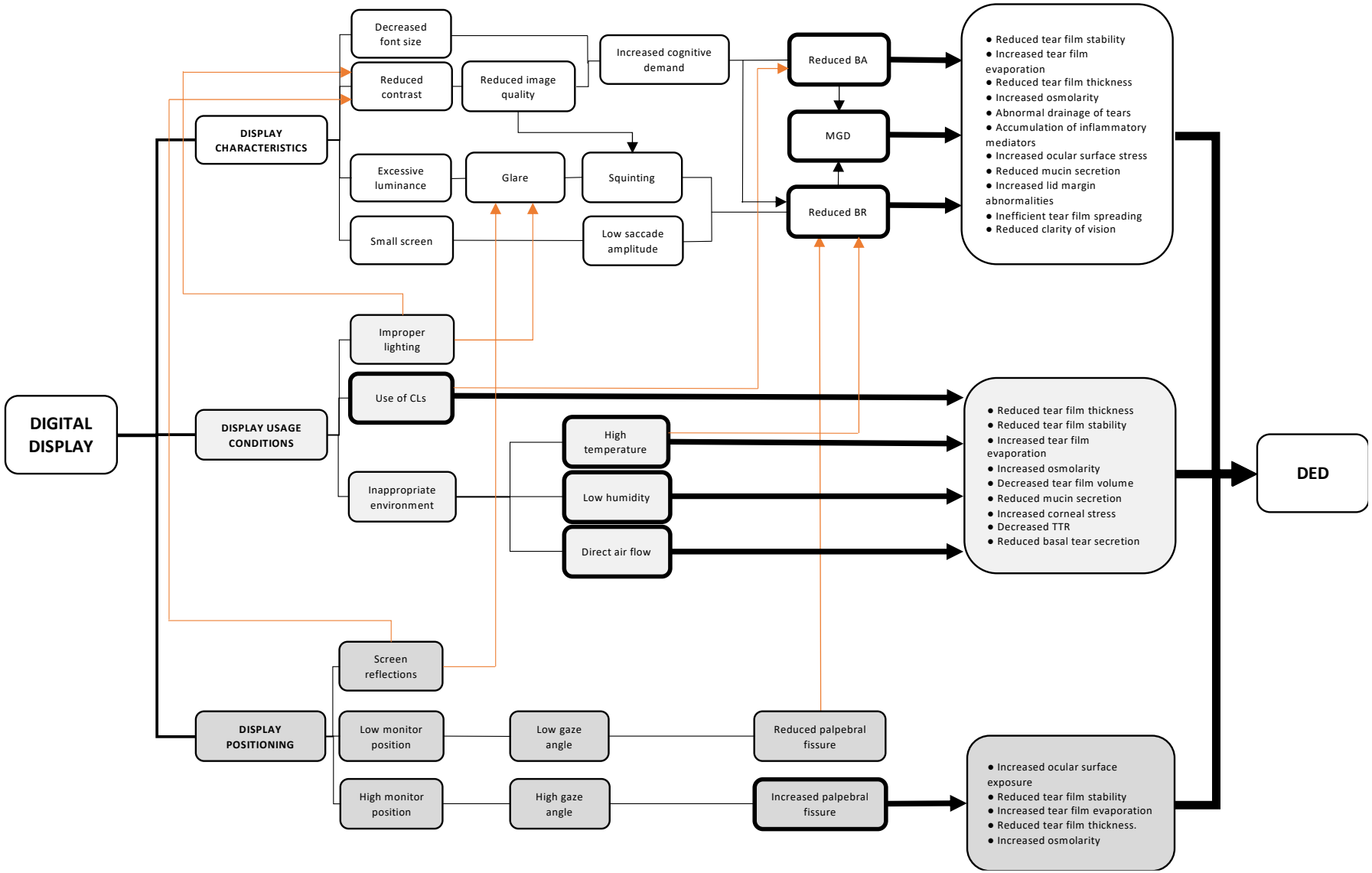


Figure 1.1. From digital display use to dry eye disease. Summary diagram of the factors and mechanisms of digital display use leading to ocular surface and tear film alterations and dry eye disease. Orange arrows correspond to interactions between dry eye inducing factors of different classification group. Black bold arrows indicate ultimate factors responsible for tear film and ocular surface abnormalities. BA = Blink amplitude; BR = Blink rate; CLs = Contact lenses; DED = Dry eye disease; MGD = Meibomian gland disfunction; TTR = Tear turnover rate.

2.

Justification and objectives

With the emergence of new technologies DES has become increasingly prevalent. According to recent findings, the prevalence of DES lies between 33% to 65% (Ganne et al., 2021; Sheppard & Wolffsohn, 2018) and tends to be highest among young adults with an estimated prevalence of 74 to 77% (Cantó-Sancho et al., 2021; Sánchez-Brau et al., 2020).

The impact of computer use on the ocular surface has been primarily attributed to sustained gazing, which leads to decreased blink rate and amplitude (i.e., an increase in incomplete blinking) (Portello et al., 2013), and increased ocular surface exposure associated with high visualization angles (Ranasinghe et al., 2016; Tsubota & Nakamori, 1993), ultimately leading to tear film instability and evaporation (Pansell et al., 2007; Tsubota, 1995).

Substantial research advises of an increased prevalence of dry eye signs and symptoms among digital display users (Choi et al., 2018; Ribelles et al., 2015; Uchino et al., 2013; Wu et al., 2014; Yazici et al., 2015). Ocular surface and tear film abnormalities, including reduced tear stability (Cardona et al., 2011; Choi et al., 2018; Doguizi et al., 2019; Hirota et al., 2013; Kim et al., 2017; Yazici et al., 2015), alterations in tear volume (Cardona et al., 2011; Doguizi et al., 2019; Kojima et al., 2011; Nakamura et al., 2010; Ribelles et al., 2015; Su et al., 2006; Yazici et al., 2015) and tear composition (Choi et al., 2018; Ribelles et al., 2015; Y. Uchino et al., 2014; Yazici et al., 2015), increased oxidative stress (Choi et al., 2018; Yazici et al., 2015), ocular surface inflammation (Ribelles et al., 2015) and even meibomian gland dysfunction (Wu et al., 2014) have all been reported in digital display users. Accordingly, the TFOS DEWS II epidemiology report listed computer use as a consistent risk factor for DED (Stapleton et al., 2017), which may explain the relatively high prevalence of DED observed in younger individuals (20-40 years) (Stapleton et al., 2017).

Digital displays play an integral part in our everyday life, with people using these devices in every aspect of their professional and private life. This tremendous change in work and lifestyle experienced in the recent decades has been accompanied by an increase in health-related complaints, that motivated research in this area. Recently, the growing reports of eye discomfort in younger individuals and the increase in technological resources worldwide since the coronavirus (COVID-19) pandemic, have given rise to a renewed interest in the effects of digital screens on the eyes.

Although our understanding of the effects of digital display use on the ocular surface has increased considerably since the turn of the century, several major questions

are yet to be answered. Likewise, technological advances and the appearance of new forms of digital displays demand continuous research.

The primary aim of the present work was to deepen the understanding of the effects of digital display use on the ocular surface. Specifically, this thesis aimed to explore the association between DES and dry eye-related risk factors, assess the impact of various forms of digital displays on blinking kinematics and the ocular surface and identify predisposing factors for digital display-induced dry eye. Additionally, it sought to evaluate the impact of digital display use on the ocular surface of CL wearers and post-laser in situ keratomileusis (LASIK) patients and the effects of computer use on visual function, quality of vision and optical quality, as well as the impact of computer use on the sensitivity of the cornea. Other objectives of this thesis included determining the best management strategy for reducing the impact of digital display use on dry eyes and evaluating the benefits of the 20-20-20 rule. Finally, considering the global changes in the patterns of education and technology usage following the COVID-19 outbreak, this work aimed to investigate the implications of switching to an online lecture format on dry eye symptoms and associated risk factors.

3.

General methods

3.1 Design and ethical considerations

This doctoral thesis presents a total of 12 independent studies divided into different chapters (Chapters 4-15). Each study has its own design, which, when possible, mirrored that of previous studies, in order to fill a particular gap in the existing literature. Broadly, the present work consists of prospective, controlled, clinical studies, of experimental or observational nature with either a cross-sectional or longitudinal design. Also, studies derived from quantitative, cross-sectional surveys are presented.

To test the studies' hypotheses, a wide range of measurements and devices have been used (see later). The study samples consisted of young to middle-aged students and workers from the University of Valencia (Valencia, Spain), Aston University (Birmingham, UK), University of Minho (Braga, Portugal) and University of New South Wales (UNSW, Sydney, Australia), depending on the study. Recruitment criteria are described in each chapter. Participants were invited to participate by means of email and poster advertisements.

Studies followed the tenets of the Declaration of Helsinki, and a favourable opinion from the ethical committee of the University of Valencia, Aston University, University of Minho or UNSW was obtained. All the participants were informed about the nature of the study and gave their written consent before initiating the experiments.

3.2 Measurements and devices

This section describes the technical and operating information of the devices used for data collection. All the instruments had been previously validated. Following the TFOS DEWS II diagnostic methodology report (Wolffsohn et al., 2017), non-invasive tests were chosen over invasive, and measurements were taken from least disruptive to most disruptive to minimize the impact of the measurement procedures on subsequent measurements. The specific order of the measurements is described in each chapter. All the measurements were taken by the same experienced examiner (the author of this thesis). Laboratory conditions were kept constant throughout each study, and temperature and humidity were constantly monitored using digital thermo-hygrometers.

3.2.1 Symptomatology questionnaires

The following validated questionnaires were used to assess participants' subjective experience of dry eye symptoms, ocular discomfort, DES and quality of vision. The questionnaires were self-administered.

3.2.1.1 Ocular Surface Disease Index

The Ocular Surface Disease Index (OSDI) was used to evaluate participants' dry eye symptoms. This questionnaire was chosen following the TFOS DEWS II diagnostic methodology report (Wolffsohn et al., 2017), which recommends its use due to its strong establishment in the field. The OSDI is the most widely used questionnaire for DED clinical trials due to its multidimensionality, versatility, and evaluation of changes in the patient's quality of life.

This 12-item questionnaire, created by Outcomes Research Group at Allergan Inc, assesses dry eye symptoms and their effects on vision-related function in the past week of the patient's life (Schiffman, 2000). The questionnaire has 3 subscales: ocular symptoms, vision-related function, and environmental triggers. Patients rate their responses on a 0 to 4 scale with 0 corresponding to "none of the time" and 4 corresponding to "all of the time." The score is calculated as OSDI = [(sum of severity for all questions answered) × 100] / [(total number of questions answered) × 4], and ranges from 0 to 100 with scores 0 to 12 representing normal; 13 to 22 representing mild dry eye; 23 to 32 representing moderate dry eye; and greater than 33 representing severe dry eye. The OSDI questionnaire is enclosed in *Appendix A.*

3.2.1.2 5-item Dry Eye Questionnaire

The 5-item Dry Eye Questionnaire (DEQ-5) was used to further evaluate participants' dry eye symptoms. As for the OSDI, DEQ-5 was chosen following the TFOS DEWS II diagnostic methodology report (Wolffsohn et al., 2017), which recommended its use due to its short length and discriminative ability.

This 5-item questionnaire is a shortened version of the DEQ developed by Begley et al. (2002), which was created to diagnose DED and quantify its severity level. The DEQ-5 consists of five questions with a recall of symptoms over the past month that assess the following: frequency of watery eyes, discomfort and dryness and late-day discomfort and dryness intensity (Chalmers et al., 2010). Patients rate their responses to

the frequency questions on a 0 to 4 scale, with 0 corresponding to "never" and 4 corresponding to "constantly". Severity questions are scored from 0 to 5, with 0 corresponding to "never have it" and 5 corresponding to "very intense". DEQ-5 scores range from 0 to 22 with higher scores representing greater symptoms. The final score is calculated as the summation of the responses. A score between 6 and 11 represents mild to moderate dry eye and values greater than 12 mean severe dry eye. The DEQ-5 questionnaire is enclosed in *Appendix B.*

3.2.1.3 Symptom Assessment in Dry Eye

The Symptom Assessment in Dry Eye (SANDE) questionnaire is a short and intuitive questionnaire based on a visual analogue scale that quantifies both the severity and frequency of dry eye symptoms (Schaumberg et al., 2007). The SANDE is comprised of two questions and each question employs a 100 mm horizontal linear visual analogue scale. In the first version of the questionnaire (SANDE I), the measurement of symptom frequency ranges from "rarely" to "all of the time," and the symptom severity from "very mild" to "very severe. The second version of the questionnaire (SANDE II) queries the difference in the perceived frequency and severity of dry eye symptoms compared to the previous visit. This time, the frequency of symptoms ranges from "much less frequent" to "much more frequent" and the severity from "much less severe" to "much more severe". In the present work, the SANDE II was adapted to the study by examining the change in dry eye symptoms compared to the previous visit or before the study intervention, depending on the study design. The SANDE I and II questionnaires are enclosed in *Appendix C.*

3.2.1.4 Ocular Comfort Index

The Ocular Comfort Index (OCI) questionnaire was developed by Johnson and Murphy (2007) as an instrument that allows for quick assessment of ocular discomfort caused by ocular surface disease. The questionnaire was conceived in response to deficiencies in existing instruments for use in clinical trials. It has 6 areas of questioning (dryness, grittiness, stinging, tiredness, pain, and itching) which were identified from interviews with patients and a literature review. Each area is split into two subparts that sequentially inquire about the frequency and intensity over the last week, leading to a

total of 12 items. The final score is calculated using the OCI Excel calculator and ranges from 0 to 100. The OCI questionnaire is enclosed in *Appendix D.*

3.2.1.5 Instant Ocular Symptoms Survey

The Instant Ocular Symptoms Survey (IOSS) comprises two items to elicit the instantaneous intensity of ocular surface dryness and discomfort (Boga et al., 2019). The items are rephrased versions of questions 1b and 2b of the DEQ-5. The total IOSS score is calculated from the sum of the scores for the two items, with a maximum of 10 which represents the greatest discomfort. The IOSS questionnaire is enclosed in *Appendix E.*

3.2.1.6 8-item Contact Lens Dry Eye Questionnaire

The 8-item CL Dry Eye Questionnaire (CLDEQ-8) is the result of item reduction from the much longer CLDEQ in which items that best reflected the status and overall opinion of soft CLs were selected. The CLDEQ instrument was originally designed in parallel to the DEQ and is similar, except that patients are asked about dryness symptoms when they are wearing CLs (Begley et al., 2000). The CLDEQ-8 queries the frequency and late-day intensity of eye discomfort, eye dryness, and changeable, blurry vision and the frequency of closing eyes for relief and removal of lenses earlier than planned for relief of symptoms, with a recall of symptoms over the past two weeks (Chalmers et al., 2012). As in the DEQ, patients rate their responses to the frequency questions on a 0 to 4 scale, with 0 corresponding to “never” and 4 corresponding to “constantly” and to the severity questions on a 0 to 5 scale, with 0 corresponding to “never have it” and 5 corresponding to “very intense”. The CLDEQ-8 questionnaire is enclosed in *Appendix F.*

3.2.1.7 Computer Vision Syndrome Questionnaire

The Computer Vision Syndrome Questionnaire (CVS-Q) was developed by Seguí et al. (2015) to measure ocular symptoms related to exposure to digital displays in the workplace. The questionnaire comprises 16 items selected based on a literature review and related to the frequency and intensity of dry eye and accommodative and binocular vision stress during computer work. To measure the frequency of occurrence, the questionnaire uses a rating scale of 0 to 2 points, with 0 corresponding to “never”, 1 corresponding to “occasionally” (sporadic episodes or once a week) and 2 corresponding to “often or always” (2 or 3 times a week or almost every day). The strength of symptoms

is graded similarly, on a scale of 1 to 2 points, where 1 corresponds to “moderate” and 2 to corresponds to “intense”.

The responses to the two rating scales for each symptom are combined multiplicatively into one rating scale for the analysis, resulting in a single symptom severity score. The final severity score of each symptom is recoded as 0 = 0; 1 or 2 = 2; 4 = 2. Finally, the total score is calculated as the summation of the individual severity scores. The scores obtained on the questionnaire range from 0 to 24 and a score of 6 or more is defined as having DES. The CVS-Q questionnaire is enclosed in *Appendix G.*

3.2.1.8 Quality of Vision

The Quality of Vision questionnaire (QoV) features 10 items regarding the patient’s perception of glare, halos, starburst, hazy vision, distortion, multiple images, fluctuation, focusing difficulties, and depth (McAlinden et al., 2010). The questionnaire is scored on a Rasch scale across three subscales: frequency of symptoms, severity of symptoms and bothersomeness of symptoms, with higher scores indicating worse quality of vision. The questionnaire is suitable for measuring the subjective quality of vision in patients with all types of refractive correction, eye surgery, and eye disease that cause vision problems. The final score is calculated using the QoV Excel calculator and ranges from 0 to 100. This questionnaire cannot be shared publicly in this work and is available upon request from the copyright holder.

3.2.2 Oculus Keratograph 5M

The Oculus Keratograpgh 5M (Oculus Optikgerate, Wetzlar, Germany) is an advanced corneal topographer with a built-in real keratometer and a colour camera optimized for external imaging. It is a multipurpose device, with several imaging modalities used to characterize the ocular surface and tear film. The instrument includes a high-resolution colour camera, an integrated magnification changer and different illuminations (Placido ring illumination and light emitting diodes, LEDs) integrated for every function. Figure 3.1 shows a photo of the device. The metrics described below were used to characterize the ocular surface and tear film of the participants with the Oculus Keratograph 5M.

Figure 3.1. Oculus Keratograph 5M used in this work.

3.2.2.1 Tear meniscus height

The height of the tear meniscus (TMH) was measured using the integrated ruler and the various magnification options of the device. The participants were instructed to fixate on the target while maintaining normal blinking. Before each measurement, participants were instructed to blink and then keep their eyes open. An image of the inferior eyelid was captured using the integrated infrared light, approximately 2 s after the final blink. The distance between the lower eyelid margin and the last reflex of the meniscus was measured perpendicular to the lid margin at three points (nasal and temporal limbus and pupil centre) (Abdelfattah et al., 2015) (Figure 3.2).

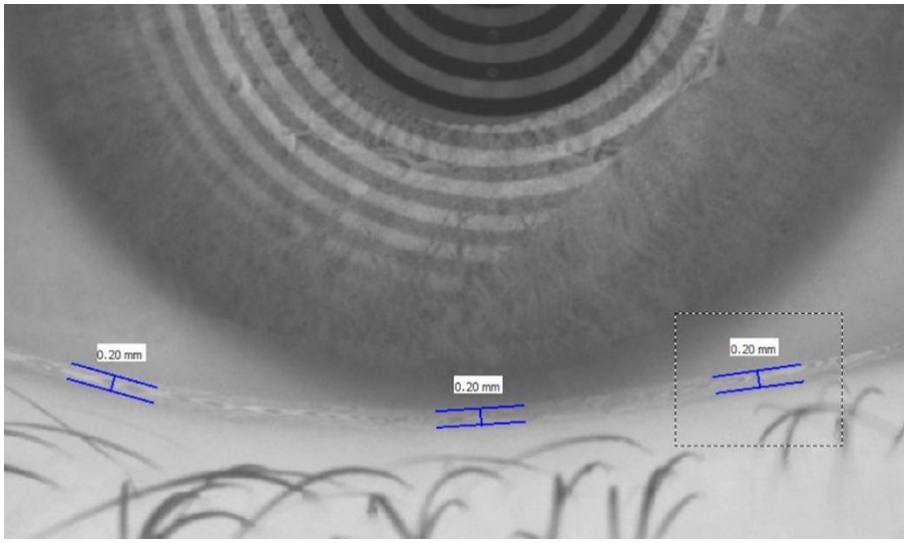


Figure 3.2. Example of the measurement of the tear meniscus height obtained using the Keratograph 5M.

3.2.2.2 Corneal aberrations

Corneal aberrations are automatically computed by the device using the corneal topographic map data (Figure 3.3). Participants were instructed to fixate on the target while maintaining normal blinking. Before each measurement, participants were instructed to blink and then keep their eyes open. Aberrations were taken approximately 1 s after the final blink (Vasudevan et al., 2015). Aberrations were reconstructed using Zernike polynomials for pupil diameters of 3 and 5 mm – these diameters were chosen based on previous studies (Berntsen et al., 2005; García-Marqués et al., 2022b; Montés-Micó et al., 2013). Aberration coefficients were downloaded and transferred into Microsoft Excel spreadsheets (Microsoft, Redmond, WA, USA). The root mean square (RMS) of HOAs up to the 6th order was calculated.

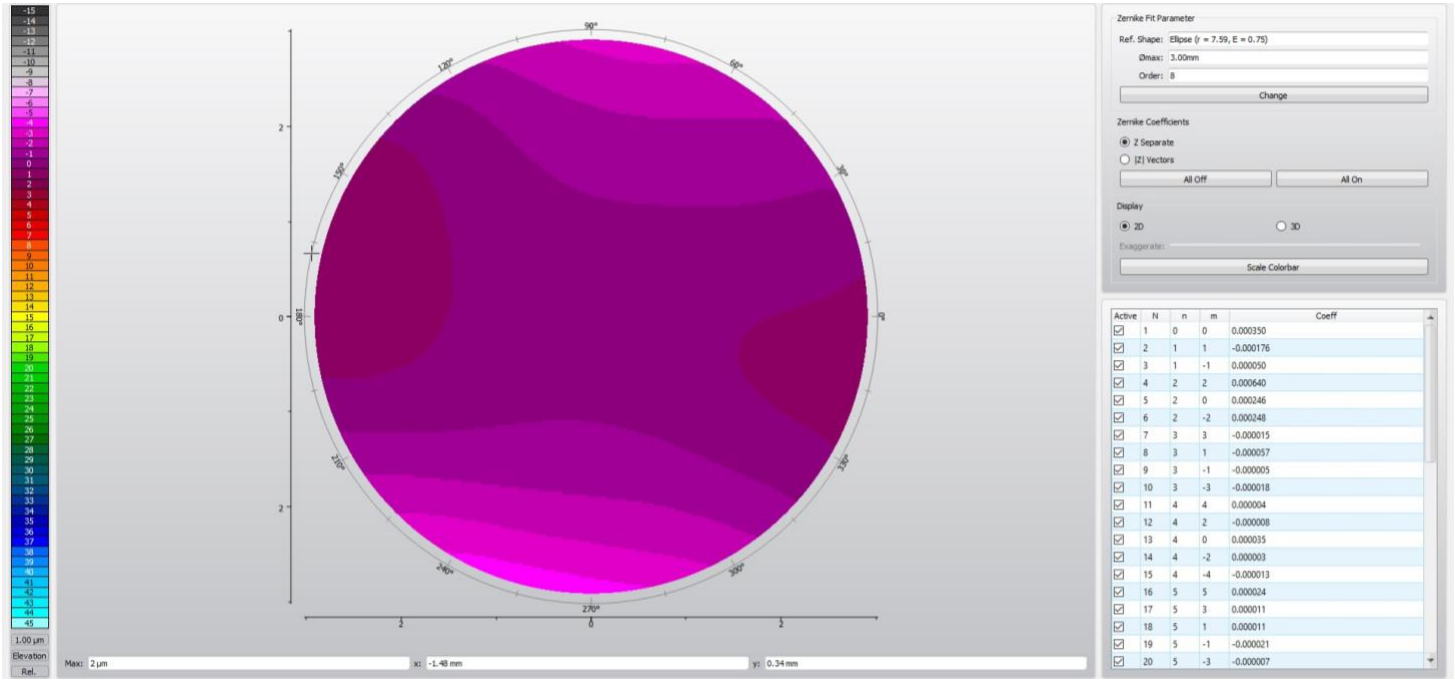


Figure 3.3. Example of the measurement of corneal aberrations obtained using the Keratograph 5M.

3.2.2.3 Conjunctival redness

For the measurement of conjunctival redness, the instrument uses the white-illumination system which scans the exposed bulbar and limbal conjunctiva and immediately generates an image of 1156 × 873 pixels and five redness scores on the computer screen (Wu et al., 2015) (Figure 3.4). These scores are continuous variables (0.0-4.0 in 0.1 steps) based on the percentage area ratio between the blood vessels and the

rest of the analysed area. The five scores correspond to the redness of the temporal and nasal regions of the bulbar and limbal conjunctiva and a total bulbar redness score.

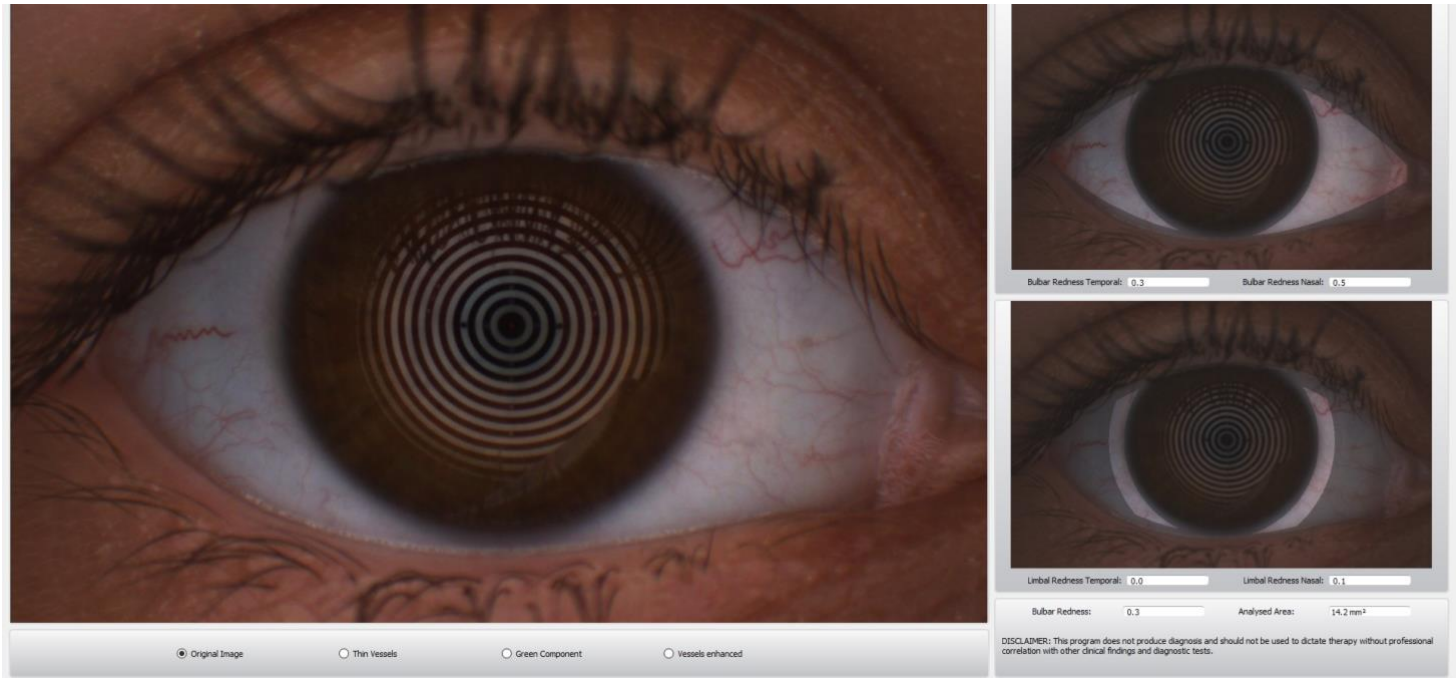


Figure 3.4. Example of the measurement of conjunctival redness obtained using the Keratograph 5M.

3.2.2.4 Lipid layer thickness

The LLT was assessed using a magnification of ×1.4, which enables the observation of subtle changes in the interference pattern and the debris floating over the surface of the tear film. Once the lipid layer was properly focused, the interference pattern was recorded using white light (Ren et al., 2018). The participants were instructed to look at the central fixation stimulus of the device and blink freely. The lipid layer pattern was graded using the validated Guillon grading scale as 1 = open meshwork; 2 = closed meshwork; 3 = wave; 4 = amorphous; 5 = 1st order colours; and 6 = 2nd order colours (Guillon, 1998).

3.2.2.5 Blinking pattern

The spontaneous blinking of the participants was assessed in terms of the blink rate (i.e., total number of blinks) and percentage of incomplete blinks through the recording of a 60-s video sequence. The "high frame rate" option was selected from the software's menu to increase the temporal resolution of the device to its maximum.

Participants were instructed to look at the fixation target with no need to stare at the stimulus and were not actively told that their blink movements were being recorded. Next, the recorded video was played at 0.25 times its original speed and blinks were manually counted. Small twitches of the upper eyelid with particularly small amplitudes were not counted as a blink.

3.2.2.6 Non-invasive keratograph break-up time

The instrument measures the tear film break-up time non-invasively and fully automatically using infrared illumination to prevent glare and reflex tearing during the examination. A Placido disk-illuminated pattern is projected onto the cornea and the distortion of the reflected mires throughout the recording time is automatically registered as a break-up of the tear film (Hong et al., 2013). The instrument generates a polar-type grid representing tear film break-up over the entire corneal area and two NIKBUT scores: the time when the first breakup of tear film occurs and the average time of all breakup incidents (Figure 3.5). In the present work, the NIKBUT score corresponding to the time of the first break-up was used as a measurement of tear stability in all studies. NIKBUT was measured three consecutive times and an average value was obtained. A 1-minute stabilization period was left between consecutive measurements.

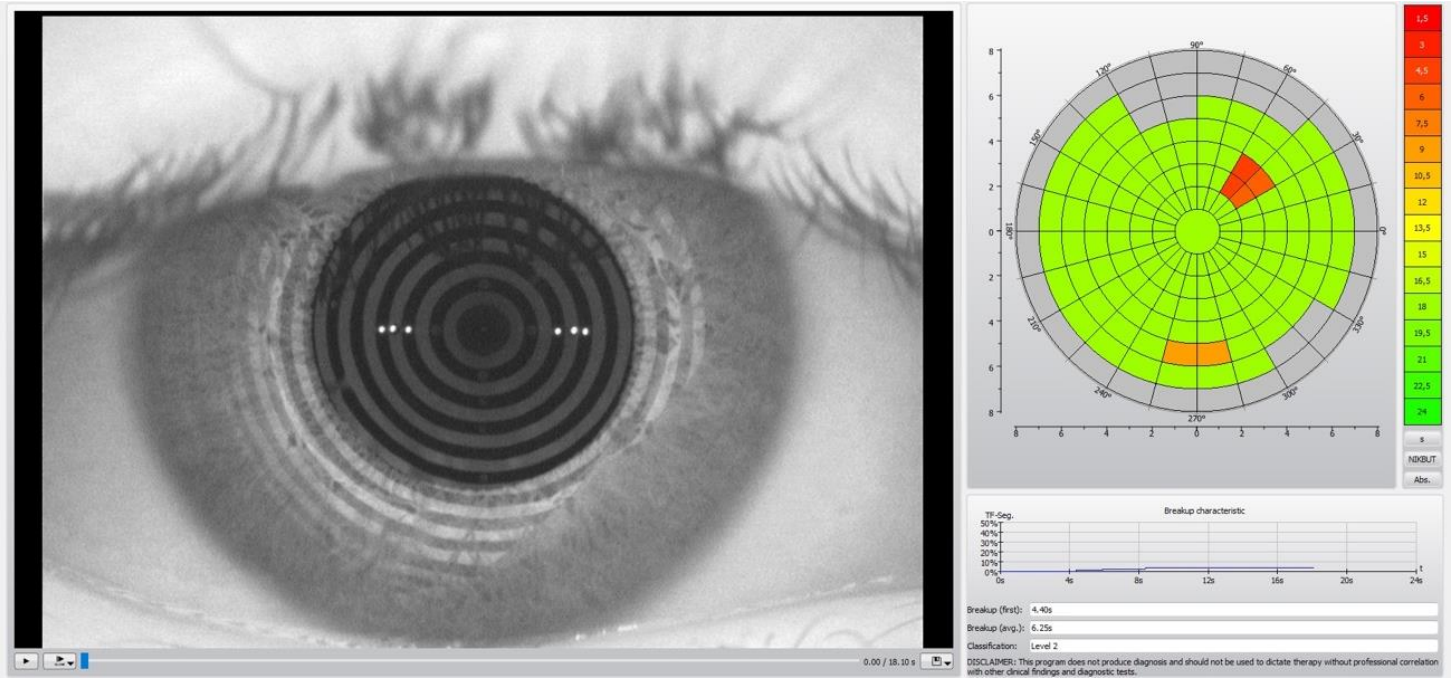


Figure 3.5. Example of the measurement of non-invasive keratograpgh break-up time obtained using the Keratograph 5M.

3.2.2.7 Ocular surface staining

Corneal, conjunctival and lid margin staining were evaluated using sodium fluorescein and lissamine green ophthalmic dyes. The recommendations of the TFOS DEWS II diagnostic methodology report were followed (Wolffsohn et al., 2017). For corneal staining, a saline drop was placed on a fluorescein strip without contact with the bottle and the excess fluorescein was flicked off. The strip was applied flat to the temporal canthal lid margin area while the participant looked up. Fluorescein staining was assessed approximately 1-3 minutes after instillation. For the assessment of conjunctival damage, the dye strip was wet with saline and allowed to soak into the strip for at least 5 s. This time, the whole drop was applied inside the temporal canthal area while the participant looked up. The conjunctival was viewed 1-4 minutes after instillation.

Finally, the lid was subsequently everted to reveal any damage to the lid margins which had been stained with the fluorescein and lissamine green already instilled in the eye. For all measurements, participants were instructed to look in different directions and blink normally, while pictures and video recordings of the area of interest were obtained using various magnifications and illuminations. Corneal and conjunctival staining were later graded using the Oxford grading scale (Bron et al., 2003). Lid wiper epitheliopathy (LWE) was graded in terms of horizontal length and sagittal width (Korb et al., 2005a).

3.2.2.8 Meibography

Meibomian gland morphology was assessed by non-contact infrared meibography using the Meibo-Scan tool of the Keratograph 5M after eyelid eversion (Ngo et al., 2014). Default settings were used with a magnification of ×0.5. Images were downloaded and transferred into the ImageJ tool (Wayne Rasband, National Institutes of Health, Bethesda, MD). The gland drop-out percentage was calculated using the polygon selection tool as the ratio between the eyelid area and gland loss area (García-Marqués et al., 2022a) (Figure 3.6).

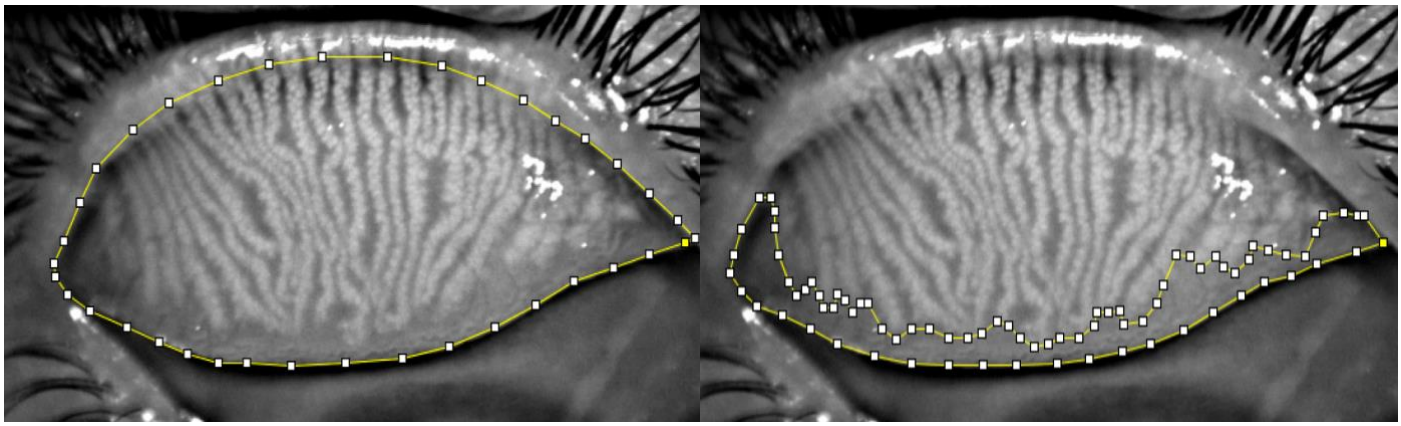


Figure 3.6. Example of the assessment of meibomian gland drop-out using the ImageJ tool. Left: Selection of the entire eyelid area; Right: Selection of the gland drop-out area.

3.2.3 TearLab Osmolarity System

Tear film osmolarity was measured using the TearLab Osmolarity System (TearLab Corp. San Diego, CA, USA) (Figure 3.7). For each measurement, a TearLab osmolarity test card was attached onto the pen and a tear sample of 40 nl was automatically collected after touching the tip of the Pen to the tear fluid meniscus located above the lower eyelid (Wolffsohn et al., 2017). After a successful collection, the pen was docked into the reader, which displayed a quantitative tear osmolarity test result on the liquid crystal display (LCD) of the device. Reusable electronic check cards were used every morning during the study period as procedural quality control to confirm the function and calibration of the system within manufacturer specifications. The device and test cards were stored in the laboratory where the measurements were taken, away from direct sunlight and at ambient temperature. A 25-minute warm-up was left between switching on the reader and its use.

Figure 3.7. TearLab Osmolarity System used in this work.

3.2.4 Schirmer I test

Schirmer test strips (Bio-Tech Vision Care Pvt. Ltd.) were used to assess basal and reflex tear volume, linked to lacrimal gland function, without anaesthesia (Schirmer I test). Without touching the filter paper strip, the paper strip (5 x 35 mm) was folded at the notch and the folded end was hooked over the temporal one-third of the lower lid margin (Wolffsohn et al., 2017). The test was administered with the participant's eyes closed to minimize the variability of results. The score was measured as the length of wetting from the notch, after a period of 5 minutes.

3.2.5 Medmont E300

The Medmont E300 (Medmont International Pty Ltd, Melbourne, Australia) is a small-cone, Placido disc-based corneal topographer which uses automated videokeratoscopy to measure the quality of the tear film and NIBUT, through detecting distortion in the contours of the reflected Placido disc mires over time (Figure 3.8). It determines the distance from the corneal apex to the instrument's camera and automatically captures images. It has 32 Placido rings and measures 9600 data points per scan (Wang et al., 2012). The metrics related to the tear film status described below were obtained with the Medmont E300 corneal topographer.

Figure 3.8. Medmont E300 used in this work.

3.2.5.1 Tear film surface quality

The tear film surface quality (TFSQ) algorithm analyses the structure of the Placido disk pattern reflected onto the tear film over time, which provides a non-invasive measure of tear film quality and stability. The software calculates TFSQ values at 300 radial analysis points along each of the 32 rings (Downie, 2015). The device automatically calculates three tear film indices with each measurement: TFSQ, TFSQ area and TBUT (Figure 3.9). The local TFSQ value at a given analysis point is calculated by finding the standard deviation (SD) of the radial distances to the next innermost ring for n = 8 points on either side of the analysis point (Downie, 2015). TFSQ values range from 0 to 1, with higher scores corresponding to greater distortions in the ring pattern and indicating a more destabilized tear film. The TFSQ area corresponds to the percentage of the area assessed with a TFSQ value greater than 0.30, while the auto TBUT is the time in seconds in which the TFSQ area is at least 5% in two consecutive images (Downie, 2015).

The participants were instructed to fixate on the centre of the inner green ring and blink normally while the device was being centred. Then, they were asked to blink twice and suppress blinking for as long as possible. Three consecutive measurements were

taken, and an average value was obtained. A 1-minute stabilization period was left between consecutive measurements.

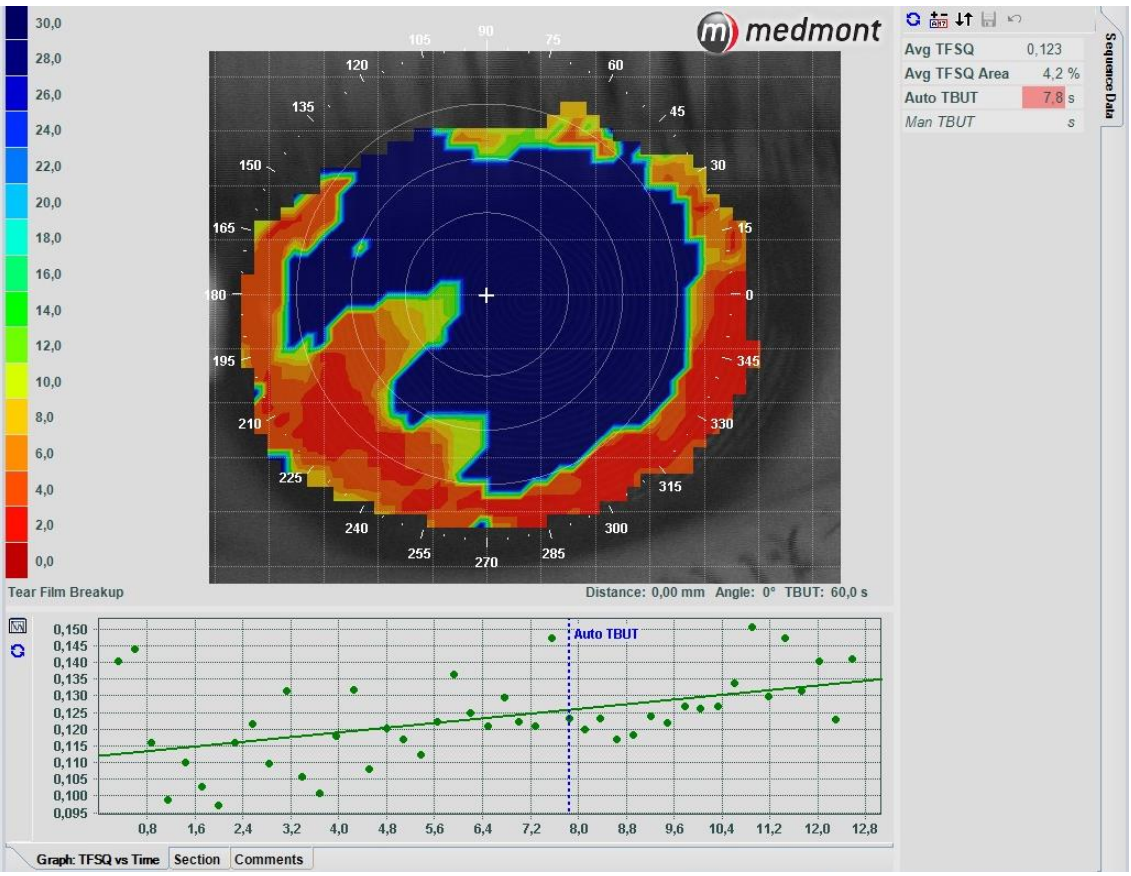


Figure 3.9. Example of the measurement of tear film surface quality (TFSQ), tear film surface quality area and tear break-up time (TBUT) obtained using the Medmont E300.

3.2.6 UNSW Liquid Jet Aesthesiometer

Corneal mechanical and cold sensation thresholds at the central cornea were determined using the UNSW Liquid Jet Aesthesiometer (LJA) (UNSW, Sydney, Australia). In brief, a microvalve which switches on and off at variable 'on' periods allows a droplet of adjustable volume to be propelled onto the ocular surface to generate a stimulus of variable intensity (Figure 3.10) (Ehrmann et al., 2018; Ehrmann et al., 2023). The ocular surface sensation threshold is determined based on the participants' 'felt' or 'not felt' subjective feedback, provided via a handheld pushbutton, which feeds into an automated double staircase algorithm. After the high and low starting staircases have converged for the first time, 9 more stimulations were applied, and the sensation threshold was automatically calculated as the mean droplet volume of these last 9 stimulations.

In the present work, the 'pulse duration' mode, whereby a fixed number of pulses is ejected over a variable duration, was selected from the software settings. Each stimulus consisted of 1 pulse. The liquid used was phosphate buffered saline (PBS) in sterile 15 mm ampoules (Reclens, Aaxis Pacific, NSW, Australia). This PBS has pH and osmolarity levels close to those of normal tears, to avoid stimulation of corneal polymodal neuroreceptors which are sensitive to chemical stimuli (Belmonte, et al., 2004a; Belmonte, et al., 2004b; Vereertbrugghen & Galletti, 2022). To determine the threshold of mechanical stimulation, the PBS was heated to corneal temperature (36°C) to likewise avoid stimulation of cold-sensitive neuroreceptors and generate a true mechanical stimulus (Nosch et al., 2022). To determine the threshold of cold stimulation the PBS was cooled to 15°C while keeping the mechanical stimulation at a sub-threshold level. The duration of the pulses varied to achieve a total projected volume of liquid between 0.15 and 4.75 µl per stimulus for mechanical sensitivity and between 0.02 and 0.10 µl per stimulus for cold sensitivity. The initially large step size (20% of the full scale) was halved twice with each reversal within the high or low staircase. The minimum step size was set at 5% of the full scale and the initial rising and falling values were set at the 10th and 90th percentiles of the scale, respectively. The stimuli were presented within a random delay of 1-2 s.

Optical and acoustic clues were minimized by performing the tests in a dark room and using noise-cancelling headphones with white noise in the background. A dim fixation light in the distance was used to assist the participants in maintaining a steady eye position with the contralateral (non-test) eye. A minimum of 5 s recovery time was allowed between stimuli and participants were encouraged to blink normally in between. A typical measurement was completed within 2-3 minutes.

Figure 3.10. Photos of the UNSW Liquid Jet Aesthesiometer in use. Room lights were turned on for the photos.

3.2.7 irx3 aberrometer

The optical quality of the eye was assessed by measuring ocular aberrations using a Hartmann-Shack aberrometer (irx3, Imagine Eyes, Orsay, France) (Figure 3.11). All the measurements were obtained under mesopic conditions. Aberrations were reconstructed using Zernike polynomials for pupil diameters of 3 and 5 mm (Berntsen et al., 2005; García-Marqués et al., 2022b; Montés-Micó et al., 2013). The RMS was calculated for lower-order aberrations (LOAs), HOAs up to the 8th order, and total aberrations. Additionally, the Strehl ratio for HOAs obtained by the apparatus was recorded.

Figure 3.11. irx3 aberrometer used in this work.

3.2.8 Optec 6500 Functional Vision Analyzer

The Optec 6500 Functional Vision Analyzer (Stereo Optical Inc., Chicago, IL, USA) is a multipurpose device that allows the assessment of visual function under different lighting conditions (Figure 3.12). The functional acuity contrast test (FACT) and the early treatment diabetic retinopathy study (EDTRS) charts implemented in the Optec 6500 Functional Vision Analyzer were used to measure contrast sensitivity function (CSF) and corrected distance visual acuity (CDVA), respectively. Testing was performed under 2 different conditions: day (photopic, 85 cd/m^2) and night (mesopic, 3 cd/m^2).

The stimuli in the FACT imply linear sinewave grating charts of 1.5, 3, 6, 12 and 18 cpd in nine circular patches (diameter: 1.7°) (Hohberger et al., 2007). For each spatial frequency sine-wave gratings in 0.15 log contrast sensitivity decrements are presented (Hohberger et al., 2007). The gratings are inclined -15°, 0° or +15° to remain in the spectrum of the visual channel. The orientation of the stripe pattern is reported according to left, upside or right, and the last correct response for each spatial frequency was written down.

Figure 3.12. Optec 6500 Functional Vision Analyzer used in this work.

3.2.9 Light Disturbance Analyzer

Light disturbance is a phenomenon caused by the light from a central luminous point which forms a halo surrounding the light source (Klyce, 2007). The Light Disturbance Analyzer (LDA, CEORLab, Braga, Portugal) analyses the size and shape of the halo surrounding a bright light against a dark background under dim illumination conditions. The test consists of detecting peripheral stimuli (240 small, white LEDs of 1 mm) along various semi-meridians (angular separation of 15°), around a central bright stimulus (LED of 5 mm) acting as a source of glare (Figure 3.13). A detailed description of the system can be found elsewhere (Ferreira-Neves et al., 2015; Linhares et al., 2013). This device has been used to successfully measure the effects of different conditions on visual function (Amorim-de-Sousa et al., 2019; García-Marqués et al., 2020, 2022b). In the present work, the in-out routine was selected from the software settings: stimuli were presented from the centre to the periphery at 24 semi-meridians, in random order, until detected by the participant.

The following metrics related to the size and shape of the light disturbance were assessed: disturbance area (sum of the areas of all sectors formed between each pair of semi-meridians); light disturbance index (LDI, percentage of the total tested area not

visible because of the light disturbance; higher values indicate greater disturbance); best-fit circle radius (BFCR, circle that best fits the polygonal shape of the disturbance area); best-fit circle irregularity (BFCI, deviation of the obtained polygonal shape from the best-fit circle; higher values indicate greater disparity from rotationally or meridionally symmetric shapes); and best-fit circle irregularity standard deviation (BFCI-SD, standard deviation of the best-fit circle irregularity; higher values indicate greater disturbance irregularity).

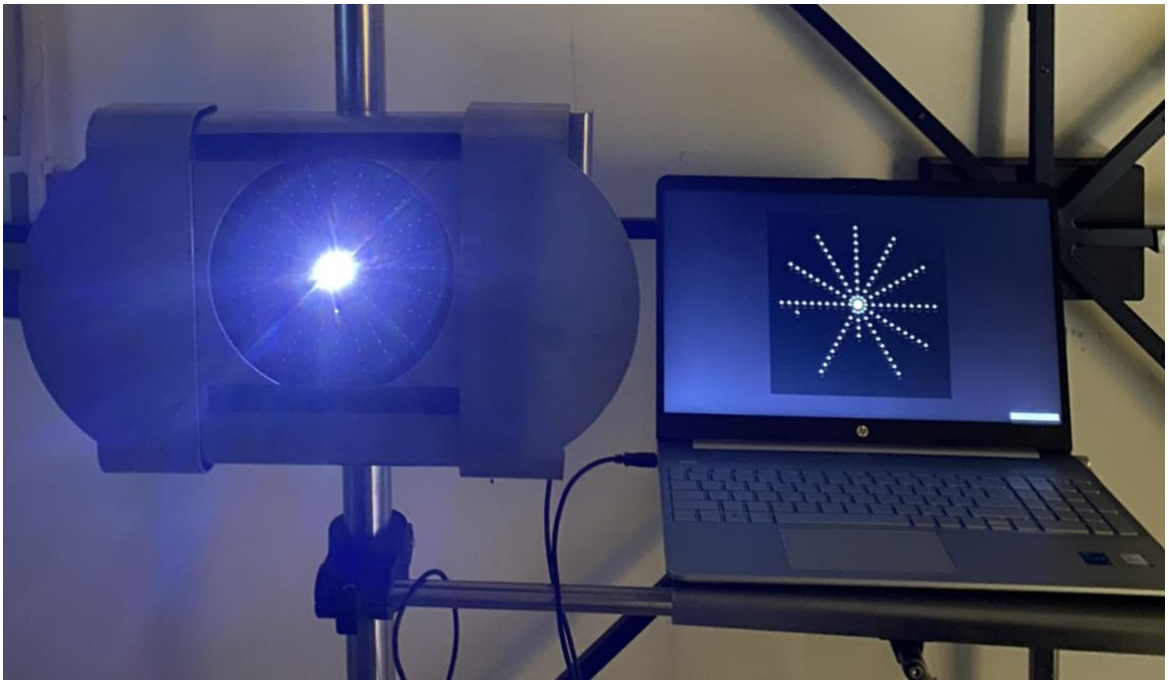


Figure 3.13. Photos of the Light Disturbance Analyzer in use.

3.2.10 High-Speed Visual Eye-Tracker

The High-Speed Visual Eye-Tracker (HSVET) (Cambridge Research Systems Ltd, Rochester, UK) is an infrared video-based eye tracker working at a sample rate of 250 fps. The HSVET consists of a high-speed infrared camera, with a resolution of 320 per 240 pixels, a visible/infrared dichroic beamsplitter and a chin rest (Figure 3.14). Due to the configuration of the device, the image of the eye is reflected on the infrared mirror without interfering with the observer's line of sight, simulating natural viewing conditions (Sanchis-Jurado et al., 2020).

The HSVET was used to record the blinking pattern of the participants while they performed different visualization tasks. With the participant resting still on the device chin rest, the frames obtained when recording eyelid movement can be used to follow the

temporal evolution of the position of the ocular structures. Taking the same column of pixels for every frame in the sequence, and appending them all together, an artificial image of the variation of the different structures can be generated (Figure 3.15 (a)). This artificial image was then used to analyse the blinking movement (Figure 3.15 (b)). Once the frames on each video sequence were extracted, they were automatically analysed using a set of self-developed tools using Matlab software R2018a (Mathworks, Natick, MA, USA). The image processing-based method used for the automatic analysis of blinking has been previously described in the literature (Sanchis-Jurado et al., 2020). Overall, this automatic, non-invasive procedure provided a detailed description of the blinking pattern in terms of blink rate, number of complete and incomplete blinks, percentage of incomplete blinks, blink amplitude, opening and closing blink speeds and opening, closing, contact and total blink durations.

Figure 3.14. High-Speed Visual Eye-Tracker used in this work.

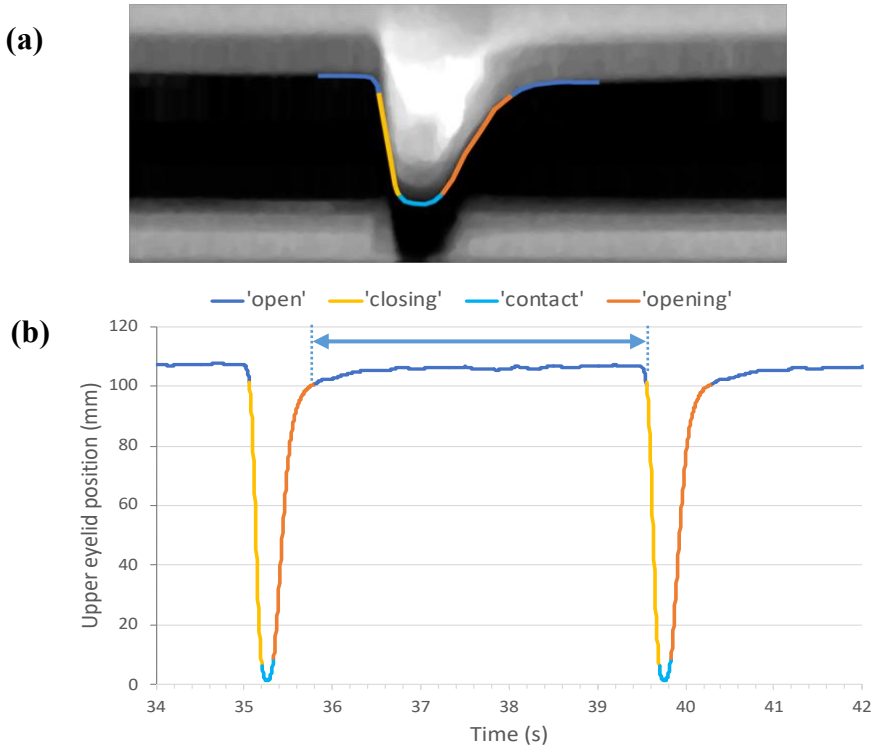


Figure 3.15. (a) Example of artificial image extracted when appending together a selected column of pixels obtained from every frame in the video sequence. (b) Upper eyelid position measured relatively with respect to the lower eyelid position for two randomly selected blinks. Each blink movement was divided into the following phases: eyelids completely open (dark blue line), closing phase (yellow line), contact phase (light blue line), and opening phase (orange line).

3.3 Statistical analysis

Data analysis was carried out using Microsoft Excel spreadsheets (Microsoft, Redmond, WA, USA) and SPSS software v.26/28 (IBM Corp., Armonk, NY, USA). The general statistical procedures used in this work for data analysis are explained below. The specific statistical analyses used in each study are described in each chapter. Data was only collected from one eye in all studies to ensure the independence of measurements (Armstrong, 2013).

3.3.1 Sample size

The sample size was estimated based on the data from previous studies of a similar nature for the primary endpoint/s of each chapter, using the G-Power tool v3.1 (Faul et

al., 2007). With $\alpha = 0.05$, power $(1-\beta) = 0.80$ and two tailed tests, the number of participants needed to observe a particular effect size was calculated. Slightly greater samples than the estimated were recruited accounting for possible study dropouts.

3.3.2 Descriptive statistics

Data are presented as mean ± SD, median (interquartile range, IQR), 95% confidence intervals (CIs), or as the number and percentage of participants, depending on the study variable. Histograms, ladder plots and/or box plots were constructed to represent the results.

3.3.3 Inferential statistics

Parametric or non-parametric tests, depending on the distribution of data, were used. Box plots and scatter plots were constructed to check the distribution of data and the presence of outliers. P-values of < 0.05 were considered statistically significant in all cases.

3.3.3.1 Normality of data

The normality of data was evaluated by means of the Shapiro-Wilk or Kolmogorov-Smirnov test, depending on sample size. The Shapiro-Wilk test was used for samples of up to 50 participants ($n \leq 50$), while the Kolmogorov-Smirnov test was used for larger samples ($n > 50$). Additionally, normal Q-Q plots were represented to check the proximity of data (quantiles from the variable distribution) to the diagonal line of the graph (theoretical quantiles from the normal distribution).

3.3.3.2 Differences between two groups/measurements

An unpaired t-test or the Mann-Whitney U test, depending on the data distribution, was used to compare two independent variables. The unpaired t-test was used to compare continuous variables between two groups whose data followed a normal distribution. The homogeneity of variance was checked using Levene's test. The Mann-Whitney U test was used when parametric test assumptions were not met, or the variables were ordinal.

A paired-sample t-test was used to compare two related measurements. The non-parametric Wilcoxon paired signed-rank test was used when parametric test assumptions were not fulfilled.

Finally, the chi-square test of independence was used to assess the association between two categorical variables. In addition, a contingency table was created to obtain the frequency distribution of the two categorical variables.

3.3.3.3 Differences between three or more repeated measurements

A repeated-measures analysis of variance (ANOVA) was used to analyse the differences among repeated measurements taken at more than two time points. The Mauchly test was used to evaluate the assumption of sphericity. If sphericity could not be assumed, the Greenhouse-Geisser correction was applied. Whenever the repeated-measures ANOVA pointed to a statistical significance, post-hoc pairwise comparisons were carried out using Bonferroni correction. The non-parametric Friedman test for repeated measures with Dunn-Bonferroni post-hoc analysis was used when parametric test assumptions were not fulfilled, or the data was ordinal.

3.3.3.4 Interaction between variables

Two-way mixed ANOVA was used to compare the mean differences between groups that had been split into two factors (independent variables), where one factor was a within-subjects factor and the other a between-subjects factor. This analysis was generally used to assess the interaction between the changes in a variable over two or more time points (within-subjects factor) and a particular characteristic in the sample (between-subjects factor). Two-way mixed ANOVA was applied for continuous variables with an approximately normal distribution since this analysis is robust to non-normality. Levene's test was used to evaluate the assumption of homoscedasticity. The Mauchly test was used to evaluate the assumption of sphericity. If sphericity could not be assumed, the Greenhouse-Geisser correction was applied.

3.3.3.5 Correlation analysis

The strength and direction of the associations between two continuous variables were obtained by means of the Pearson or Spearman correlation coefficients. The linear association between two continuous variables normally distributed was evaluated using the Pearson test. The Spearman test was used as a non-parametric alternative.

3.3.3.6 Regression analysis

Simple linear regression models were constructed to predict a continuous variable (dependent variable) based on a continuous explanatory variable (independent variable). Multiple linear models were constructed when considering two or more predictors. Scatter plots were created to evaluate the relationship between variables and to check for homoscedasticity of residuals (plot of studentized residuals vs unstandardised predicted values). Independent variables with a linear relationship with the outcome variable were included in the model. Histograms and normal Q-Q plots of the studentized residuals were constructed to assess the normality of their distribution. The Durbin-Watson test was used to check the independence of errors. Multicollinearity was tested using variance inflation factors.

Binomial logistic regression models were constructed to predict the probability that an observation would fall into one of two categories of a nominal, dichotomous variable (dependent variable) based on one or more predictors (independent variables). Preliminary univariate logistic regression was used to identify potential predictive factors. Multivariate logistic regression for these factors was then performed, incorporating variables with a univariate association threshold of $p < 0.15$ (Wang et al., 2020). Multicollinearity was tested using variance inflation factors. Additionally, the linearity of independent variables and logit transformation of the dependent variable was checked.

Finally, bivariate generalised linear mixed models (GLMM) were constructed to predict the probability of an observation based on predictive variables with different distributions and which involved repeated measures, while including both fixed and random effects. Assumptions for general linear models were checked (linearity between predictive variables and response, homoscedasticity, normality of residuals and independence of errors).

4.

Dry eye-related risk factors for digital eye strain

4.1 Introduction

DES describes "a group of eye and vision-related problems that result from prolonged computer, tablet, e-reader and cell phone use" (American Optometric Association, 2023). Dry eye-related symptoms, including eye burning, irritation, ocular dryness, tearing, tired eyes, foreign body sensation, and eye discomfort belong to one of the main groups of DES symptomatology (Portello et al., 2012; Sheedy et al., 2003a). As addressed in the introduction chapter (*1.1 Digital eye strain and dry eye, 1. Introduction*; Talens-Estarelles et al., 2021), studies have reported a significant association between dry eye and computer use (Courtin et al., 2016; Sánchez-Valerio et al., 2020). Several other factors such as CL wear, environmental exposure, diet, or lifestyle factors such as smoking, alcohol consumption or caffeine intake have been shown to influence dry eye to different extents (Stapleton et al., 2017). Overall, DED and DES, despite describing distinct conditions, have relevant symptoms in common, and therefore, risk factors for one condition may be associated with the other.

The aim of this chapter was to explore the association between DES and several dry eye-related lifestyle and demographic factors, through an in-depth survey based on risk factor-related inquiries and several validated questionnaires in a large sample of university students, to increase the understanding of DES and its relationship with dry eye.

4.2 Methods

4.2.1 Participants

An anonymous online survey was carried out among university students. The invitation to the survey was sent to all undergraduate and postgraduate students of the Science Campus of the University of Valencia. This population group was chosen given their considerable exposure to digital screens and risk of DES. The survey was completed by a total of 903 respondents, out of which 851 were finally selected and analysed (317 males and 534 females).

The study followed the tenets of the Declaration of Helsinki, and a favourable opinion from the ethical committee of the University of Valencia was obtained. All the participants were informed about the nature of the study and gave their consent.

4.2.2 Procedure

The survey was created using the Google Forms platform and distributed to potential participants through a web link sent through the institutional e-mail of the University of Valencia. The survey was sent on the first week of June 2021 and was left open for 1 week. The survey had no time limit, although the time spent by the participants to answer all the questions in the survey was recorded, without the participants being aware.

4.2.3 Questionnaires and risk factors

The survey comprised a total of four validated questionnaires related to DES and DED: (1) CVS-Q, (2) OSDI, (3) DEQ-5, and (4) CLDEQ-8. Detailed information on the questionnaires can be found in Chapter 3 (*3.2.1 Symptomatology questionnaires, 3. General methods*). Both OSDI and DEQ-5 were included to assess a broader range of dry eye symptoms and provide a detailed study of the association between DES and dry eye. The CLDEQ-8 was included to assess the association between DES and having symptoms of dryness attributable to CL wear. Additionally, participants answered several questions about DED risk factors contemplated in the TFOS DEWS II epidemiology report (Stapleton et al., 2017), including questions about age, gender, ethnicity, smoking, alcohol consumption, caffeine intake, water intake, diet quality, hours of sleep, environmental exposures including outdoor activity and exposure to air conditioning, exercise, stress levels, diet, general health, pathologies, medication, ocular surgery, CL wear, and several questions about digital display use. Participants graded the quality of their diet as good (excellent or good quality) if the participants had a balanced intake of protein, carbohydrates, fruits, and vegetables or poor (poor or fair quality) if their diet was unbalanced, associated with the intake of ultra-processed foods, ready-to-eat products, and sugars. Additionally, after recent findings, questions regarding the use of face masks were also incorporated by being considered potential risk factors for DED (Aksoy & Simsek, 2021; Krolo et al., 2021).

Participants were instructed to read all questions carefully. The survey sequence was as follows: (1) demographic questions, (2) DED risk factors, (3) CVS-Q, (4) CLDEQ-8, (5) OSDI, and (6) DEQ-5.

4.2.4 Statistical analysis

First, the results from the survey were downloaded and transferred into Microsoft Excel spreadsheets (Microsoft, Redmond, WA, USA). Every individual answer to each of the questions posed in the survey was double-checked and illogical or irrational answers were excluded. To ensure the reliability of the data analysed, participants who answered the survey in less than 8 minutes (10th percentile of the response time distribution) were excluded from the analysis.

Statistical analysis was carried out using SPSS software v.26 (IBM Corp, Armonk, NY, USA). Participants were divided into two groups based on the score obtained in the CVS-Q: DES (CVSQ $\geq$ 6) or non-DES (CVS-Q < 6). The normality of data for each group was assessed using the Kolmogorov-Smirnov test. Significant differences between the DES and the non-DES group for each questionnaire score and every demographic and DED risk factor were assessed using an unpaired t-test, the Mann-Whitney U test or chi-square analysis, depending on the sample distribution and type of variable.

Preliminary univariate logistic regression was used to identify potential factors associated with the DES group. Multivariate logistic regression for these factors was then performed, incorporating variables with a univariate association threshold of $p \leq 0.15$. Please refer to Chapter 3 for more information on regression analysis (*3.3.3.6 Regression analysis, 3. General methods*). To properly perform logistic regression analysis, dichotomous variables exclusively related to a particular group of individuals (i.e., pelvic pain in female participants, oral contraceptive therapy, and hormone replacement therapy) were binary coded to 1 if the participant met the condition or to 0 if the participant did not meet the condition or did not apply to him. Likewise, CL-related variables were given a value of 0 if the participant was not a CL wearer.

The sample size was selected based on previous studies of similar nature (al Tawil et al., 2020; Cantó-Sancho et al., 2021; Sánchez-Brau et al., 2020; Zayed et al., 2021). Assuming a margin of error of 5% and "p" as the predicted prevalence of DES in the population, the sample size required for this study was estimated using the following formula: $n = p \times (1 - p) (1.96/0.05)^2$, resulting in a minimum sample of 294 participants.

4.3 Results

Nine hundred and three students completed the survey, of which 851 (307 males and 544 females), ranging in age from 17 to 51 years (22 ± 4 years) were finally included

for subsequent analysis. The mean response time to complete the survey was 16 ± 7 minutes.

From the total sample, 628 participants (73.9%) were classified into the group with DES (CVS-Q ≥ 6) and 222 (26.1%) into the group without DES (CVS-Q < 6); thus, the calculated prevalence of DES in the study sample was 73.9%. Table 4.1 shows the comparison between the DES and non-DES groups for each questionnaire and every dry eye demographic and lifestyle factor assessed. In comparison with non-DES participants, participants with DES slept fewer hours ($p = 0.03$), spent more hours indoors with air conditioning ($p = 0.002$), drank more caffeinated beverages ($p = 0.01$), used the computer for longer periods ($p = 0.005$), reported poorer health quality ($p = 0.001$), were more stressed ($p < 0.001$), and obtained a significantly higher score in CVS-Q, OSDI, DEQ-5, and CLDEQ-8 ($p < 0.001$). Moreover, the DES group had a significantly higher percentage of female participants ($p < 0.001$) and participants suffering from acne, anxiety, migraine headaches, vitamin deficiency, pelvic pain, and polycystic ovary syndrome ($p \leq 0.03$). Likewise, a higher percentage of participants with DES took oral contraceptive therapy ($p < 0.001$), antihistamines ($p = 0.01$), anxiolytics ($p = 0.02$), and antidepressants ($p = 0.04$).

Table 4.2 shows the results for the univariate and multivariate-adjusted logistic regression analyses, along with the odds ratios (ORs) of the DES group for each risk factor and questionnaire incorporated into the multivariate analysis. Female gender, using the computer or the tablet for more hours a day, drinking more caffeinated drinks per day, sleeping fewer hours, spending more hours outdoors, doing less exercise, wearing CLs, being more stressed, suffering from acne, allergies, depression, vitamin deficiency, migraine headaches, anxiety, pelvic pain, and polycystic ovary syndrome and taking oral contraceptive therapy, antihistamines, or anxiolytics, and obtaining a higher score in OSDI, DEQ-5, and CLDEQ-8, all exceeded the univariate association threshold ($p < 0.15$). Of these factors, the multivariate logistic regression revealed that the following were independently associated with DES: stress ($p = 0.04$, OR = 2.37), CL wear ($p = 0.01$, OR = 1.93), hours of computer use per day ($p = 0.01$, OR = 1.10), migraine headaches ($p = 0.01$, OR = 3.21), and a higher OSDI ($p < 0.001$, OR = 1.12) and DEQ-5 score ($p < 0.001$, OR = 1.32).

Table 4.1. Comparison between the DES and non-DES groups for each dry eye questionnaire and factor evaluated.

Characteristic	non-DES (CVS-Q < 6) (n = 222)	DES (CVS-Q ≥ 6) (n = 628)	p-value
Dry eye risk factors			
Demographics			
Age *(median; IQR [min, max])*	21; 19-22 [17, 46] years	21; 19-23 [17, 51] years	0.93[1]
Female sex *(N of participants; percentage)*	99; 44.6%	431; 68.6%	< 0.001*[2]
East Asian ethnicity *(N of participants; percentage)*	3; 1.4%	8; 1.3%	0.94[2]
Digital displays			
Hours of computer use per day *(median; IQR [min, max])*	6; 4-8 [0, 12] hours	6; 5-8 [0, 16] hours	0.005*[1]
Days of computer use per week *(median; IQR [min, max])*	7; 6-7 [0, 7] days	7; 6-7 [0, 7] days	0.92[1]
Hours of mobile phone use per day *(median; IQR [min, max])*	4; 3-5 [1, 14] hours	4; 3-5 [1, 14] hours	0.21[1]
Hours of tablet use per day *(median; IQR [min, max])*	0; 0-0 [0, 7] hours	0; 0-1 [0, 15] hours	0.14[1]
Hours watching television per day *(median; IQR [min, max])*	1; 0-2 [0, 6] hours	1; 0-1 [0, 14] hours	0.75[1]
N of devices used simultaneously *(median; IQR [min, max])*	3; 2-3 [1, 5] devices	3; 2-3 [1, 5] devices	0.20[1]
Lifestyle factors			
Smokers *(N of participants; percentage)*	21; 9.5%	76; 12.1%	0.27[2]
Days smoked per week *(median; IQR [min, max])*	0; 0-0 [0, 7] days	0; 0-0 [0, 7] days	0.49[1]
Cigarettes per day *(median; IQR [min, max])*	0; 0-0 [0, 20] cigarettes	0; 0-0 [0, 20] cigarettes	0.48[1]
Cigarettes per week *(median; IQR [min, max])*	0; 0-0 [0, 140] cigarettes	0; 0-0 [0, 140] cigarettes	0.52[1]
Alcohol consumers *(N of participants; percentage)*	133; 59.9%	375; 59.7%	0.97[2]
Units of alcohol per week *(median; IQR [min, max])*	1; 0-2 [0, 15] units	1; 0-3 [0, 20] units	0.37[1]
Not caffeine drinkers *(N of participants; percentage)*	88; 39.6%	191; 30.4%	0.01*[2]
Units of caffeinated drinks per day *(median; IQR [min, max])*	1; 0-1 [0, 7] units	1; 0-2 [0, 8] units	0.001*[1]
Litres of water per day *(median; IQR [min, max])*	2; 1-2 [0, 6] litres	2; 1-2 [0, 6] litres	0.57[1]
Hours of sleep per day *(median; IQR [min, max])*	7; 7-8 [5, 10] hours	7; 7-8 [1, 10] hours	0.03*[1]
Hours outdoors per day *(median; IQR [min, max])*	2; 1-3 [0, 8] hours	2; 1-2 [0, 11] hours	0.11[1]
Hours indoors with air conditioning per day *(median; IQR [min max])*	2; 0-6 [0, 22] hours	4; 1-6 [0, 22] hours	0.002*[1]
Hours of exercise per week *(median; IQR [min, max])*	3; 1-5 [0, 22] hours	3; 2-4 [0, 18] hours	0.33[1]
Poor diet quality *(N of participants; percentage)*	53; 23.9%	147; 23.4%	0.90[2]
High use of face mask *(N of participants; percentage)*	171; 77.0%	488; 77.7%	0.64[2]
Hours of face mask wear per day *(median; IQR [min, max])*	6; 4-7 [0, 13] hours	6; 4-8 [0, 19] hours	0.65[1]
Contact lenses			
Contact lens wear *(N of participants; percentage)*	50; 22.5%	178; 28.3%	0.08[2]
Soft contact lens wear *(N of participants; percentage)*	41; 18.5%	156; 24.8%	0.22[2]
Days of contact lens wear per week *(median; IQR [min, max])*	0; 0-0 [0, 7] days	0; 0-1 [0, 7] days	0.10[1]
Hours of contact lens wear per week *(median; IQR [min, max])*	0; 0-0 [0, 100] hours	0; 0-5 [0, 112] hours	0.06[1]
Health conditions			
Poor health quality *(N of participants; percentage)*	22; 9.9%	121; 19.3%	0.001*[2]
Stress *(N of participants; percentage)*	12; 5.4%	104; 16.6%	< 0.001*[2]
Refractive surgery *(N of participants; percentage)*	2; 0.9%	15; 2.4%	0.17[2]
Acne *(N of participants; percentage)*	21; 9.5%	122; 19.4%	0.001*[2]
Allergies *(N of participants; percentage)*	36; 16.2%	138; 21.9%	0.06[2]
Anxiety *(N of participants; percentage)*	19; 8.6%	144; 22.9%	< 0.001*[2]
Migraine headaches *(N of participants; percentage)*	10; 4.5%	102; 16.2%	< 0.001*[2]
Eczema *(N of participants; percentage)*	9; 4.1%	42; 6.7%	0.15[2]
Asthma *(N of participants; percentage)*	10; 4.5%	43; 6.8%	0.21[2]
Psoriasis *(N of participants; percentage)*	3; 1.4%	9; 1.4%	0.92[2]
Depression *(N of participants; percentage)*	5; 2.3%	32; 5.1%	0.07[2]
Vitamin deficiency *(N of participants; percentage)*	2; 0.9%	30; 4.8%	0.009*[2]
Rosacea *(N of participants; percentage)*	2; 0.9%	9; 1.4%	0.54[2]
Pelvic pain in females *(N of participants; percentage)*	2; 0.9%	31; 4.9%	0.007*[2]

Polycystic ovary syndrome *(N of participants; percentage)*	4; 1.8%	33; 5.3%	0.03*[2]
Diabetes *(N of participants; percentage)*	2; 0.9%	5; 0.8%	0.89[2]
Fertility problems *(N of participants; percentage)*	2; 0.9%	5; 0.8%	0.89[2]
Thyroid disease *(N of participants; percentage)*	5; 2.3%	15; 2.4%	0.90[2]
Irritable bowel syndrome *(N of participants; percentage)*	3; 1.4%	15; 2.4%	0.35[2]
Sclerosis *(N of participants; percentage)*	1; 0.5%	6; 1%	0.47[2]
Liver disease *(N of participants; percentage)*	1; 0.5%	2; 0.3%	0.78[2]
Medication			
Oral contraceptive therapy *(N of participants; percentage)*	14; 6.3%	104; 16.6%	< 0.001*[2]
Antihistamines *(N of participants; percentage)*	14; 6.3%	78; 12.4%	0.01*[2]
Anxiolytics *(N of participants; percentage)*	2; 0.9%	26; 4.1%	0.02*[2]
Antidepressants *(N of participants; percentage)*	0; 0%	12; 1.9%	0.04*[2]
Hormone replacement therapy *(N of participants; percentage)*	5; 2.3%	11; 1.8%	0.65[2]
Anti-inflammatories *(N of participants; percentage)*	2; 0.9%	11; 1.8%	0.37[2]
Analgesics *(N of participants; percentage)*	1; 0.5%	2; 0.3%	0.78[2]
Dry eye questionnaires			
CVS-Q *(median; IQR [min, max])*	4; 2-5 [0, 5]	10; 8-13 [6, 32]	< 0.001*[1]
OSDI *(median; IQR [min, max])*	4.2; 2.1-8.3 [0.0, 70.8]	15.9; 10.4-25.0 [0.0, 90.0]	< 0.001*[1]
DEQ-5 *(median; IQR [min, max])*	4; 2-6 [0, 18]	10; 6-13 [0, 23]	< 0.001*[1]
CLDEQ-8 *(mean ± SD [min, max])*	11 ± 6 [1, 26]	16 ± 7 [1, 34]	< 0.001*[3]

CLDEQ-8 = 8-item Contact Lens Dry Eye Questionnaire; CVS-Q = Computer Vision Syndrome Questionnaire; DEQ-5 = 5-item Dry Eye Questionnaire; IQR = Interquartile range; OSDI = Ocular Surface Disease Index; N = Number. * Indicates statistically significant values ($p < 0.05$). [1] Mann-Whitney U test. [2] chi-square test. [3] Unpaired T-test.

Table 4.2. Univariate and multivariate logistic regressions analysis and odds ratios of the DES group.

Characteristic	Unadjusted univariate logistic regression		Multivariate-adjusted logistic regression	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Dry eye risk factors				
Demographics				
Female sex	2.95 (2.14–4.08)	< 0.001*	-	-
Digital displays				
Hours of computer use per day	1.08 (1.02–1.15)	0.008*	1.10 (1.06–1.13)	0.01*
Hours of tablet use per day	1.10 (0.98–1.24)	0.10		
Lifestyle factors				
Not caffeine drinkers	0.66 (0.47–0.91)	0.01*	-	-
Units of caffeinated drinks per day	1.22 (1.05–1.41)	0.008*	-	-
Hours of sleep per day	0.86 (0.73–1.02)	0.08	-	-
Hours outdoors per day	0.92 (0.83–1.01)	0.08	-	-
Hours of exercise per week	0.94 (0.89–0.99)	0.01*	-	-
Contact lenses				
Contact lens wear	1.38 (0.96–1.98)	0.08	1.93 (1.16–3.21)	0.01*
Health conditions				
Poor health quality	2.21 (1.36–3.59)	0.001*	-	-
Stress	3.52 (1.89–6.54)	< 0.001*	2.37 (1.06–5.29)	0.04*
Acne	2.34 (1.43–3.83)	0.001*	-	-
Allergies	1.47 (0.98–2.21)	0.06	-	-
Depression	2.35 (0.90–6.11)	0.08	-	-
Vitamin deficiency	5.56 (1.32–23.48)	0.02*	-	-
Migraine headaches	4.17 (2.13–8.14)	< 0.001*	3.21 (1.27–8.10)	0.01*
Anxiety	3.23 (1.95–5.37)	< 0.001*	-	-
Pelvic pain in females	5.76 (1.37–24.27)	0.02*	-	-
Polycystic ovary syndrome	3.05 (1.07–8.70)	0.04*	-	-
Medication				
Oral contraceptive therapy	2.99 (1.67–5.34)	< 0.001*	-	-
Antihistamines	2.13 (1.18–3.85)	0.01*	-	-
Anxiolytics	4.79 (1.13–20.34)	0.03*	-	-
Dry eye questionnaires				
OSDI	1.20 (1.17–1.24)	< 0.001*	1.12 (1.08–1.16)	< 0.001*
DEQ-5	1.46 (1.37–1.55)	< 0.001*	1.32 (1.23–1.42)	< 0.001*
CLDEQ-8	1.13 (1.07–1.19)	< 0.001*	-	-

CI = Confidence interval; CLDEQ-8 = 8-item Contact Lens Dry Eye Questionnaire; DEQ-5 = 5-item Dry Eye Questionnaire; OR = Odds ratio; OSDI = Ocular Surface Disease Index. * Indicates statistically significant values ($p < 0.05$).

4.4 Discussion

According to the results of the present study, individuals with DES had several health disorders associated with dry eye and took more medication suspected to promote dryness. Most importantly, conditions such as the use of CLs, migraine, or stress revealed a strong association with DES.

Individuals obtaining a CVS-Q score ≥ 6 are considered as suffering from DES (Seguí et al., 2015). In the present study, the calculated prevalence of this disorder was

73.9%. Other studies have reported a prevalence between 82.4% and 33.2%, the latter in the general population (Cantó-Sancho et al., 2021; Ganne et al., 2021; Sánchez-Brau et al., 2020; Sheppard & Wolffsohn, 2018; Zayed et al., 2021). Discrepancies are probably due to the range of methodologies that have been applied to identify sufferers and the different population groups analysed. For instance, Cantó-Sancho et al. (2021) obtained a prevalence of 76.6% in Spanish university students using the CVS-Q questionnaire, which is considerably in line with the results of the present study.

Moreover, according to the present survey, participants with DES used the computer for more hours a day than participants without DES. Not only this but using the computer for more hours was independently associated with DES. As addressed in the introduction chapter (*1. Introduction*; Talens-Estarelles et al., 2021), the hazardous effects of computer use on the ocular surface and DES are widely acknowledged. Therefore, these findings are not unanticipated. Similarly, the hours of tablet use per day were also spotted as a potential risk factor for DES. Nevertheless, no independent association was found with obtaining a positive CVS-Q score. These results are likely to have occurred because of the interaction of other variables included in the multivariate model. Additionally, computer use is suspected to cause a greater impact on dry eye signs and symptoms than handheld devices, mainly because of higher viewing angles compared with handheld screens that are usually viewed in downgaze (Pansell et al., 2007; Sánchez-Valerio et al., 2020). This could explain the dominance of computer use as an independent risk factor for DES over other displays.

Female gender is widely accepted as a risk factor for the development of DED (Stapleton et al., 2017). In the present study, the DES group had significantly more female participants. Likewise, female gender was identified as a potential risk factor for DES in the univariate analysis, with female participants being almost three times more likely to have DES than males, although failed to reach statistical significance as an independent factor. Previous studies of similar nature have reported a significant association between female sex and DES (Portello et al., 2012; Ranasinghe et al., 2016). Consequently, special attention should be paid to female display users.

As addressed in detail in the introduction chapter (*1.5.3 Environmental conditions, 1. Introduction*; Talens-Estarelles et al., 2021), environmental factors, low humidity or direct airflow exposure, typical of office-like environments, have been shown to promote dryness and are suspected to play a relevant role in DES (Ranasinghe et al., 2016; Zayed et al., 2021). In parallel, previous research has reported an association between lower

levels of physical activity and sedentary behaviour and dry eye (Kawashima et al., 2014). According to the univariate regression analysis carried out in the present study, low physical activity and spending less time outdoors may act as risk factors for DES, although an independent association with DES was not observed. Finally, caffeine consumption has been shown to act as a protective factor against ocular dryness by stimulating tear secretion (Osei et al., 2014). In the present study, caffeine intake was identified as a potential, yet not independent, predictor of DES, probably because of the association of caffeine consumption with other surveyed factors.

CL wear is recognized as one of the main factors leading to dry eye (Stapleton et al., 2017), with data suggesting a prevalence of DED up to 4 times higher in CL users (Paulsen et al., 2014). In the present study, CL wear was independently associated with having DES, with CL users being almost twice more likely of suffering from DES than non-wearers. Similarly, Tauste et al. (2016) found that workers who wore CLs and used a computer for more than 6 hours per day were more likely to suffer from DES than non-CL wearers who worked on a computer for the same amount of time. Conversely, Meyer et al. (2021) recently found that soft CL wearers did not experience symptoms of DES at a higher frequency or severity than non-CL wearers.

Also, the group with DES had a greater proportion of participants who suffered from several affective disorders related to dry eye. The multivariate-adjusted logistic regression analysis revealed that stress and migraine headaches were independently associated with having DES. Whether these disorders precede or arise as a consequence of DES is difficult to determine, although these circumstances are not mutually exclusive. Stress has been associated with dry eye and could act as a trigger in some cases (Ahn et al., 2014; Asiedu et al., 2018; Hyon et al., 2019; Na et al., 2015); thus, the same may be generalized to DES. However, migraine headaches have been suggested to share etiopathogenic neuropathic mechanisms with DED (Ahn et al., 2014). Conversely, internal symptoms of DES are related to refractive, accommodative or vergence anomalies and generally include strain, eye ache, and headaches behind the eyes (Portello et al., 2012; Sheedy et al., 2003a). Accordingly, migraine headaches may confound the findings of DES in individuals who suffer from this disorder.

Finally, having greater symptoms of dry eye (OSDI and DEQ-5) or greater CL-related dry eye symptoms (CLDEQ-8) were potential predictors of DES. This is in accordance with the aforementioned associations between digital display use or CL wear with dry eye and DES.

The present study had some limitations to consider. First, risk factors were self-reported by volunteers, which might have induced recall bias. Nevertheless, this can be considered an inherent limitation of any survey-based study. In addition, the study was carried out at the same university, which may have introduced selection bias. Finally, recruitment by means of advertisement might have resulted in a higher prevalence of individuals with dry eye symptoms and DES than expected in the population. Nevertheless, this prevalence was similar to that reported in an analogous sample of university students (Cantó-Sancho et al., 2021).

In conclusion, individuals with DES had a significantly higher prevalence of dry eye-related lifestyle risk factors and health conditions than those without DES. Participants with DES reported poorer health quality, more stress, allergies, vitamin deficiency, and anxiety, among others. They also took more medication, such as antihistamines, anxiolytics antidepressants, and oral contraceptives, proven to promote dryness. Moreover, using the computer for longer periods, CL wear, and suffering from stress and migraine were independently associated with having DES. Similarly, having greater dry eye symptoms increased the odds of DES.

Considering the strong association between DES and dry eye, special attention should be paid to screen users with dry eye. Likewise, clinicians should acknowledge the relevance of triaging questions, systemic comorbidities, and DED risk factors when dealing with individuals who use digital displays for extended periods. Future work in developing case-control studies to explore the identified commonalities in DES and DED individuals is needed.

5.

Blinking kinematics characterization during digital displays use

5.1 Introduction

As elucidated in the introduction chapter (*1.2.1 Blinking abnormalities, 1. Introduction*; Talens-Estarelles et al., 2021), blinking abnormalities make up one of the main DES-inducing mechanisms (Chu et al., 2010, 2014; Portello et al., 2013). A reduced blink rate and a reduced blink amplitude have both been reported during computer use (Cardona et al., 2011; Chu et al., 2010, 2014; Freudenthaler et al., 2003; Himebaugh et al., 2009; Patel et al., 1991; Portello et al., 2013; Tsubota & Nakamori, 1993). Given that appropriate blinking is crucial for maintaining ocular surface integrity and tear film stability (Cruz et al., 2011), it is not surprising that computer use has been listed as a consistent risk factor for DED (Stapleton et al., 2017).

Nowadays, new forms of digital displays other than desktop computers, such as laptops, tablets, smartphones, or e-readers have emerged. Up to 75% of individuals claim to use handheld devices to access the internet daily (Eurostat, 2022). Despite this, when it comes to handheld devices, research is still limited, and results are conflicting. Conditions such as viewing distance, angle of gaze and screen size have all been shown to influence blink frequency to different extents (Argilés et al., 2015; Nielsen et al., 2008). Therefore, one may expect that the differences in the nature of the displays and the ways that they are set up and used may contribute to differences in their impact on blinking and symptoms.

Blinks occur after a complex and coordinated interaction of different skeletal muscles acting antagonistically, with each stage depending on different muscle actions and interactions (Evinger et al., 1991). As previously seen, blinking during digital display use has traditionally been described in terms of the blink rate and number of incomplete blinks, this description being, by itself, scant for fully characterizing the process of blinking. Recently, high-speed video cameras, implemented with image processing algorithms, have been used to precisely and non-invasively gather and analyse blink kinematic variables in natural viewing conditions, allowing a full and in-depth description of the process of blinking (Kimura et al., 2017; Kwon et al., 2013; Sanchis-Jurado et al., 2020).

The aim of this chapter was to analyse and compare in detail the kinematic characteristics of blinking while reading on a laptop computer, tablet, e-reader, and smartphone under natural viewing conditions, and after a control measure, using for the purpose a newly developed technique for the non-invasive characterization of blinking.

5.2 Methods

5.2.1 Participants

Thirty-two young, healthy volunteers, ranging in age from 20 to 26 years, participated in this study. Inclusion criteria were CDVA better or equal to 20/20 (0.00 logMAR) in both eyes, normal binocularity, and normal colour vision. Exclusion criteria were prior ocular history of injury, anterior or posterior segment pathology, eye surgery, current use of topical medications, and CL wear. Additionally, participants were instructed not to use artificial tears within 2 hours before the visit. Likewise, participants had no known neurological disorders or took any medications that could affect blinking. To comply with the inclusion/exclusion criteria, participants with DED were excluded following the guidelines of the TFOS DEWS II diagnostic approach (Wolffsohn et al., 2017).

The study followed the tenets of the Declaration of Helsinki and was approved by the University of Valencia human research ethics committee. All the participants were informed about the nature of the study and gave their written consent.

5.2.2 Experimental design

Blinking was assessed during a reading task with a laptop computer, a tablet, an e-reader, and a smartphone and a non-device control condition. For the control condition, the participants were instructed to direct their gaze to a Maltese cross, arranged at eye level and placed 3 m in front of them. For the digital display tasks, the participants were instructed to read the text displayed on the screen of the devices.

The text presented on all 4 displays was matched in font style (Georgia font with black letters on white background), angular size (appropriately chosen for each device for a 0.15 logMAR visual acuity), angular line spacing, number of words per line and page, page angular width (appropriately chosen for each device for a 25° width), and text alignment (left-justified). Screen luminance was equalised by adjusting the brightness level in settings. Regarding the e-reader, this device is designed to simulate printed paper by reflecting rather than emitting light from behind the screen.

Moreover, digital displays were positioned based on a typical viewing distance and angle of usage: that is, 60-cm distance and approximately 10° below eye level for the laptop computer; 45 cm and 25° for the tablet and the e-reader; 30 cm and 45° for the

smartphone (Bababekova et al., 2011; Wu, 2011). Additionally, the 4 screens were set at an inclination angle of 100° from the plane of the desk. An adjustable stand was used to arrange the handheld devices accordingly.

The participants carried out the tasks with their heads fixed on a chin and forehead rest. To ensure participants' comfort and correct alignment with the display screen, the height of the chin rest could be adjusted, as well as that of the chair. The whole experiment was carried out under constant artificial illumination. Room illuminance was maintained at approximately 220 lux on the plane of the participant's eyes and was provided by indirect lighting to avoid any glare sources. Chroma Meter CL-200 lux meter (Konica Minolta; Ramsey, NJ, USA) was used to measure photometric values. Room temperature and humidity were monitored and remained stable at 23.8 ± 1.6°C and 44 ± 5%, respectively.

5.2.3 Apparatus

During task performance, the participants' eye movements were recorded with the HSVE (Cambridge Research Systems Ltd, Rochester, UK), without the participants being aware. Please refer to Chapter 3 for detailed information on this device (*3.2.10 High-Speed Visual Eye-Tracker, 3. General methods*).

Text material was a book with a recompilation of Allan Poe's full stories. The text was displayed using Kindle (2021) reading application (app) (Amazon Inc., Seattle, WA, USA). Text characteristics were matched for all displays and selected from the Kindle app interface. An optical microscope focused on the screens of the devices was used to select text size and line spacing after the trigonometric calculation based on the linear size.

Digital displays included a MacBook Pro laptop computer (Apple Inc., Cupertino, CA, USA) with a 13-inch screen, a resolution of 227 ppi, a refresh rate of 60 Hz, and a contrast ratio of 1350:1; a third-generation iPad tablet (Apple Inc.) with a 9.7-inch screen, 264 ppi, 60-Hz refresh rate, and 1000:1 contrast ratio; a third-generation Kindle Paperwhite e-reader (Amazon Inc.) based on electronic ink (e-ink) technology, with a 6-inch screen, 330 ppi, and 15:1 contrast ratio (backlight mode turned off); and an iPhone 6 smartphone (Apple Inc.) with a 4.7-inch screen, 326 ppi, 60-Hz refresh rate, and 1000:1 contrast ratio. Digital displays with similar screen characteristics were considered, except for the e-reader, based on e-ink technology, which seeks to simulate printed paper.

5.2.4 Protocol

All the measurements were taken in the same laboratory. Each condition was tested in separate sessions and with a rest period of 7 days between sessions. Participants completed each of the 5 experimental conditions in the following order: (1) control, (2) computer, (3) tablet, (4) e-reader, and (5) smartphone. The approximate duration of each session was 35 minutes. To minimize day-to-day variability, each session was carried out on the same day of the week, at the same time of the day (first thing in the morning, at 9 am), and under constant environmental conditions (temperature and humidity). Additionally, the participants were asked not to use other digital displays before the session and not to drink any beverage containing caffeine 24 hours before the measurements.

Fifteen minutes before the entry of the participants, the laboratory was acclimatized, and the experimental conditions were set up. Once the participant arrived, he/she received instructions on the session's task. In the case of reading on a digital display, the participant was given a few minutes to choose between one of the stories from the book and was taught how to handle the device for the reading. To minimize the effects of outdoor conditions on the way to the laboratory, a 15-minute acclimatization period was allowed between entry into the room and the start of the task. Then, the participants were seated comfortably and instructed to rest on the HSVET chinrest and carry out the respective task for 15 minutes, until the examiner told them to stop. Sufficient material was provided for 15 minutes of reading without repetition.

During the last 150 s of the task (minutes 12.5-15), the participant's eye movements were recorded with the HSVET. The right eye of all the participants was recorded. The participants were not actively told that their eyeblinks were being recorded. Each measurement generated a sequence of 37,500 images of the participants' right eye that were stored onto an external hard drive and subsequently studied by means of image analysis, to obtain a non-invasive, detailed description of the eye blink movement. The image processing-based method used for the automatic analysis of blinking has been previously described in the literature (Sanchis-Jurado et al., 2020). Blinks were evaluated in terms of kinematic variables including blink rate, number of complete and incomplete blinks, percentage of incomplete blinks, blink amplitude, opening and closing blink speeds, and closing, contact, opening and total blink durations. A complete blink was

defined as that in which the position of the superior eyelid reached the median height level of the inferior eyelid.

5.2.5 Statistical analysis

The results were evaluated using SPSS software v.26 (IBM Corp., Armonk, NY, USA). The normality of data was assessed using the Shapiro-Wilk test. When normality could be assumed, a repeated-measures ANOVA was used to examine the statistical significance of the blink kinematic variables for the 5 task conditions. More information on repeated-measures ANOVA can be found in Chapter 3 (*3.3.3.3 Differences between three or more repeated measurements, 3. General methods*). The nonparametric Friedman test for repeated measures with the Dunn-Bonferroni post-hoc analysis was used when parametric test assumptions were not fulfilled.

5.3 Results

Thirty-six Caucasian volunteers were initially recruited out of which 32 (12 males and 20 females) ranging in age from 20 to 26 years (23 ± 2 years) met the inclusion/exclusion criteria and completed all visits.

Table 5.1 shows the intra-average mean values and 95% confidence intervals of the blinking kinematic variables and characteristics assessed in this study during the control measurement and during the reading task with each device. The table additionally presents the statistical results of the comparison of all 5 examination conditions.

Figure 5.1 illustrates boxplots of the blink rate (a), number of complete blinks (b), number of incomplete blinks (c), and percentage of incomplete blinks (d) obtained in the control condition and during the reading task with each device. Post-hoc comparisons revealed statistically significant differences in all variables between conditions ($p < 0.001$). The blink rate was significantly lower when reading on all displays compared to the control condition ($p < 0.001$), although no differences were obtained between devices ($p > 0.05$). The number of complete blinks performed was significantly lower when reading on all devices, except the smartphone, compared to the control task ($p < 0.001$). Likewise, the number of complete blinks was significantly higher when reading on the smartphone compared to the rest of the displays ($p \leq 0.04$). Additionally, the number of incomplete blinks was significantly lower when reading on the smartphone in comparison to the rest of the devices ($p \leq 0.04$ for all) and the control task ($p < 0.001$) and was also

lower when using the e-reader compared to the control condition ($p = 0.006$). Finally, the percentage of incomplete blinks was significantly lower when reading on the smartphone compared to the other 3 displays ($p \leq 0.02$) and the control condition ($p = 0.004$), while significantly more incomplete blinks were performed when reading on the computer compared to the control condition ($p = 0.04$) or when using the e-reader ($p = 0.03$).

Furthermore, Figure 5.2 illustrates boxplots of the duration of each of the phases of blinking for the 5 examination conditions. As evidenced, no differences in the closing or opening durations were obtained between conditions ($p > 0.05$). Conversely, blinks had a significantly lower contact time when reading on the computer compared to the control measurement ($p = 0.004$) and reading on the smartphone ($p = 0.001$) and were significantly shorter than during the control task ($p = 0.02$).

Finally, Figure 5.3 illustrates boxplots of the blinking amplitude (a) and the blinking closing (b) and opening (c) speeds. Blinks had a significantly smaller amplitude while reading on the smartphone compared to the other devices and the control measurement ($p \leq 0.001$). On the contrary, blinks had a greater amplitude when reading on the computer compared to the tablet and the e-reader ($p \leq 0.05$) and when looking straight ahead during the control condition compared to the digital display reading tasks ($p \leq 0.003$). Furthermore, blinks were significantly slower during the closing phase of blinking when using the smartphone in comparison to the rest of the conditions ($p \leq 0.04$), while they were faster during the control and the computer conditions compared to the tablet ($p < 0.001$ and $p = 0.007$, respectively) and the e-reader ($p < 0.001$ and $p = 0.02$, respectively). Lastly, the opening speed of blinking was significantly lower when reading on the smartphone compared to all other digital displays ($p \leq 0.03$) and the control condition ($p < 0.001$).

Table 5.1. Blinking kinematic variables obtained during the control task and during the reading task with each device and statistical results of the comparisons. Data are presented as intra-average mean [95% confidence intervals].

Variable	Control (CT)	Computer (C)	Tablet (T)	E-reader (Er)	Smartphone (S)	p-value	Statistically significant post-hoc differences (p-value)
Blink Rate (*Total Number of Blinks*) (blinks/min)	20 (*51*) [16 – 25]	10 (*25*) [7 – 13]	10 (*26*) [7 – 13]	10 (*24*) [7 – 12]	11 (*28*) [9 – 14]	< 0.001*	CT – C (< 0.001) CT – Er (< 0.001) CT – T (< 0.001) CT – S (< 0.001)
Number of Complete Blinks	34 [23 – 44]	12 [6 – 16]	15 [10 – 20]	15 [11 – 20]	26 [19 – 32]	< 0.001*	CT – C (< 0.001) CT – T (< 0.001) CT – Er (< 0.001) C – S (< 0.001) T – S (0.03) Er – S (0.04)
Number of Incomplete Blinks	17 [12 – 23]	13 [8 – 18]	11 [7 – 14]	9 [6 – 12]	2 [1 – 3]	< 0.001*	CT – Er (0.006) CT – S (< 0.001) C – S (< 0.001) T – S (< 0.001) Er – S (0.04)

Percentage of Incomplete Blinks (%)	38 [28 – 48]	56 [45 – 67]	43 [34 – 52]	37 [27 – 48]	10 [4 – 15]	< 0.001*	CT – C (0.04) CT – S (0.004) C – S (< 0.001) C – Er (0.03) T – S (< 0.001) Er – S (0.02)
Amplitude (mm)	5.4 [4.8 – 6.0]	4.3 [4.0 – 4.7]	3.8 [3.5 – 4.1]	3.8 [3.5 – 4.2]	3.1 [2.7 – 3.4]	< 0.001*	CT – C (0.003) CT – T (< 0.001) CT – Er (< 0.001) CT – S (< 0.001) C – T (0.001) C – Er (0.04) C – S (< 0.001) T – S (0.001) Er – S (< 0.001)
Closing Duration (ms)	41.6 [37.0 – 46.2]	38.9 [35.8 – 41.9]	42.1 [40.0 – 44.1]	43.0 [39.7 – 46.3]	40.4 [38.3 – 42.4]	0.26	—
Contact Duration (ms)	73.0 [59.3 – 86.6]	44.7 [39.3 – 50.2]	54.5 [46.4 – 62.5]	59.4 [49.8 – 69.0]	70.9 [58.4 – 83.3]	0.001*	CT – C (0.004) C – S (0.001)
Opening Duration (ms)	185.0 [156.7 – 213.3]	158.8 [133.5 – 184.1]	161.4 [134.8 – 188.0]	159.9 [135.8 – 184.1]	166.9 [147.0 – 186.8]	0.15	—

Total Duration (ms)	299.7 [261.2 – 338.1]	242.1 [214.7 – 269.5]	255.6 [226.9 – 284.3]	257.6 [232.0 – 283.3]	278.8 [255.0 – 302.6]	0.009*	CT – C (0.02)
Closing Speed (mm/s)	139.2 [125.2 – 153.2]	118.6 [106.0 – 131.1]	96.0 [86.6 – 105.3]	95.7 [85.5 – 106.0]	76.4 [70.0 – 82.8]	< 0.001*	CT – S (< 0.001) CT – T (< 0.001) CT – Er (< 0.001) C – S (< 0.001) C – T (0.007) C – Er (0.02) T – S (0.04) Er – S (0.02)
Opening Speed (mm/s)	39.8 [30.9 – 48.6]	37.5 [30.6 – 44.4]	30.7 [26.4 – 35.0]	30.6 [25.4 – 35.9]	21.5 [19.0 – 24.0]	< 0.001*	CT – S (< 0.001) C – S (< 0.001) T – S (0.01) Er – S (0.03)

* Indicates statistically significant values ($p < 0.05$).

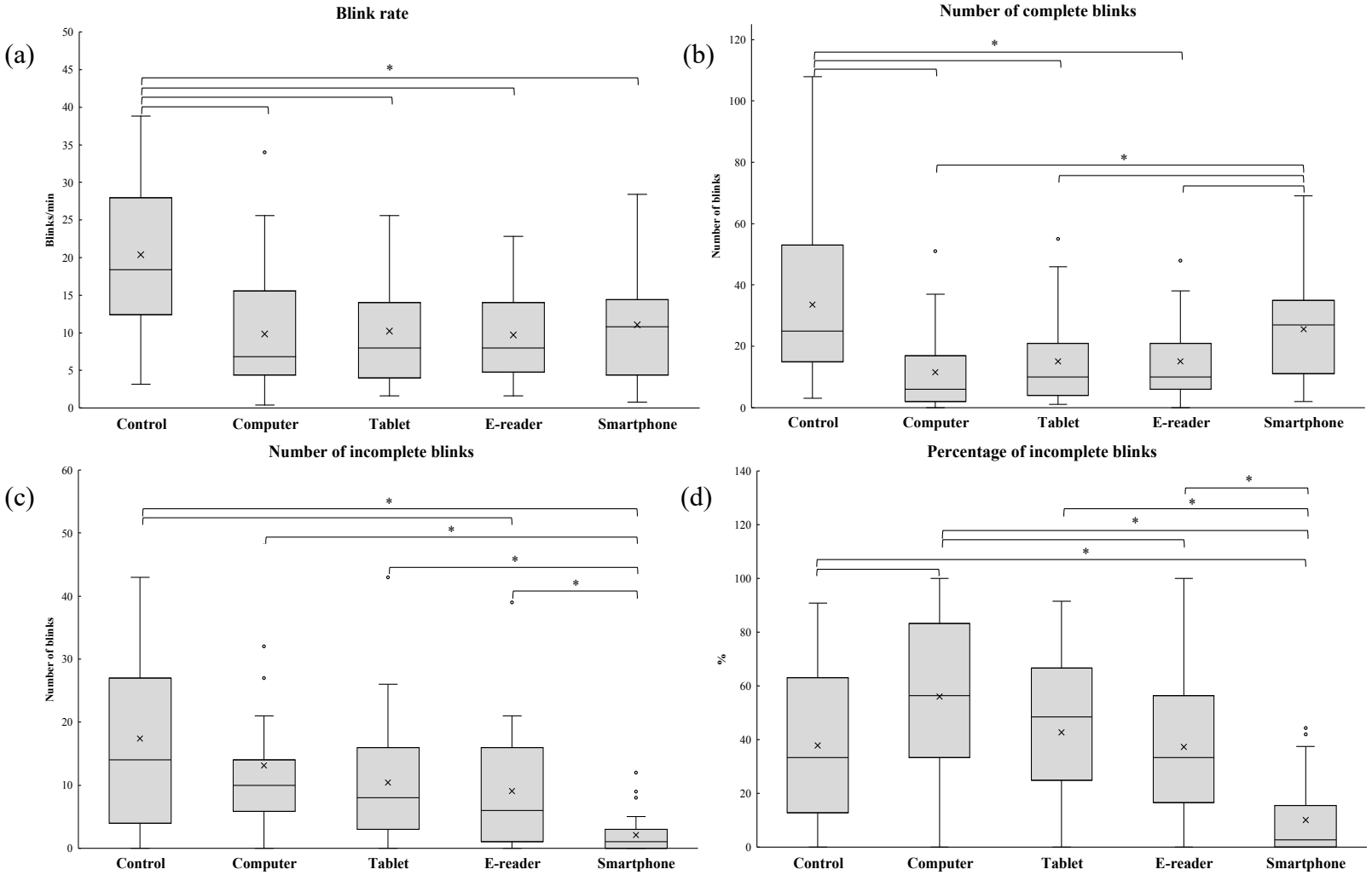


Figure 5.1. Boxplots of (a) blink rate, (b) number of complete blinks, (c) number of incomplete blinks and (d) percentage of incomplete blinks obtained during the control task and during the reading task with each device. * Indicates statistical significance ($p < 0.05$).

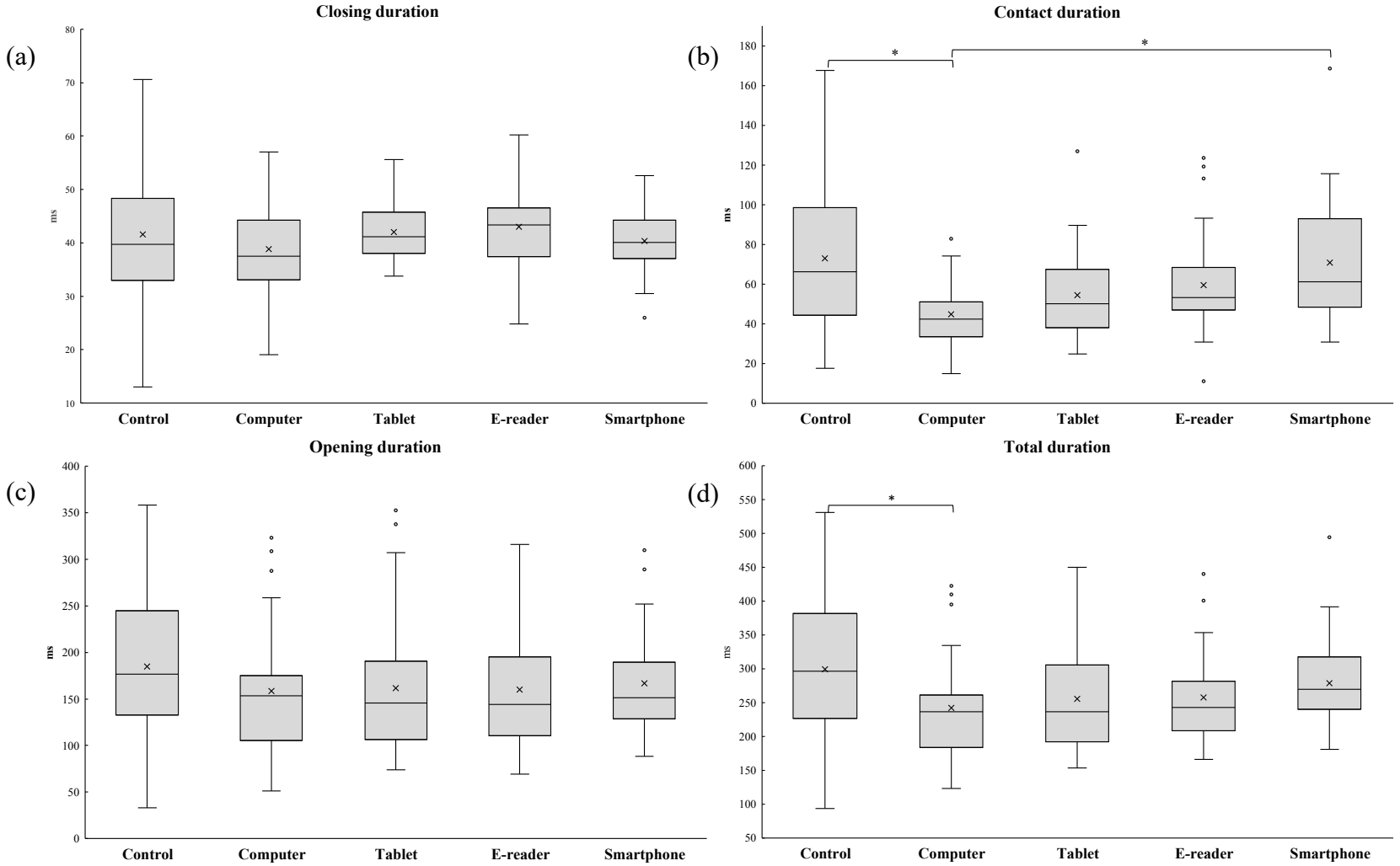


Figure 5.2. Boxplots of the duration of each of the phases of blinking obtained during the control task and during the reading task with each device. (a) closing duration, (b) contact duration, (c) opening duration and (d) total duration. * Indicates statistical significance ($p < 0.05$).

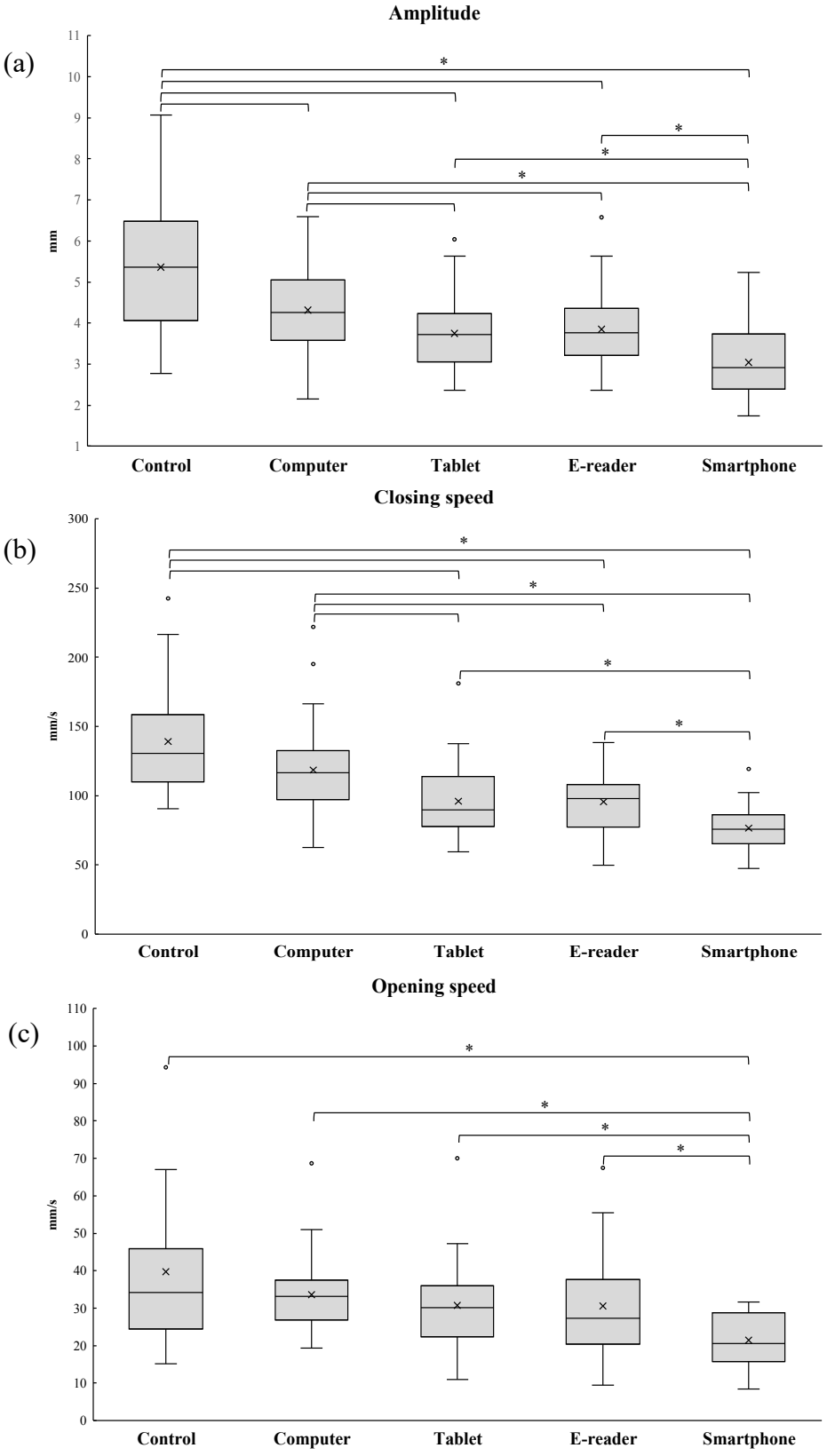


Figure 5.3. Boxplots of (a) the blinking amplitude and (b) the closing and (c) opening speeds obtained during the control task and during the reading task with each device. * Indicates statistical significance ($p < 0.05$).

5.4 Discussion

As highlighted on several occasions, the impact of digital display use on blinking is widely acknowledged and is globally accepted as the main mechanism leading to digital display-induced dry eye (Cardona et al., 2011; Chu et al., 2010, 2014; Freudenthaler et al., 2003; Himebaugh et al., 2009; Patel et al., 1991; Portello et al., 2013; Tsubota & Nakamori, 1993). The process of blinking is key for preserving ocular surface and tear film homeostasis, by maintaining adequate levels of humidity and hydration, promoting the expression of tear lipids and spreading them through the precorneal film, and helping in the drainage of tears, among other functions (Doane, 1981; Holly, 1980; Korb et al., 1994). Blinking is a complex process, composed of different stages, each of which involves different muscle interactions (Evinger et al., 1991). Nevertheless, despite the complexity and relevance of blinking, no study to date has addressed the influence of digital display use on blinking kinematics, with most studies focused merely on the blink rate or number of incomplete blinks. Likewise, the appearance of handheld devices such as tablets, smartphones, or e-readers, which differ in many aspects of their pattern of use and characteristics, makes differences between them probable.

In the present study, the total number of blinks during the recording period (i.e., blink rate), was reduced by 45-55% when reading on all displays. As expected, this decrease in blink frequency was linked to a decrease in both the number of complete and incomplete blinks. This is in line with previous research and with the acknowledged mechanism behind ocular surface desiccation associated with computer use (Freudenthaler et al., 2003; Patel et al., 1991; Schlote et al., 2004; Tsubota & Nakamori, 1993b; Wong, 2002). Nevertheless, when it comes to handheld devices, research is still limited.

Smaller screens lead to a lower amplitude of saccades and consequently no requirement of combined blinking, which has been suggested to reduce blink rate further (Argilés et al., 2015; Choi et al., 2018). Nevertheless, in the present study, the text displayed on all devices was matched in many parameters, including page angular width and number of words per line and lines per page; thus, both the number of saccades and their amplitude remained constant when reading on all displays. Likewise, a correlation between gaze angle and blink frequency during computer use has been proposed. Nielsen et al. (2008) found that lowering the position of the monitor decreased the blink rate significantly. This decrease is suspected to be a direct consequence of the reduction in

exposed ocular surface area. In the present study, handheld devices were associated with lower areas of exposure related with closer distances compared with the control condition and the computer: 154 ± 32 mm^2 for the control, 140 ± 37 mm^2 for the computer, 120 ± 29 mm^2 for the tablet, 118 ± 42 mm^2 for the e-reader, and 80 ± 31 mm^2 for the smartphone. However, blink rate did not differ between displays.

As previously mentioned, the e-reader is based on e-ink technology which simulates printed paper. Considering both modes of presentation (e-reader and printed paper) to be equivalent, the blink rate was probably governed by the cognitive demand of the task rather than the form of presentation. Therefore, the marked reduction in blink rate when using the displays was probably due to the higher cognitive demand of the reading task compared to the lower cognitive demand of the control task (Cardona et al., 2011; Portello et al., 2013). After comparing the blink rate of 25 individuals who performed a 20-minute reading task on either a desktop computer screen or a printed hard copy page with matched characteristics, Chu et al. (2014) concluded that "previously observed differences in blink rate were more likely to be produced by changes in cognitive demand rather than the method of presentation". Later, Rosenfield et al. (2015) confirmed this hypothesis and pointed to incomplete blinking as the current cause behind the dry eye symptoms experienced by users with modern digital displays.

As for incomplete blinking, more than half of the blinks performed during computer use were incomplete, and this number was on average considerably higher compared to the control task (56% vs 38%, respectively). Conversely, the number of incomplete blinks was greater during the control task than during computer and e-reader use, although this was probably a direct consequence of the lower blink rate obtained while reading. This is in line with previous research and explains the evoked dry eye signs and symptoms during computer use (Chu et al., 2010, 2014; Portello et al., 2013; Rosenfield et al., 2015). Harrison et al. (2008) pointed out that incomplete blinks may occur to not interrupt concentration, which links to the suggestion that incomplete blinks may be the result of unsuccessful inhibition of a spontaneous blink during visually demanding tasks (McMonnies, 2007).

Interestingly, both the proportion and the number of incomplete blinks gradually decreased as the displays were positioned closer and at lower gaze angles, reaching statistical significance when using the smartphone, in comparison to the other devices and the control task. To the authors' knowledge, no study to date has directly addressed the relationship between gaze angle or distance and incomplete blinking. A simple

explanation for the decrease in incomplete blinking when looking down may be that with smaller palpebral fissures the distance the upper eyelid must travel is shorter, increasing the chances of contact with the lower eyelid margin. Contrary to our results, Golebiowski et al. (2020) found an increase in incomplete blinks with the duration of smartphone use. Similarly, Argilés et al. (2015) obtained a greater percentage of incomplete blinks while reading on a tablet (14.5%) compared to printed text (5%). Nevertheless, the lack of studies involving handheld devices, along with the differences in experimental conditions and settings, makes comparisons challenging. Based on our findings and considering the effects of ocular surface exposure, the computer may have the greatest impact on the ocular surface and the tear film, while the smartphone may partially prevent ocular surface dryness.

No studies to date have examined the impact of gaze angle on blink amplitude with digital devices, including computers. In the present study, blink amplitude was greatest during the control task (looking at a fixation target at eye level) and decreased significantly as the angle of use of the screens decreased, probably due to the close relationship between gaze angle and palpebral fissure. Despite the difference in blink amplitude, closing and opening blink durations remained unchanged between conditions and therefore, closing and opening speeds were progressively slower (slower when reading on the smartphone and faster when reading on the computer or during the control task). The relationship between the amplitude of a blink and its maximum speed is considered to be linear (Evinger et al., 1991; Garcia et al., 2010; Sanchis-Jurado et al., 2020). This characteristic of blinking is known as the main sequence and indicates that as the amplitude increases so does maximum speed, which means that the greater the distance that a blink covers the faster it is (Bahill et al., 1975; Cruz et al., 2011).

In addition to this, contact duration was slower while reading on the computer than during the control task or when reading on the smartphone, which resulted in a shorter total blink duration compared to the control task. This shorter contact duration was probably due to a significantly higher percentage of incomplete blinks during computer use. A blackout in the visual input to the brain occurs each time we blink. However, this periodic decrement in retinal luminance is not perceived due to blink suppression, in which neural activity involved in visual perception is actively reduced during blinking (Volkmann et al., 1980). This suppression occurs not only during blinking but also 50 to 100 ms and 100 to 150 ms before and after a blink, respectively, with the total time lost being dependent on the duration of the blink (Volkmann et al., 1980).

Considering the greater amplitude of blinks with higher palpebral fissures, along with the high cognitive demand of the reading task, a higher proportion of incomplete blinks may have been unconsciously performed during computer reading in an attempt to minimize the duration of the contact phase of blinking and the associated blackout in the visual input.

Finally, the present study had some limitations to consider. Given the high temporal resolution of the image recording device, the duration of blink recording was limited by data volume and chosen as a compromise between sampling time and volume of information. Also, the results had some limitations attributable to the image processing technique used, which have already been described in detail elsewhere (Sanchis-Jurado et al., 2020). Finally, given the lack of studies assessing blinking kinematics during screen use, some of the results could not be contrasted with the literature and, therefore, further studies are required to confirm these findings.

In conclusion, the blink rate was significantly reduced when reading on all displays compared to a non-device, low-demanding control task, probably as a consequence of the higher cognitive demand of reading, while no differences between digital displays were observed. Incomplete blinking increased as displays were placed further and at higher gaze angles, and were greater when reading on the computer, possibly due to an additive effect between larger palpebral fissures and a higher cognitive demand. Blink amplitude was directly related to gaze angle, and it was lower for devices with lower visualization angles. Furthermore, closing and opening blink durations did not vary between the devices, while opening and closing speeds were higher during computer use and the control task and decreased progressively with gaze angle and distance, and were found to be lowest when using the smartphone. Finally, total blink duration was shorter during computer use compared to the control, probably due to a shorter contact duration associated with a higher percentage of incomplete blinks.

This study highlights the relevance of fully characterizing the process of blinking during digital display use and establishes the basis for future works in this field. Additionally, it underlines the utility of image processing-based methods using high-speed video cameras to precisely and non-invasively analyse blinking kinematics during digital display use.

6.

How do different digital displays affect the ocular surface?

6.1 Introduction

Nowadays, numerous new kinds of digital displays have been developed, and the use of digital electronic screens is no longer restricted to desktop computers. These may include a wide range of displays such as laptops, smartphones, tablets, or e-readers, each used at different distances and gaze angles and with different screen and text characteristics.

As highlighted in previous chapters (Chapters 4 and 5), dry eye-related complaints associated with digital display use may be related to the nature of the displays and the way that these are set up and used. For instance, a common source of explanation for the increased dry eye symptoms in computer users is the greater corneal exposure associated with a higher gaze angle compared with conventional reading tasks, which proportionally increases tear evaporation (Coles-Brennan et al., 2019; Pansell et al., 2007; Rosenfield, 2011; Talens-Estarelles et al., 2021; Thomson, 1998). Additionally, conditions such as viewing distance, angle of gaze, and screen size have been suspected to influence blinking to different extents (Argilés et al., 2015; Nielsen et al., 2008). Indeed, in Chapter 5 (*5. Blinking kinematics characterization during digital displays use*; Talens-Estarelles et al., 2022a), it was found that, although blink rate was comparably reduced when reading on a computer, tablet, e-reader and smartphone, incomplete blinking and blinking kinematics varied significantly with the form of presentation. Based on these results, it was hypothesised that the computer may have the greatest impact on the ocular surface of all displays, although research in specifically designed studies is required.

Accordingly, the aim of this chapter was to compare the impact of four common digital displays (computer, tablet, e-reader and smartphone) on the ocular surface and tear film of young individuals.

6.2 Methods

6.2.1 Participants

Thirty-one young, healthy volunteers, ranging in age from 20 to 26 years, participated in this study. Given the young age of the sample, the participants in this study were especially familiarized with the use of digital displays. All the participants had CDVA better or equal to 20/20 (0.00 logMAR) in both eyes, normal binocularity, and normal colour vision. The participants had no ocular history of injury, anterior or posterior

segment pathology, surgery, or current use of topical medications and were not CL wearers, nor did they use artificial tear substitutes. To comply with the inclusion/exclusion criteria, participants with DED were excluded following the guidelines of the TFOS DEWS II diagnostic approach (Wolffsohn et al., 2017).

The study followed the tenets of the Declaration of Helsinki and was approved by the University of Valencia human research ethics committee. All the participants were informed about the nature of the study and gave their written consent.

6.2.2 Experimental design

The study methodology was similar to that of Chapter 5 (*5. Blinking kinematics characterization during digital displays use*; Talens-Estarelles et al., 2022a) and of previous studies of a similar nature (Cardona et al., 2011).

The ocular surface and tear film were evaluated after executing a reading task with four different digital displays (laptop computer, tablet, e-reader, and smartphone; details of the devices used are given later) and a control condition, under two different measurement conditions: with and without initial instillation of artificial tears. Nine different experimental configurations were consequently tested (control + four digital displays with and without instillation of artificial tears). For the control condition, the participants were instructed to direct their gaze to a Maltese cross, arranged at eye level and placed 3 m in front of them. For the digital display tasks, the participants were instructed to read the text displayed on the screen of the devices.

Text characteristics were set as equal on the different digital devices in terms of font style (Georgia font with black letters on a white background), angular size (appropriately chosen for each device for a 0.15 logMAR visual acuity), number of words per line and page, page angular width (appropriately chosen for each device for a 25° width), and text alignment (left justified). Screen luminance was equalised by modifying the display brightness level in settings. With respect to the e-reader, this device is designed to simulate printed paper by reflecting rather than emitting light from behind the screen.

Furthermore, each digital display was positioned based on a typical viewing distance and angle of usage: that is, 60-cm distance and approximately 10° below eye level for the laptop computer, 45 cm and 25° for the tablet and the e-reader, and 30 cm and 45° for the smartphone. Additionally, the 4 screens were set at an inclination angle of 100° from the plane of the desk. An adjustable stand was used to arrange the handheld devices accordingly.

To ensure the repeatability of the measurement conditions, the participants carried out the tasks with their heads fixed on a chin and forehead rest. To ensure their comfort and correct alignment with the display screen, the height of the chin rest could be adjusted, as well as that of the chair. The whole experiment was carried out under constant artificial illumination. Room illuminance was maintained at approximately 220 lux on the plane of the participant's eyes and was provided by indirect lighting to avoid any glare sources. Chroma Meter CL-200 lux meter (Konica Minolta, Ramsey, NJ, USA) was used to measure photometric values. Room temperature and humidity were constantly monitored and remained stable at 23.5 ± 2.0°C and 45 ± 5%, respectively.

6.2.3 Apparatus

Text material was a book with a recompilation of Allan Poe's full stories. The text was displayed using Kindle (2019) reading app (Amazon Inc., Seattle, WA, USA). Text characteristics were selected from the Kindle app interface and matched for all displays, as previously described. An optical microscope focused on the screens of the devices was used to select text size and line spacing after the trigonometric calculation based on the linear size.

Digital displays included a MacBook Pro laptop computer (Apple Inc., Cupertino, CA, USA) with a 13-inch screen, a resolution of 227 ppi, a refresh rate of 60 Hz, and a contrast ratio of 1350:1; a third-generation iPad tablet (Apple Inc.) with a 9.7-inch screen, 264 ppi, 60-Hz refresh rate, and 1000:1 contrast ratio; a third-generation Kindle Paperwhite e-reader (Amazon Inc.) based on electronic ink technology, with a 6-inch screen, 330 ppi, and 15:1 contrast ratio; and an iPhone 4 smartphone (Apple Inc.) with a 3.5-inch screen, 326 ppi, 60-Hz refresh rate, and 1000:1 contrast ratio. Digital displays with similar screen characteristics were considered, with the exception of the e-reader, based on e-ink technology, which seeks to simulate printed paper.

After task performance, the participants' ocular surface and tear film were evaluated. Tear film and ocular surface variables, including TMH, conjunctival redness, and NIKBUT, were assessed using the Keratograph 5M (Oculus Optikgerate, Wetzlar, Germany). In addition, tear film osmolarity was measured using TearLab Osmolarity System (TearLab Corp., San Diego, CA, USA), and tear volume was assessed with Schirmer I test strips (Bio-Tech Vision Care Pvt. Ltd., Gujarat, India). Moreover, dry eye symptoms and DES symptoms were evaluated using the OSDI and CVS-Q, respectively.

Please refer to Chapter 3 for detailed information on these devices and measurement procedures (*3.2 Measurements and devices, 3. General methods*).

6.2.4 Protocol

All the measurements were taken in the same laboratory. Participants completed, one by one, each of the nine experimental conditions in the following order: (1) control, (2) computer, (3) computer after artificial tear instillation, (4) tablet, (5) tablet after artificial tear instillation, (6) e-reader, (7) e-reader after artificial tear instillation, (8) smartphone, and (9) smartphone after artificial tear instillation. Each condition was tested in separate sessions and with a rest period of 7 days between sessions. The approximate duration of each session was 45 minutes. To minimize day-to-day variability of the tear film, each session was carried out on the same day of the week, at the same time of the day (first thing in the morning, at 9 am, after the same number of hours awake), and under the same, constant environmental conditions (temperature and humidity). Additionally, the participants were asked not to use other digital displays before the session and not to drink any beverage containing caffeine 24 hours before the measurements.

Fifteen minutes before the entry of the participants, the laboratory was acclimatized, and the experimental conditions were set up. Once the participant arrived, he/she received instructions on the task. In the case of reading on a digital display, the participant was given a few minutes to choose between one of the stories from the book and was taught how to handle the device for the reading. To minimize the effects of outdoor conditions on the way to the laboratory, a 15-minute acclimatization period was allowed between entry into the room and the start of the task. When required, one drop of Aquamax (Tiedra SL, Alcorcon, Madrid, Spain) single-dose artificial tears were instilled in each eye, 2 minutes before the reading. Then, the participants were seated comfortably and instructed to rest on the chinrest and carry out the respective task for 15 minutes until the examiner told them to stop. Sufficient material was provided for a 15-minute reading session without repetition.

After the 15-minute reading task, the participants underwent a battery of standard clinical tests of ocular surface evaluation. Measurements were performed in the following order: TMH, conjunctival redness, osmolarity, NIKBUT, Schirmer I test, OSDI, and CVS-Q. NIKBUT was measured three times, and an average value was obtained. The measurements were performed on the right eye for all the participants and within 3

minutes after the reading or control task. All the measurements were taken by the same experienced examiner.

6.2.5 Statistical analysis

The results were evaluated using SPSS software v.26 (IBM Corp., Armonk, NY, USA). The normality of data was assessed by using the Shapiro-Wilk test. When normality could be assumed, a repeated-measures ANOVA was used to examine the statistical significance of the ocular surface and tear film results for the nine task conditions. More information about repeated-measures ANOVA can be found in Chapter 3 (*3.3.3.3 Differences between three or more repeated measurements, 3. General methods*). The non-parametric Friedman test for repeated measurements with Dunn-Bonferroni post-hoc analysis was used when parametric test assumptions were not fulfilled.

6.3 Results

Thirty-nine Caucasian volunteers were initially recruited, out of which 31 (6 males and 25 females), ranging in age from 20 to 26 years (21 ± 2 years), met the inclusion/exclusion criteria and completed all visits. A small survey concerning the participants' daily display use revealed that 100% of participants had two or more devices in possession and that 60% had three or more. The display that the participants reported using most was the smartphone (5 ± 2 hours/day), followed by the computer (3 ± 2 hours/day) and the tablet (1 ± 1 hours/day). Other devices such as e-readers and television, represented 1 ±1 hours of daily use. In total, the survey showed that the participants spent an average of 9 ± 4 hours per day in front of digital screens.

Table 6.1 shows the ocular surface and visual fatigue variables obtained after the control condition and the digital displays reading tasks. The table additionally displays the statistical results of the comparison of all nine examination conditions.

Figure 6.1 illustrates bar chart plots of the symptom scores obtained following the different study conditions. Significantly greater OSDI and CVS-Q scores were obtained after reading on the computer compared to reading on the e-reader ($p \leq 0.005$) or the smartphone ($p \leq 0.03$). Similarly, a significantly higher CVS-Q score was obtained following tablet use compared to e-reader use ($p = 0.01$). In addition, reading on the computer led to a higher CVS-Q score compared to the control task ($p = 0.006$), while no

differences between the control condition and the devices were observed ($p \geq 0.05$). Finally, OSDI and CVS-Q scores obtained after reading on the e-reader or smartphone with artificial tears were significantly lower than those obtained after tablet or computer use without artificial tear instillation ($p \leq 0.02$).

Figure 6.2 illustrates bar chart plots of the tear film variables obtained after the control condition and the reading tasks with the devices. As shown, a significantly lower TMH was observed after reading on the computer compared to reading on the e-reader ($p = 0.02$) or the smartphone ($p = 0.01$). On the contrary, no significant differences between the devices were found in Schirmer I scores ($p \geq 0.05$). Furthermore, no differences in tear film osmolarity were observed between the conditions ($p \geq 0.05$), except for a higher value following computer use compared to the smartphone ($p < 0.001$). Lastly, NIKBUT was significantly shorter after computer use compared to the control ($p = 0.03$).

Regarding the instillation of artificial tears, TMH was significantly higher after reading on the handheld devices with prior instillation of artificial tears compared to reading on the computer without tear instillation ($p \leq 0.04$). Similarly, a higher TMH was found after computer, tablet and e-reader use compared to the control condition when artificial tears were instilled ($p \leq 0.01$). No other differences were observed.

Finally, Figure 6.3 illustrates the bar chart plot of the conjunctival redness results. As shown, no differences in conjunctival redness were observed between the conditions ($p \geq 0.05$), except for greater redness following computer use compared to smartphone use ($p = 0.007$).

Table 6.1. Ocular surface, tear film and visual fatigue variables obtained after the control and the different digital displays tasks, with (Artificial tear) and without (Normal) initial instillation of artificial tears and statistical results of the comparisons. Data are presented as mean [95% confidence intervals].

Variable		Control (CT)	Computer (C)	Tablet (T)	E-reader (Er)	Smartphone (S)	p-value	Statistically significant post-hoc differences (p-value)
OSDI	Normal (N)	5.8 [3.8 – 7.8]	11.3 [6.9 – 15.6]	6.4 [3.4 – 9.4]	4.5 [1.3 – 7.6]	5.2 [1.8 – 8.5]	< 0.001*	Er-N / C-N (0.005) Er-AT / C-N (0.002) S-N / C-N (0.008) S-AT / C-N (< 0.001)
	Artificial Tear (AT)		6.5 [3.9 – 9.1]	4.9 [2.9 – 6.9]	3.4 [1.4 – 5.3]	4.5 [0.8 – 8.2]		
CVS-Q	Normal (N)	2 [2 – 3]	5 [4 – 6]	3 [2 – 4]	2 [1 – 2]	3 [2 – 4]	< 0.001*	CT / C-N (0.006) T-AT /C-N (< 0.001) Er-N / C-N (< 0.001) Er-N / T-N (0.01) Er-AT / C-N (< 0.001) Er-AT / T-N (0.003) S-N / C-N (0.03) S-AT / C-N (< 0.001) S-AT / T-N (0.01)
	Artificial Tear (AT)		3 [2 – 4]	2 [1 – 3]	2 [1 – 2]	2 [1 – 3]		
TMH (mm)	Normal (N)	0.27 [0.24 – 0.29]	0.26 [0.22 – 0.30]	0.30 [0.27 – 0.34]	0.31 [0.27 – 0.35]	0.30 [0.27 – 0.34]	< 0.001*	C-AT / CT (0.008) C-AT / C-N (< 0.001) T-AT / CT (0.01) T-AT / C-N (< 0.001)

	Artificial Tear (AT)		0.35 [0.28 – 0.42]	0.33 [0.28 – 0.37]	0.33 [0.29 – 0.38]	0.33 [0.27 – 0.39]		Er-N / C-N (0.02) Er-AT / CT (0.01) Er-AT / C-N (< 0.001) S-N / C-N (0.01) S-AT / C-N (0.04)
Schirmer I (mm)	Normal (N)	47 [27 – 66]	28 [15 – 41]	37 [19 – 54]	37 [19 – 55]	40 [21 – 59]	0.03*	CT / C-N (0.02)
	Artificial Tear (AT)		34 [21 – 48]	40 [22 – 58]	39 [22 – 55]	33 [18 – 49]		
NIKBUT (s)	Normal (N)	15.0 [12.8 – 17.2]	11.5 [9.3 – 13.7]	14.0 [11.6 – 14.4]	12.6 [10.1 – 15.1]	12.6 [10.2 – 15.0]	0.01*	CT / C-N (0.03)
	Artificial Tear (AT)		13.3 [11.0 – 15.6]	12.6 [10.2 – 15.0]	13.9 [11.4 – 16.4]	12.0 [9.9 – 14.2]		
Osmolarity (mOsm/L)	Normal (N)	292 [289 – 295]	294 [291 – 296]	291 [289 – 294]	292 [289 – 294]	289 [287 – 290]	< 0.001*	S-N / C-N (< 0.001) S-AT / C-N (< 0.001)
	Artificial Tear (AT)		290 [288 – 292]	292 [290 – 294]	290 [288 – 292]	289 [287 – 291]		
Conjunctival redness	Normal (N)	0.8 [0.7 – 0.9]	0.8 [0.6 – 0.9]	0.7 [0.6 – 0.8]	0.7 [0.6 – 0.8]	0.6 [0.5 – 0.7]	0.002*	S-N / C-N (0.007)
	Artificial Tear (AT)		0.7 [0.6 – 0.8]	0.7 [0.6 – 0.7]	0.7 [0.6 – 0.8]	0.7 [0.6 – 0.7]		

CVS-Q = Computer Vision Syndrome Questionnaire; NIKBUT = Non-invasive keratograph break-up time; OSDI = Ocular Surface Disease Index; TMH = Tear meniscus height. * Indicates statistically significant values ($p < 0.05$).

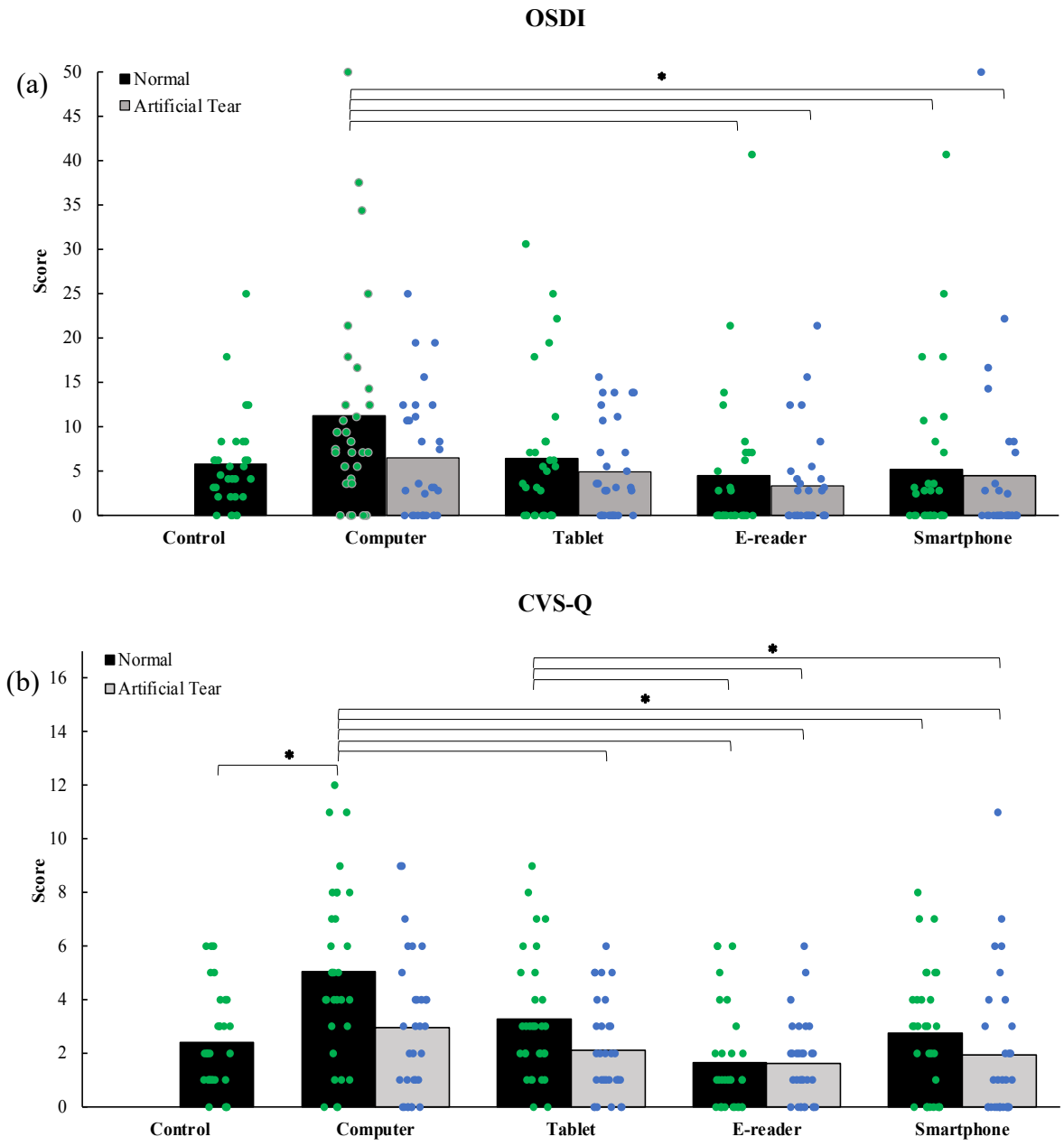


Figure 6.1. Bar chart plots of (a) Ocular Surface Disease Index (OSDI) and (b) Computer Vision Syndrome Questionnaire (CVS-Q) scores obtained after reading on different digital displays or the control condition with (Artificial tear) and without (Normal) initial instillation of artificial tears. * Indicates statistical significance ($p < 0.05$).

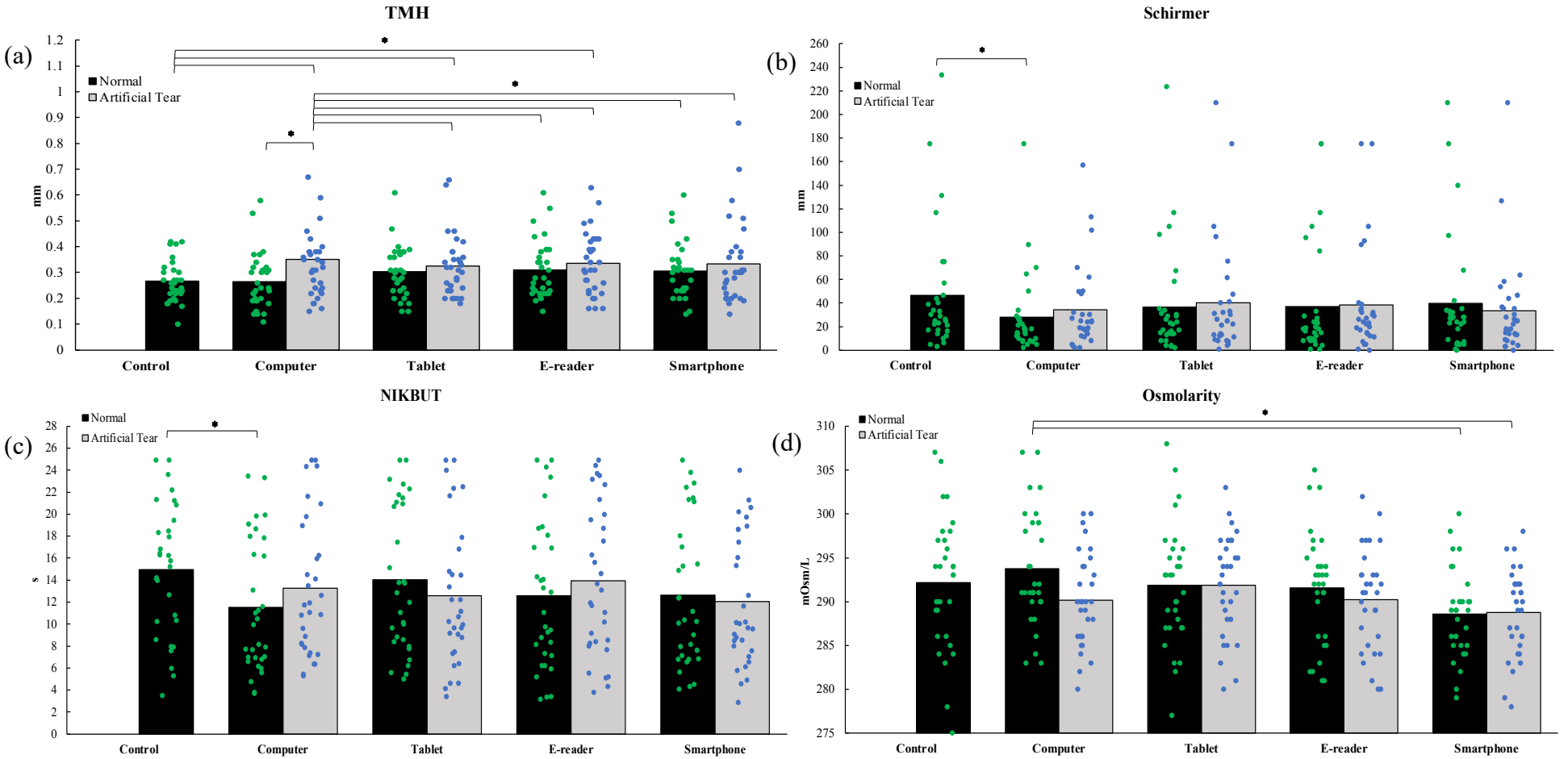


Figure 6.2. Bar chart plots of (a) tear meniscus height (TMH), (b) Schirmer I test, (c) non-invasive keratograph break-up time (NIKBUT) and (d) osmolarity obtained after reading on different digital displays or the control condition with (Artificial tear) and without (Normal) initial instillation of artificial tears. * Indicates statistical significance ($p < 0.05$).

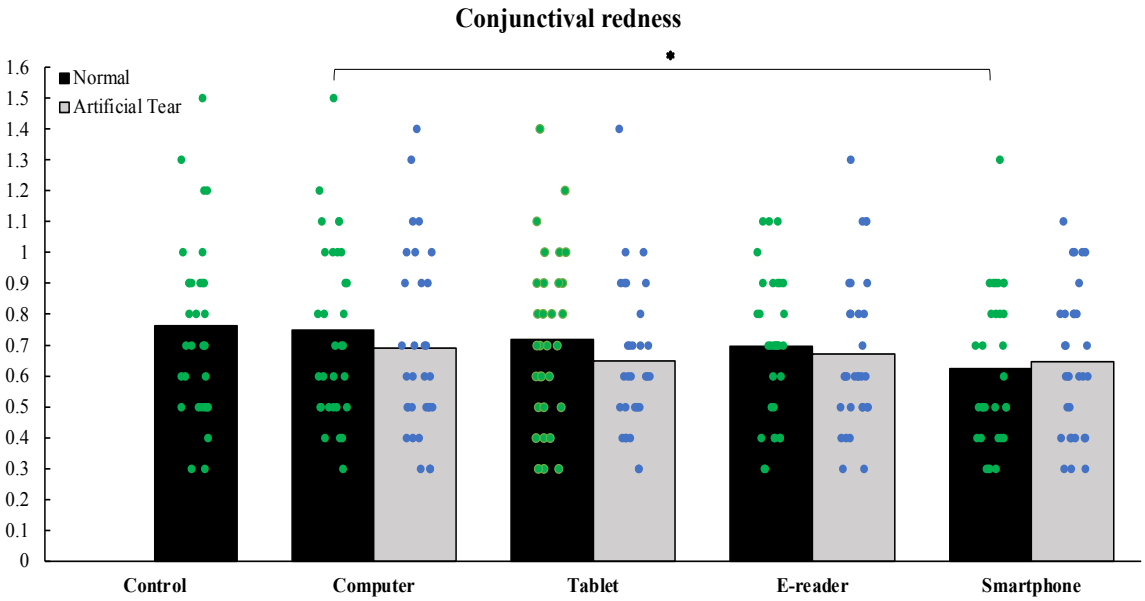


Figure 6.3. Bar chart plot of conjunctival redness obtained after reading on different digital displays or the control condition with (Artificial tear) and without (Normal) initial instillation of artificial tears. * Indicates statistical significance ($p < 0.05$).

6.4 Discussion

Hazardous effects of computer use on the ocular surface are widely acknowledged and have been known for decades. Despite this, most studies that have investigated the effects of computer use on the ocular surface are mainly questionnaire-based or describe the impact on a few ocular surface parameters. Handheld devices, such as tablets, smartphones, or e-readers, differ from conventional computers and from each other in terms of position, size, text characteristics and pattern of use. It is therefore likely that there may be key differences in their effects on the ocular surface and tear film.

Results revealed a significant increase in dry eye symptoms (OSDI) and DES (CVS-Q) after reading for 15 minutes on the computer compared with the control measurement. This is in accordance with the accepted theory of DES, recognized as a health problem for more than 30 years (Dain et al., 1988). Symptoms reported after reading on the computer were significantly greater compared to those reported after e-reader or smartphone use. Greater gaze angles result in a wider palpebral fissure and an increased ocular surface area being exposed to the effects of tear film evaporation (Pansell et al., 2007; Tsubota, 1995). In the present study, handheld devices were positioned at closer distances compared to the computer (45/30 vs. 60 cm), leading to lower gaze angles and a lower exposed ocular surface area: 150 ± 34 mm^2 for the control, 136 ± 39 mm^2 for

the computer, 118 ± 31 mm^2 for the tablet, 116 ± 42 mm^2 for the e-reader, and 80 ± 33 mm^2 for the smartphone.

Choi et al. (2018) compared the effects of smartphone and computer use on ocular symptoms after 1 and 4 hours of display use. Contrary to our results, the authors found higher symptoms after the use of the smartphone compared to the computer. These results were attributed to a possible lower blink rate with smartphone use, which, given the smaller screen size, required shorter amplitude saccades and no need for combined blinking (Choi et al., 2018). Nonetheless, in the present study, text characteristics were matched in terms of text angular size, page angular width and number of words per line and page, leading to the same amplitude of saccades with all devices, which may explain results discrepancies.

The use of lubricating eye drops has been shown to relieve (although not eliminate) symptoms during prolonged computer use (Acosta et al., 1999). The significantly lower CVS-Q score obtained following smartphone use with artificial tears compared to the normal tablet condition could be due to the combination of a lower gaze angle and the protection offered by the artificial tears. Analogously, this may explain the significantly lower symptoms (CVS-Q) reported after reading on the tablet with artificial tears compared to the computer.

Lastly, lower symptoms were reported after e-reader use compared to tablet use. This is in accordance with the results obtained by Benedetto et al. (2013) who found that reading on an LCD caused greater eyestrain compared to reading on an e-ink device. As opposed to other displays, the e-reader reflects rather than emits light from behind the screen, similar to print paper. Consequently, the physical properties of the text displayed on the e-reader, comparable to printed text, may explain the lower symptoms and greater comfort obtained with this device compared to the tablet, despite the same workstation design.

Tear volume, described in terms of TMH, was significantly lower after reading on the computer compared to e-reader or the smartphone, although no differences were found with the control condition. Golebiowski et al. (2020) found no changes in TMH after reading on a smartphone for one hour. Similarly, Maducdoc et al. (2017) found no differences after 1-hour tablet use. Conversely, reduced tear volume has been reported following computer use (Nakamura et al., 2010; Yazici et al., 2015). Nakamura et al. (2010) and Yazici et al. (2015) found decreased Schirmer test scores in computer users

compared with non-users. Likewise, Cardona et al. (2011) observed a reduced TMH after playing a computer game for 20 minutes compared to looking at a distant object.

Overall, the results of the present study could be associated with alterations of the blinking pattern following digital display use, which could have led to a greater evaporative loss of tears and reduced tear volume. On the contrary, the reduced ocular surface exposure associated with handheld devices may have counteracted blinking abnormalities and reduced tear film loss. The present study supports the hypothesis raised in Chapter 5 (*5. Blinking kinematics characterization during digital displays use*; Talens-Estarelles et al., 2022a), and confirms that, given matched text and display characteristics, the angle of gaze probably determines the effects of digital display use on the ocular surface and tear film.

Sodium hyaluronate tears, such as the ones used in the present study, have been shown to have a prolonged resident time and to significantly increase tear film volume (Carracedo et al., 2019). This may explain the significantly higher TMH observed after computer use when artificial tears were instilled compared to when they were not instilled or after the control condition. Similarly, the participants exhibited greater tear film volume (TMH) after reading on all handheld devices with artificial tears compared to reading on the computer without tear substitutes. The instillation of artificial tears, together with the favourable workstation design of handheld devices, probably explain the differences between study conditions.

Tear film stability (NIKBUT) was significantly reduced after reading for 15 minutes on the computer compared to the control condition, although no significant differences were observed with the rest of the devices. A reduced TBUT following computer use has been reported, even after as little as 30 and 20 minutes of playing a computer game (Cardona et al., 2011; Hirota et al., 2013). although no differences were observed after 15 minutes (Hirota et al., 2013). Based on the results of the present study, the effects of computer use on tear film stability may not become noticeable until approximately 15 minutes of use, although more research is needed to confirm these findings. Regarding handheld devices, Golebiowski et al. (2020) did not find any difference in TBUT after reading on a smartphone for 60 minutes. As in the case of tear volume, the lower gaze angle associated with handheld devices may delay changes in tear stability.

Furthermore, significantly higher tear film osmolarity was observed following computer use compared to smartphone use. To the authors' knowledge, this is the first

time that tear film osmolarity is assessed after the use of handheld devices. Published literature reported an increase in tear osmolarity after computer use (Yazici et al., 2015). Nevertheless, in the present study, tear film osmolarity after reading on the computer was not different from that observed after the non-device control task. Likewise, greater conjunctival redness was found after the use of the computer compared to the smartphone. This is in line with the greater signs and symptoms of dry eye observed in the present study after reading for 15 minutes on the computer compared to the smartphone.

The present study had some limitations to consider. Due to the subjective evaluation of symptoms, a nocebo/placebo effect on the results cannot be ruled out. Moreover, a 15-minute task duration was chosen, which may not be representative of modern durations of device usage. This may have led to lesser signs and symptoms of dryness than expected after longer periods of display use. Nevertheless, task duration was chosen based on previous research and to prevent fatigue effects and ensure the correct compliance of the participants with the task. Finally, although methodological choices were made to minimize the day-to-day variability of the tear film, it could have partially influenced the results of the study.

In conclusion, the results of this investigation indicate greater dry eye symptoms and DES, lower tear volume and tear stability, along with higher osmolarity and conjunctival redness, after reading for 15 minutes on a computer compared to reading on handheld devices or a non-device control measurement. The lowest impact was obtained with the smartphone and the e-reader, probably due to a lower gaze angle associated with smartphone use and to the enhanced optical properties of the e-reader. The instillation of artificial tears did not show a statistical improvement in ocular surface and tear film variables for the same device, although it attenuated the effects of display use.

7.

Ocular surface predisposing factors for digital display-induced dry eye

7.1 Introduction

Considering that computer use is a consistent risk factor for DED (Stapleton et al., 2017), it is believed that individuals with pre-existent dry eye conditions are at an increased risk of suffering from digital display-induced dryness, although with limited evidence. Dry eye symptoms experienced by computer users are often encountered in otherwise healthy individuals (Coles-Brennan et al., 2019). However, while some individuals report no complaints when using digital screens others notice their symptoms intensely and frequently (Cantó-Sancho et al., 2021). Consequently, management strategies for digital display-induced dry eye, such as artificial tear substitutes, are often prescribed after the onset of symptoms or are broadly recommended without supporting evidence that they will bring any individual benefit to sufferers (Coles-Brennan et al., 2019).

The TFOS DEWS II definition and classification report suggested that individuals with a predisposition to dry eye or with a pre-clinical state (i.e., symptoms without signs) need to be managed with preventive therapy and education (Craig et al., 2017). Therefore, effective identification of those individuals with a predisposition to the disruption of their ocular surface with display use is especially relevant, as it can provide the practitioner with a considerable advantage in managing the condition.

Accordingly, this chapter aimed to identify which ocular surface and tear film parameters are relevant predictors of the impact of computer use on dry eye signs and symptoms.

7.2 Methods

7.2.1 Participants

Eighty-two young volunteers, ranging in age from 18 to 26 years participated in this study. Participants in this study were especially familiarised with the use of digital displays, with an average time of computer use of 4.3 ± 2.5 hours per day. All the participants had CDVA better or equal to 20/20 (0.00 logMAR) in both eyes, normal binocularity, and normal colour vision. Participants had no ocular history of injury, anterior or posterior segment pathology, surgery, or current use of topical medications and were not CL wearers. Additionally, participants were instructed not to use artificial tears within 2 hours before the visit.

The study followed the tenets of the Declaration of Helsinki and was approved by the University of Valencia human research ethics committee. All the participants were informed about the nature of the study and gave their written consent.

7.2.2 Experimental design

All the measurements were taken in the same laboratory. The approximate duration of each session was 45 minutes. All the sessions were carried out at the same time of the day (first thing in the morning, at 9 am) and under the same, constant environmental conditions (temperature and humidity). In addition, participants were asked not to use other digital displays 30 minutes before the session and not to drink any beverage containing caffeine 24 hours before the measurements to prevent any disruption of the ocular surface or blinking alterations prior to the visit. Fifteen minutes before the entry of the participants, the laboratory was acclimatized. To minimise the effects of outdoor conditions on the way to the laboratory, a 15-minute acclimatisation period was allowed between entry into the room and the measurements being obtained. The whole experiment was carried out under constant background illumination. The room was free from ambient lighting. Room illuminance was maintained at approximately 220 lux on the plane of the eyes of the participants. Chroma Metre CL-200 lux metre (Konica Minolta, Ramsey, NJ, USA) was used to measure photometric values. Room temperature and humidity were constantly monitored and remained stable at 22.7 ± 1.6°C and 43 ± 5%, respectively.

7.2.3 Measurements and procedure

The dry eye symptoms and signs and spontaneous blinking pattern of the participants were assessed before (baseline/ pre-task) and after (post-task) executing a 30-minute reading task on a computer. The computer was chosen as the device for the task over other forms of presentation based on the results of the previous chapters, in which a greater impact of this display on DES (*4. Dry eye-related risk factors for digital eye strain*; Talens-Estarelles et al., 2022b), the blinking pattern (*5. Blinking kinematics characterization during digital displays use*; Talens-Estarelles et al., 2022a) and the ocular surface (*6. How do different digital displays affect the ocular surface?*; Talens-Estarelles et al., 2020) was observed in comparison to handheld devices.

First, dry eye symptoms were evaluated using the OSDI and DEQ-5. Participants were instructed to respond to the questionnaires twice: first to the standard version of the questionnaire (baseline) and then to a modified version to match the study question investigated (pre-task). The OSDI includes 3 subscales: ocular symptoms, vision-related activities of daily living, and environmental triggers. For the pre-task OSDI (OSDI-5), the participants were instructed to respond based on their sensation during the visit and only to the ocular symptoms subscale (i.e., first 5 questions), thus excluding those questions that were not applicable to the task (i.e., wind, driving at night, watching TV, etc.). The total OSDI-5 score was then calculated following the questionnaire's formula (OSDI = sum of scores for all questions answered × 100 / total number of questions answered x 4). Thus, the OSDI-5 score ranged from 0 to 100, with higher scores corresponding to the severity of the symptoms. This approach was similar to that in previous studies (Choi et al., 2018; Ribelles et al., 2015).

NIKBUT, TMH, conjunctival redness, upper eyelid meibography and spontaneous blinking were subsequently assessed using the Keratograph 5M (Oculus Optikgerate, Wetlzar, Germany) (*3.2.2 Oculus Keratograpgh 5M, 3. General methods*). NIKBUT was measured 3 times and an average value was obtained. The upper eyelid meibomian gland dropout percentage was posteriorly calculated using the ImageJ tool (Wayne Rasband; National Institutes of Health, Bethesda, MD) as the ratio between the eyelid area and the gland loss area. The spontaneous blinking of the participants was assessed in terms of the blink rate (i.e., total number of blinks) and percentage of incomplete blinks through the recording of a 60-s video sequence using the Keratograpgh 5M. Detailed information on the questionnaires and measurement procedures can be found in Chapter 3 (*3.2 Measurements and devices, 3. General methods*).

Measurements were performed in the following order: OSDI, OSDI-5, DEQ-5 baseline, DEQ-5 pre-task, spontaneous blinking (i.e., blink rate and percentage of incomplete blinks), conjunctival redness, TMH, NIKBUT and upper eyelid meibography (i.e., meibomian gland dropout percentage). Only upper eyelid meibography was measured on the basis of previous findings, which reported its best suitability over lower eyelid meibography to make an evaluation of the meibomian glands (Dogan et al., 2018). Measurements were performed on the right eye for all the participants.

After the baseline and pre-task measurements, the participants executed a 30-minute reading task with a modern laptop computer (MacBook Air Retina, 2020; Apple Inc., Cupertino, CA, USA). The device was placed in accordance with the typical viewing

distance and angle of usage: that is, 60-cm distance and approximately 10° below eye level and with an inclination angle of 100° from the surface of the desk. Participants were informed that they would be asked a series of comprehension questions at the end of the reading. Next, they were instructed to carry out the respective task until the examiner told them to stop. Sufficient material was provided for a 30-minute reading session without repetition.

After the 30-minute reading task, the battery of standard clinical tests was repeated, with the exemption of upper eyelid meibography and spontaneous blinking. The measurements were performed within 3 minutes after the task. A sole examiner performed all the measurements. Participants responded to the modified versions of the questionnaires and were instructed to report symptoms experienced during computer use, for a direct comparison with the pre-task score. Lastly, the examiner confirmed the compliance of the participants with the reading task through a brief conversation and discussion about the story previously read by the participant.

7.2.4 Material

The text material was a book with a recompilation of Allan Poe's full stories in the Spanish language, the mother tongue of all the participants. The text was displayed using Kindle (2021) reading app (Amazon Inc., Seattle, WA, USA). Text characteristics were selected from the Kindle app interface and included Georgia font style with black letters on a white background, 25°-page angular width and left-justified text alignment. Additionally, text size was chosen to meet an established angular size for a 0.15 logMAR visual acuity and was selected after the trigonometric calculation based on the linear size, measured with an optical microscope focused on the screen of the device.

7.2.5 Statistical analysis

The results were evaluated using SPSS software v.26 (IBM Corp., Armonk, NY, USA). The normality of data was assessed by using the Kolmogorov-Smirnov test. When normality could be assumed, a paired-sample t-test was used to examine the differences between the pre-task and the post-task measurements for each parameter. The non-parametric Wilcoxon paired signed-rank test was used when parametric test assumptions were not fulfilled.

The impact of computer use on dry eye signs and symptoms was assessed by calculating the difference between pre-task and post-task results (i.e., post-task – pre-task). Multiple linear regressions were then used to explore the independent associations between ocular parameters and computer-induced dry eye signs and symptoms. Multiple linear models were constructed with pre-task – post-task differences as dependent variables and potential predictors, that had statistically significant correlations, as independent variables, to assess the relative importance of each independent variable and their contribution to the change of the dependent variables.

Finally, GLMM were utilised with increased/decreased-no change dry eye signs and symptoms as the criteria variables and baseline variables (blink rate, percentage of incomplete blinks, meibomian gland dropout, positive OSDI score (score ≥ 13), positive DEQ-5 score (score ≥ 6) high baseline NIKBUT (≥ 10s), high baseline bulbar redness (> 1.0) and low baseline tear meniscus height (< 0.20 mm) and variables of change or impact (post-task – pre-task) as predictors (fixed effects) and a random effect for each participant. A total of 15 models were constructed and assessed for potential confounders (age and sex). Please refer to Chapter 3 for more information on linear regressions (*3.3.3.6 Regression analysis, 3. General methods*).

7.3 Results

Ninety Caucasian volunteers were initially recruited, out of which 82 (28 males and 54 females) ranging in age from 18 to 26 years (23 ± 2 years) met the inclusion/exclusion criteria and completed all visits. All the participants complied with the instructions of the reading task. Table 7.1 shows the baseline and/or pre-task results of the ocular parameters assessed in the present study, along with the post-task results of the dry eye questionnaires and ocular surface variables and their calculated difference. Statistical comparisons revealed significantly higher post-task dry eye symptoms for both questionnaires ($p < 0.001$). Additionally, conjunctival redness and TMH were significantly greater after reading on the computer ($p = 0.01$ and $p < 0.001$, respectively) while NIKBUT was significantly shorter ($p = 0.008$).

Multiple linear regressions showed that several baseline and pre-task variables were predictive of the impact of computer use on dry eye signs and symptoms (Table 7.2). The baseline score obtained in OSDI and DEQ-5 was independently associated and positively correlated with the impact (pre-task – post-task difference) of computer use on dry eye symptoms, explaining up to 31% of its variability ($p < 0.001$). Additionally, a

greater impact on DEQ-5 was a significant predictor of a greater impact on OSDI-5 ($p = 0.01$). Moreover, the change in NIKBUT with computer use was independently associated and negatively correlated with the change in conjunctival redness ($p = 0.006$). In parallel, a greater increase in conjunctival redness and a higher pre-task NIKBUT were predictive of a greater decrease in NIKBUT with computer use ($p = 0.005$ and $p < 0.001$, respectively). Conversely, no ocular surface variable revealed a significant association with TMH changes following computer use ($p \geq 0.05$). Similarly, blinking variables and meibomian gland dropout were not predictive of any outcome ($p \geq 0.05$).

Table 7.3 shows the results of the statistically significant predictive variables of the GLMM constructed, along with the proportions of the participants who experienced an increase or decrease in dry eye signs and symptoms for every predictive variable. A high proportion of participants who had an increase in DEQ-5 with computer use experienced a significant increase in OSDI-5 (71.7%, OR = 6.34, $p = 0.04$). An increase in OSDI-5 and a positive baseline OSDI score significantly increased the odds of experiencing a feeling of painful or sore eyes with computer operation (OR = 15.23 and $p = 0.02$ and OR 10.91 and $p = 0.01$, respectively). Additionally, most of the participants who had an increase in OSDI-5 suffered an increase in light sensitivity (46%, OR = 11.10, $p = 0.02$), blurred vision (74.0%, OR = 30.08, $p = 0.002$) and poor vision (54.0%, OR = 28.87, $p = 0.008$) with computer use. Similarly, participants with an increase in OSDI-5 and DEQ-5 had significantly greater odds of suffering an increase in eye discomfort (OR = 8.51, $p = 0.01$ and OD = 16.64 and $p = 0.006$, respectively). Lastly, 54.7% of participants with high NIKBUT experienced a reduction in tear film stability and had higher odds of suffering a reduction in NIKBUT (OR = 0.18, $p = 0.04$). Conversely, no associations were found for the change in the score of questions 2 and 3 of DEQ-5, conjunctival redness or tear meniscus height ($p \geq 0.05$).

Table 7.1. Dry eye signs and symptoms obtained before (pre-task) and after (post-task) 30-minute computer reading and their calculated difference (post-task – pre-task). Questionnaires were completed according to their original version (baseline) and to a modified version to match the study question (pre-task). Data are presented as mean [95% confidence intervals].

Variable	Baseline	Pre-task	Post-task	Difference (pre-task – post-task)	p-value (pre-task – post-task)
OSDI[a]	13.4 [10.7 – 16.1]	7.7 [5.7 – 9.8]	15.9 [12.3 – 19.4]	8.1 [5.9 – 10.2]	< 0.001*[1]
DEQ-5	7 [6 – 8]	4 [3 – 5]	7 [6 – 9]	3 [2 – 4]	< 0.001*[2]
Conjunctival redness		0.5 [0.5 – 0.6]	0.6 [0.5 – 0.6]	0.1 [0.0 – 0.1]	0.01*[1]
TMH (mm)		0.23 [0.21 – 0.24]	0.28 [0.26 – 0.31]	0.06 [0.04 – 0.08]	< 0.001*[1]
NIKBUT (s)		15.7 [14.0 – 17.5]	14.0 [12.4 – 15.5]	-1.8 [-2.7 – -0.5]	0.003*[1]
Meibomian gland dropout (%)		22 [19 – 25]	/	/	/
Blink rate (blinks/min)		16 [14 – 19]	/	/	/
Percentage of incomplete blinks (%)		52 [45 – 60]	/	/	/

DEQ-5 = 5-item Dry Eye Questionnaire; NIKBUT = Non-invasive keratograph break-up time; OSDI = Ocular Surface Disease Index; TMH = Tear meniscus heigh. [a] A shortened form of the questionnaire was used for the pre and post measurements and the full version for the baseline measurement, so these are not comparable. [1] Wilcoxon paired signed-rank test; [2] Paired T-test. * Indicates statistically significant values ($p < 0.05$).

Table 7.2. Multiple regression analysis for significant predictors of digital display-induced dry eye signs and symptoms.

Variable (post-task – pre-task)	Predictive variables	β	SE	Sβ	p-value	Adjusted R square
OSDI	OSDI (baseline)	0.36	0.08	0.43	< 0.001	0.31
	DEQ-5 (post-task – pre-task)	0.64	0.15	0.25	0.01	
DEQ-5	DEQ-5 (baseline)	0.38	0.08	0.45	< 0.001	0.30
Conjunctival redness	NIKBUT (post-task – pre-task)	-0.01	< 0.001	-0.30	0.006	0.09
TMH	/	/	/	/	/	/
NIKBUT	(Constant)	3.43	1.07		0.002	0.29
	Conjunctival redness (post-task – pre-task)	-7.14	2.44	-0.28	0.005	
	NIKBUT (pre-task)	-0.29	0.06	-0.45	< 0.001	

DEQ-5 = 5-item Dry Eye Questionnaire; NIKBUT = Non-invasive keratograph break-up time; OSDI = Ocular Surface Disease Index; Sβ = Standardized coefficient; SE = Standard error; TMH = Tear meniscus heigh; β = Unstandardized coefficient.

Table 7.3. Number and proportion of participants with an increase, no change and decrease in dry eye signs and symptoms with computer use stratified by the listed variables and statistically significant results of the generalized linear mixed models.

	Decrease in variable	No change in variable	Increase in variable	Increase:Decrease/no change, OR (95% CI)	p-value
OSDI-5 (total score)					
Increase in DEQ-5 *(N of participants; percentage)*	2; 3.3%	15; 25.0%	43; 71.7%	6.34 (0.98 – 41.02)	0.04
OSDI-5 (ocular symptoms subscale questions)					
Q1: Eyes that are sensitive to light					
Increase in OSDI-5 *(N of participants; percentage)*	7; 14.0%	20; 40.0%	23; 46.0%	11.10 (1.59 – 77.55)	0.02
Q2: Eyes that feel gritty					
Q3: Painful or sore eyes					
Increase in OSDI-5 *(N of participants; percentage)*	0; 0.0%	33; 66.0%	17; 34.0%	15.23 (1.55 – 150.10)	0.02
Baseline positive OSDI[a] *(N of participants; percentage)*	1; 2.9%	19; 54.3%	15; 42.9%	10.91 (1.95 – 70.81)	0.01
Q4: Blurred vision					
Increase in OSDI-5 *(N of participants; percentage)*	1; 2.0%	12; 24.0%	37; 74.0%	30.08 (3.62 – 249.68)	0.002
Q5: Poor vision					
Increase in OSDI-5 *(N of participants; percentage)*	1; 2.0%	22; 44.0%	27; 54.0%	28.87 (2.52 – 310.41)	0.008
DEQ-5 (total score)					
Increase in OSDI-5 *(N of participants; percentage)*	6; 11.5%	3; 5.8%	43; 82.7%	7.96 (0.94 – 67.36)	0.04
DEQ-5 (questions)					
Q1: Eye discomfort					
Increase in OSDI-5 *(N of participants; percentage)*	3; 6.1%	11; 22.4%	35; 71.4%	8.51 (1.69 – 42.91)	0.01
Increase in DEQ-5 *(N of participants; percentage)*	1; 1.7%	18; 31.0%	39; 67.2%	16.64 (2.30 – 120.49)	0.006
Q2: Eye dryness					
Q3: Watery eyes					
NIKBUT					
High pre-task NIKBUT[b]	29; 54.7%	12; 22.6%	12; 22.6%	0.18 (0.03 – 0.99)[c]	0.04

(N of participants; percentage)

Conjunctival redness	
TMH	

CI = Confidence interval; DEQ-5 = 5-item Dry Eye Questionnaire; N = number; NIKBUT = Non-invasive keratograph break-up time; OR = Odds ratio; OSDI-5 = Modified version of the Ocular Surface Disease Index. [a] OSDI score ≥ 13; [b] NIKBUT ≥ 10 s; [c] ORs are for Increase/No change: Decrease.

7.4 Discussion

The findings of the present study revealed both a statistically and clinically significant increase in dry eye signs and symptoms after reading on the computer for 30 minutes. More specifically, dry eye symptoms almost doubled for both questionnaires, while conjunctival redness increased and tear stability was significantly reduced, indicating tear film destabilisation and ocular surface stress with computer use. This is in accordance with previous findings (Cardona et al., 2011; Choi et al., 2018; Yazici et al., 2015).

For instance, in Chapter 6 (*6. How do different digital displays affect the ocular surface?;* Talens-Estarelles et al., 2020), significantly higher dry eye symptoms, conjunctival redness and tear osmolarity, and lower NIKBUT were found after reading on a computer for as little as 15 minutes in comparison to a control measurement, in a sample of university students. Similarly, Cardona et al. (2011) found a significant reduction in tear stability after 20 minutes of playing a computer game in an analogous sample of young volunteers. Accordingly, short periods of computer use can have a significant impact on the tear film and the ocular surface of individuals.

Furthermore, in the present study, tear volume (TMH) significantly increased with computer use. Conversely, some authors reported significantly lower TMH and Schirmer test results in long-term computer users (Cardona et al., 2011) while others observed no differences (Choi et al., 2018). Blinking keeps the eye surface humid and hydrated by favouring the secretion of tears and spreading them through the ocular surface (Doane, 1981; holly, 1980). Nielsen et al. (2008) reported a compensatory burst of blinks right after cessation of an active digital display task. Authors attributed this phenomenon to compensation for the oppression of blinking during the digital display task and therefore as a wetting process secondary to ocular surface disturbance, which could be the reason behind the greater post-task tear volume observed in the present study.

The findings of the present study contrast with the lower TMH observed after computer use compared to the control condition in Chapter 6 (*6. How do different digital displays affect the ocular surface?*; Talens-Estarelles et al., 2020). Unlike Chapter 6, in the present study dry eye signs and symptoms were assessed before and after the computer task, rather than only after, further minimizing day-to-day variability of the tear film and probably allowing for better evaluation of the effects of digital display use. Also, the duration of display use was twice as long as in Chapter 6 (30 minutes vs 15 minutes), thus

computer use may have caused greater ocular surface dryness, favouring the wetting process that was pressumably behind the increase in tear film volume.

Moreover, the study participants with higher dry eye symptoms at baseline (i.e., higher OSDI and DEQ-5 score) were at a greater risk of suffering an increase in symptoms with computer use, while participants reporting fewer symptoms of dryness were less likely to experience the effects of computer use. Approximately 43% of the participants with a positive OSDI score (score ≥ 13) at baseline suffered an increase in the feeling of painful or sore eyes, compared to only 3% of them who improved their symptoms. Accordingly, the odds of having a greater feeling of pain or sore eyes after computer use were 11 times higher in participants with a positive OSDI score.

Elevated dry eye symptomatology is an indispensable characteristic in individuals with DED. According to the TFOS DEWS II diagnostic criteria (Wolffsohn et al., 2017), individuals must obtain either an OSDI score ≥ 13 or a DEQ-5 score ≥ 6 – in addition to other diagnostic homoeostatic markers – to be fully considered as having DED. Similarly, some individuals might present symptoms consistent with DED but in the absence of clinical signs which might indicate a pre-clinical state or a scenario of episodic dry eye (Craig et al., 2017). Considering that participants with more symptomatology were more likely to report an increase in symptoms with computer use and that elevated dry eye symptomatology is a common characteristic in individuals with DED, special attention should be paid to individuals with DED or intermittent dry eye symptoms who use digital displays. Further research comparing the effects of digital display use between healthy and dry eye individuals is required.

Regarding the impact of computer use on the ocular surface, the results of the present study revealed that the change in tear stability following computer operation was a significant predictor of the change in conjunctival redness, and both variables had a negative relation. Thus, a greater reduction in tear stability was associated with a greater conjunctival response probably due to greater ocular surface stress. As addressed in the introduction chapter (*1. Introduction*; Talens-Estarelles et al., 2021), reduced tear stability during computer use is widely reported and has been attributed to alterations in the blinking pattern, in addition to a high ocular surface exposure consequent to screen positioning.

Tsubota and Nakamori (1995) studied the effects of exposed surface area on tear stability and reported that tear evaporation increased proportionally with ocular surface area, being 3.4 and 2.5 times greater when looking up and ahead than when looking down.

As in Chapter 6 (*6. How do different digital displays affect the ocular surface?*; Talens-Estarelles et al., 2020), considering that participants carried out a reading task with a computer device placed at a typically high angle (10° below eye level), the aforementioned effects are expected to have played a relevant role in the reduction of tear stability.

As addressed in detail in the introduction chapter (*1. Introduction;* Talens-Estarelles et al., 2021) and reported in previous chapters (Chapters 5 and 6), alterations of the blinking pattern, along with increased ocular surface exposure during digital display use, contribute to the disruption of the tear film and the reduction of its stability, leading to the exposure of the ocular surface to desiccation and damage. According to previous research, tear break-up presents a noxious stimulus to the corneal surface and is linked to ocular irritation (Zhang et al., 2017). Therefore, given that conjunctival redness has been shown to occur as a response to stimulation of the cornea (Alabi & Simpson, 2019), this may explain the association between the reduction in tear stability and the increase in conjunctival redness found in the present study.

This close relationship between tear instability and conjunctival redness can also be seen in the linear model for NIKBUT, in which a greater increase in conjunctival redness was predictive of a greater reduction in tear stability. In addition, the change in tear film stability with computer use was also independently associated with the pre-task NIKBUT, indicating that the participants with longer NIKBUT were more likely to suffer a greater decrease in NIKBUT with computer use. More precisely, having a long NIKBUT increased the odds of having a reduction in tear stability, with almost 55% of the participants with a long NIKBUT suffering a reduction in tear stability with computer use. Nevertheless, it should be noted that participants with longer NIKBUT were more likely to experience greater decrease than those with shorter tear break-up times simply as a consequence of a floor effect.

Finally, despite alterations in blinking being one of the key factors leading to digital display-induced dryness, the present study did not find any association between the spontaneous blinking pattern of the participants and the impact of screen use on dry eye signs and symptoms. Consequently, the natural blinking pattern of the participants was not significant in predicting the effects of display use on the eyes.

The present study had some limitations to consider. First, given that tear film osmolarity was not measured, some DED participants may have been misclassified using the TFOS DEWS II dry eye diagnostic algorithm as not having DED, so classification

was not attempted. Studies comparing the impact of computer use on healthy and DED patients are required. Additionally, modified versions of questionnaires were used to assess the change in symptomatology with computer use. This was done in the absence of an appropriate questionnaire to assess the change in symptoms after a short task. Finally, future studies are required to evaluate the predictability of blinking alterations during display use based on ocular parameters.

All things considered, reading on a computer for 30 minutes significantly increased dry eye signs and symptoms. Several baseline and pre-task parameters were predictive of the impact of computer use on the ocular surface. Having greater symptoms of dry eye was predictive of a greater increase in symptomatology, while a longer NIKBUT predisposed the study participants to a greater reduction in tear stability, potentially leading to a reduced NIKBUT following computer use. Furthermore, having a greater increase in conjunctival redness was a significant predictor of a greater reduction in tear stability. The baseline spontaneous pattern of blinking and meibomian gland dropout percentage were not predictors of alterations following computer use.

8.

Determining the best management strategy for preventing short-term effects of digital display use on dry eyes

8.1 Introduction

Alterations of the pattern of blinking during digital display use have been mainly attributed to higher levels of cognitive demand (Cardona et al., 2011) arising after several factors such as inadequate text legibility (Gowrisankaran et al., 2007) or glare from the device screen (Sheedy et al., 2005). In parallel, longer periods of display visualization have been shown to aggravate dryness signs and symptoms (Choi et al., 2018; Rosenfield, 2011; Wu et al., 2014). Additionally, the blue light emitted by digital displays has been recently in the spotlight as a contributing factor to ocular surface alterations (Cheng et al., 2014), although to date there is no consensus on its effects and further research is required.

Nowadays, clinicians have a range of management strategies available to prevent or reduce the effects of digital display use on the ocular surface (*1.6 Management strategies, 1. Introduction,* Talens-Estarelles et al., 2021). These strategies mainly include the instillation of lubricating eye drops, blink training and control, taking regular breaks, and more recently the use of blue light screen filters. Nevertheless, research on some of these strategies is still scarce. Likewise, to the best of the authors' knowledge, no study to date has compared the benefits of different management strategies. Considering that the use of digital displays is reaching all-time highs, it is particularly relevant for the clinician to be aware of the effectiveness of the most common management strategies as well as the best option to most effectively reduce the impact of digital display use on the ocular surface.

Accordingly, this chapter aimed to assess and compare the effectiveness of four main management strategies for preventing short-term effects of digital display use on dry eyes, including the instillation of high-viscosity artificial tears, taking regular breaks, blink control, and the use of blue light filters in a sample of young, healthy individuals.

8.2 Methods

8.2.1 Participants

Forty-seven young, healthy volunteers ranging in age from 18 to 26 years participated in this study. Participants were especially familiarized with the use of digital displays with a reported average time of computer use of 4.7 ± 2.7 hours per day. All the participants had CDVA better or equal to 20/20 (0.00 logMAR) in both eyes and reported normal binocularity (i.e., no history of strabismus, amblyopia, or others) and normal

colour vision. The participants had no ocular history of injury, anterior or posterior segment pathology, surgery, or current use of topical medications and were not CL wearers nor did they use artificial tear substitutes.

The study followed the tenets of the Declaration of Helsinki and was approved by the University of Valencia human research ethics committee. All the participants were informed about the nature of the study and gave their written consent.

8.2.2 Experimental design and material

Dry eye symptoms, ocular surface and tear film were evaluated before and after executing a 20-minute reading task with a modern laptop computer (MacBook Air Retina, 2020; Apple Inc., Cupertino, CA, USA), under five different experimental conditions: (1) control condition with no management strategy, (2) initial instillation of artificial tears, (3) taking a brief break halfway through, (4) using a blue light screen filter, and (5) blink control. A 20-minute task was chosen following previous chapters (Chapters 6 and 7) and research of a similar nature which reported significant tear film changes after similar periods of display use (Ang et al., 2014; Cardona et al., 2011). The experimental design mirrored that of previous chapters (Chapters 5-7).

The text material was a book with a recompilation of Allan Poe's full stories in the Spanish language, the mother tongue of all participants. The text was displayed using Kindle (2021) reading app (Amazon Inc., Seattle, WA, USA). Text characteristics were selected from the Kindle app interface and included Georgia font style with black letters on a white background, 25°-page angular width, and left-justified text alignment. Screen luminance was maintained by controlling the display brightness level in settings. In addition, the text size was chosen to meet an established angular size for a 0.15 logMAR visual acuity. Furthermore, the device was placed in accordance with the typical viewing distance and angle of usage: that is, 60-cm distance and approximately 10° below eye level and with an inclination angle of 100° from the surface of the desk.

The whole experiment was performed under constant illumination. Room illuminance was maintained at approximately 220 lux on the plane of the participant's eyes and was provided by indirect lighting to avoid any glare sources. Chroma Meter CL-200 lux meter (Konica Minolta, Ramsey, NJ, USA) was used to measure photometric values. Room temperature and humidity were constantly monitored and remained stable at 23.1 ± 1.6°C and 43 ± 5%, respectively.

8.2.3 Protocol

The participants completed, one by one, each of the five experimental conditions in a randomized order. Each condition was tested in separate sessions. To minimize day-to-day variability of the tear film, each session was performed on the same day of the week, at the same time of the day, and under the same, constant environmental conditions (temperature and humidity). In addition, participants were asked not to use other digital displays 30 minutes before the session and not to drink any beverage containing caffeine 24 hours before the measurements. Fifteen minutes previous to the participant's visit, the laboratory was acclimatized, and the experimental conditions were set up. To minimize the effects of outdoor conditions on the way to the laboratory, a 15-minute acclimatization period was allowed between entry into the room and the measurements being obtained.

After the mentioned acclimatization period, participants underwent a battery of standard clinical tests of ocular surface and tear film evaluation. Dry eye symptoms were evaluated using the OSDI and DEQ-5. Participants were instructed to respond to a modified version of the questionnaire to match the study question investigated. The OSDI includes three subscales: ocular symptoms, vision-related activities of daily living, and environmental triggers. The participants were instructed to respond only to the ocular symptoms subscale (i.e., first five questions), thus excluding those questions that were not applicable (i.e., wind, driving at night, watching TV, etc.). Thus, the OSDI score ranged from 0 to 100, with higher scores corresponding to the severity of the symptoms. This approach was like that of Chapter 7 (*7. Ocular surface predisposing factors for digital display-induced dry eye*; Talens-Estarelles et al., 2022c) and of previous studies (Choi et al., 2018; Yazici et al., 2015).

The ocular surface and tear film were assessed by means of TMH, conjunctival redness and NIKBUT, using the Keratograph 5M (Oculus Optikgerate, Wetzlar, Germany) (*3.2.2 Oculus Keratograpgh 5M, 3. General methods*). Measurements were performed in the following order: OSDI, DEQ-5, TMH, conjunctival redness and NIKBUT. NIKBUT was measured three times, and an average value was obtained. The measurements were performed on the right eye for all the participants. Detailed information on the questionnaires and measurement procedures can be found in Chapter 3 (*3.2 Measurements and devices, 3. General methods*).

Next, participants received instructions on the task and were given a few minutes to choose between one of the stories from the book. Finally, participants were seated

comfortably and instructed to carry out the respective reading task in silence for 20 minutes until the examiner told them to stop. Sufficient material was provided for a 20-minute reading session without repetition.

When required, one drop of Systane Ultra (Alcon SL, Geneva, Switzerland) single-dose artificial tears was instilled on each eye, 2 minutes before the reading. In one of the sessions, participants were told to rest for 30 s looking at a distance target (through the window) halfway through the task (i.e., 10 minutes from the beginning) and were then ordered to continue with the task for the remaining time. Before another visit, the computer screen's night shift mode was activated from the display's settings for the whole of the reading, without participants being actively told. This configuration comes with the computer and acts as a screen filter by adjusting the spectral composition of the display to reduce the short-wavelength light emissions. Finally, in another session, participants were instructed to blink following a sound signal every 4 s (Portello & Rosenfield, 2010). The sound signal consisted of a periodic beep with a duration of 1 s and a low noise level, similar to a verbal command. One of the authors checked the compliance to blinking following the sound signal throughout the entire task.

After the 20-minute reading task, the battery of standard clinical tests was repeated. Measurements were performed within 3 minutes posterior to the task. A sole examiner performed all the measurements. Finally, the examiner confirmed participants' compliance with the reading task throughout various comprehension questions.

8.2.4 Statistical analysis

The results were evaluated using SPSS software v.26 (IBM Corp, Armonk, NY, USA). The normality of data was assessed by using the Shapiro-Wilk test. When normality could be assumed, a paired-sample t-test was used to examine the differences between the pre-task and the post-task measurements for each ocular surface variable. The non-parametric Wilcoxon-paired signed-rank test was used when parametric test assumptions were not fulfilled. To compare the effectiveness of the management strategies, the difference between the post-task and the pre-task measurements was calculated for each variable (post-task – pre-task). A repeated-measures ANOVA was used to examine the statistical significance of the results for the five task conditions. Please refer to Chapter 3 for more information on repeated-measures ANOVA (*3.3.3.3 Differences between three or more repeated measurements, 3. General methods*). The

nonparametric Friedman test for repeated measures with Dunn-Bonferroni post-hoc analysis was used when parametric test assumptions were not fulfilled.

8.3 Results

Fifity Caucasian volunteers were initially recruited, out of which 47 (18 males and 29 females) ranging in age from 18 to 26 years (21 ± 2 years) met the inclusion/exclusion criteria and completed all visits. Table 8.1 shows the mean values and 95% CIs of each ocular surface and tear film variable assessed in this study, before and after computer use, under the different study conditions. The table additionally displays the statistical results of the pre-task and post-task comparisons.

The statistical comparisons revealed significantly higher post-task OSDI and DEQ-5 scores following the computer control task ($p < 0.001$) and when using the computer with the blue light filter ($p = 0.001$ and $p < 0.001$, respectively) compared to before the task. In addition, a significantly higher post-task DEQ-5 score was reported when performing a brief break halfway through computer reading ($p = 0.01$). Likewise, significantly greater conjunctival redness and shorter NIKBUT were obtained after the computer control task ($p < 0.001$ and $p = 0.006$, respectively) and the computer task with the blue light filter compared to before ($p = 0.003$ and $p = 0.04$, respectively), whereas no significant differences were obtained for the rest of the management strategies ($p \geq 0.05$). Moreover, a significant increase in TMH was found after the task for all conditions compared to before ($p \leq 0.002$), except for blink control ($p = 0.52$).

Table 8.2 shows the mean and 95% CIs of the calculated post-task/pre-task differences of each variable, along with the statistical results of the comparisons of all five examination conditions. Figures 8.1 and 8.2 illustrate box plots of the dry eye symptomatology and ocular surface and tear film post-task/pre-task differences, respectively. The comparisons revealed statistically significant differences between management strategies for all variables ($p < 0.001$), except for conjunctival redness ($p = 0.05$). Significantly less worsening of dry eye symptoms (OSDI and DEQ-5) was reported following computer use with instillation of artificial tears and when blinking was controlled compared to the non-management control condition ($p \leq 0.008$). Similarly, despite a significantly greater post-task DEQ-5 compared with pre-task (Table 8.1), taking a brief break led to a smaller increase in dry eye symptoms (OSDI and DEQ-5) compared to the control ($p \leq 0.04$). In addition, significantly less worsening of dry eye symptoms

(OSDI and DEQ-5) was obtained with the instillation of artificial tears in comparison to the use of a blue light filter ($p \leq 0.02$). As for the tear film, a significantly greater increase in TMH was obtained when artificial tears were instilled compared to the rest of the conditions ($p \leq 0.002$). Finally, significantly less worsening of NIKBUT was observed when artificial tears were instilled or when blinking was controlled compared to the control condition ($p = 0.005$ and $p < 0.001$, respectively) and when blinking was controlled compared to the use of a blue light filter ($p = 0.008$).

Table 8.1. Ocular surface and tear film variables obtained before (pre-task) and after (post-task) the control computer task and the computer tasks with the different management strategies and statistical results of the comparisons. Data are presented as mean [95% confidence intervals].

	Control			Artificial tear			Blue filter			Brief break			Blink control		
	Pre-task	***Post-task***	**p-value**	***Pre-task***	***Post-task***	**p-value**	***Pre-task***	***Post-task***	**p-value**	***Pre-task***	***Post-task***	**p-value**	***Pre-task***	***Post-task***	**p-value**
OSDI	6.4 [4.0 – 8.8]	14.9 [10.7 – 19.1]	< 0.001*	5.9 [3.2 – 8.5]	6.7 [4.5 8.9]	0.32	6.8 [3.2 – 10.4]	11.6 [7.2 – 16.0]	0.001*	6.4 [3.3 – 9.6]	8.3 [5.2 – 11.5]	0.06	6.5 [4.1 – 8.8]	6.3 [4.2 – 8.3]	0.62
DEQ-5	3 [2 – 4]	6 [5 – 8]	< 0.001*	3 [2 – 4]	2 [1 – 3]	0.13	2 [1 – 3]	4 [3 – 6]	< 0.001*	3 [2 – 4]	4 [3 – 5]	0.01*	2.6 [1.6 – 3.5]	2.5 [1.5 – 3.4]	0.88
TMH (mm)	0.24 [0.22 – 0.26]	0.28 [0.25 – 0.31]	0.002*	0.22 [0.20 – 0.24]	0.30 [0.27 – 0.33]	< 0.001*	0.23 [0.21 – 0.25]	0.27 [0.24 – 0.29]	0.001*	0.21 [0.20 – 0.23]	0.24 [0.22 – 0.26]	< 0.001*	0.22 [0.20 – 0.23]	0.22 [0.20 – 0.24]	0.52
CR	0.5 [0.4 – 0.6]	0.6 [0.5 – 0.7]	< 0.001*	0.5 [0.4 – 0.6]	0.5 [0.4 – 0.6]	0.54	0.4 [0.4 – 0.5]	0.5 [0.4 – 0.6]	0.003*	0.4 [0.4 – 0.5]	0.5 [0.4 – 0.5]	0.11	0.5 [0.4 – 0.6]	0.5 [0.4 – 0.6]	0.29
NIKBUT (s)	16.3 [14.2 – 18.5]	13.8 [11.7 – 15.8]	0.006*	15.2 [13.1 – 17.3]	16.3 [14.1 – 18.4]	0.11	16.5 [14.4 – 18.6]	15.6 [13.3 – 17.9]	0.04*	15.3 [13.1 – 17.5]	15.2 [13.0 – 17.4]	0.90	15.4 [13.0 – 17.7]	16.4 [14.1 – 18.6]	0.09

CR = Conjunctival redness; DEQ-5 = 5-item Dry Eye Questionnaire; NIKBUT = Non-invasive keratograph break-up time; OSDI = Ocular Surface Disease Questionnaire; TMH = Tear meniscus height. * Indicates statistically significant values ($p < 0.05$).

Table 8.2. Differences between post-task and pre-task ocular surface and tear film variables obtained for the computer control task and the computer tasks with the different management strategies and statistical results of the comparisons. Data are presented as mean [95% confidence intervals].

Variable	Control (CT)	Artificial tear (AT)	Blue filter (BF)	Brief break (BB)	Blink control (BC)	p-value	Statistically significant post-hoc differences (p-value)
OSDI	8.5 [5.3 – 11.7]	0.9 [-1.4 – 3.1]	4.8 [2.1 – 7.5]	1.9 [-0.1 – 3.8]	-0.2 [-2.0 – 1.6]	< 0.001*	CT – AT (0.008) CT – BB (0.04) CT – BC (0.001)
DEQ-5	4 [3 – 5]	-1 [-2 – 0]	2 [1 – 3]	1 [0 – 2]	0 [-1 – 1]	< 0.001*	CT – AT (< 0.001) CT – BB (0.002) CT – BC (< 0.001) AT – BF (0.02)
TMH (mm)	0.04 [0.02 – 0.07]	0.08 [0.06 – 0.11]	0.04 [0.02 – 0.06]	0.03 [0.01 – 0.04]	0.00 [-0.01 – 0.02]	< 0.001*	CT – AT (0.007) AT – BF (0.002) AT – BB (< 0.001) AT – BC (< 0.001)
Conjunctival redness	0.1 [0.0 – 0.1]	0.0 [0.0 – 0.1]	0.1 [0.0 – 0.1]	0.0 [0.0 – 0.1]	0.0 [0.0 – 0.1]	0.05	—
NIKBUT (s)	-2.6 [-4.4 – -0.8]	1.1 [-0.3 – 2.4]	-1.0 [-2.0 – 0.1]	-0.1 [-1.6 – 1.5]	1.0 [0.0 – 2.0]	< 0.001*	CT – AT (0.005) CT – BC (< 0.001) BF – BC (0.008)

DEQ-5 = 5-item Dry Eye Questionnaire; NIKBUT = Non-invasive keratograph break-up time; OSDI = Ocular Surface Disease Questionnaire; TMH = Tear meniscus height. * Indicates statistically significant values ($p < 0.05$).

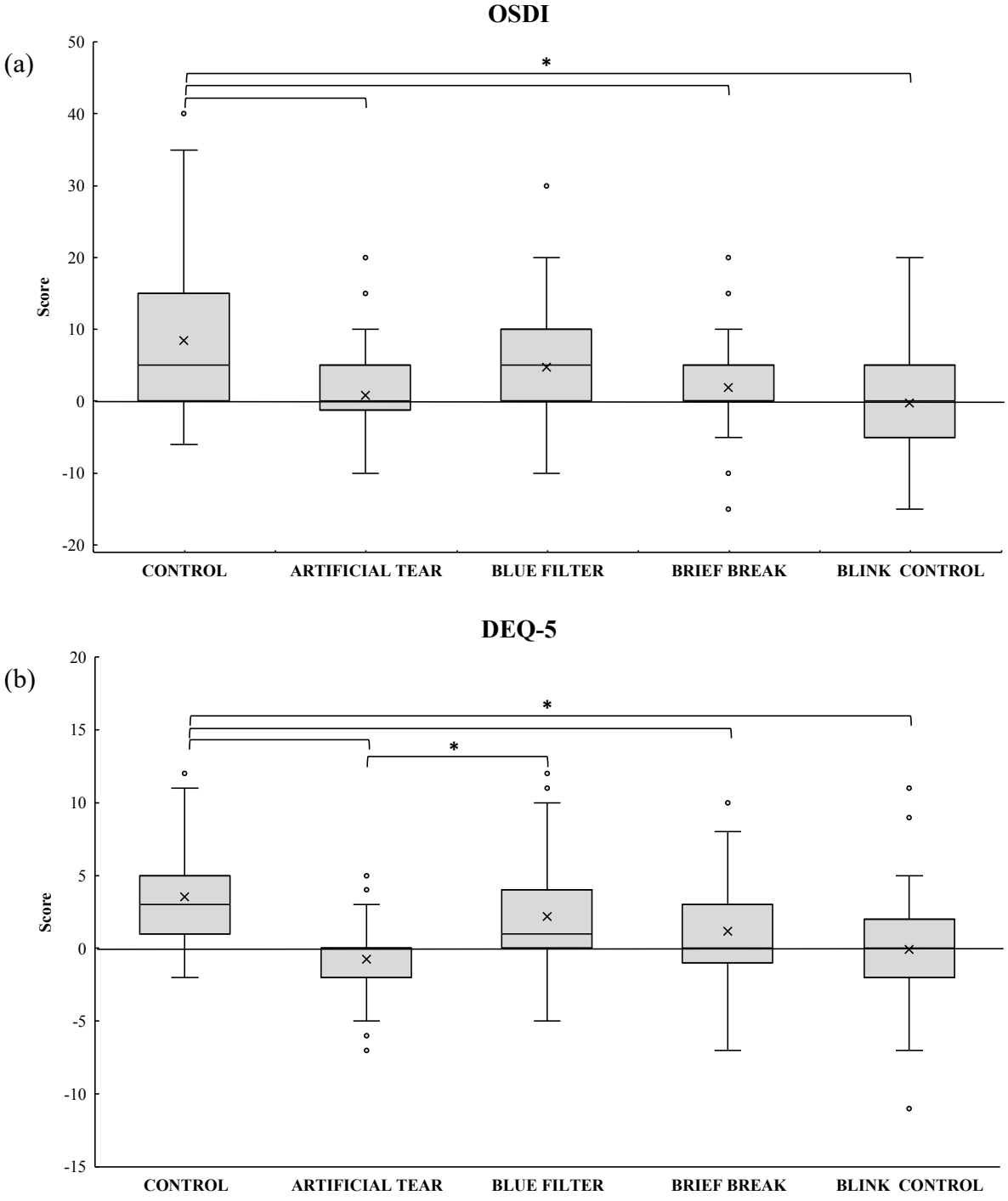


Figure 8.1. Boxplots of the differences in dry eye symptoms reported before and after the control computer task and the computer task with the different management strategies: (a) Ocular Surface Disease Index (OSDI), (b) 5-item Dry Eye Questionnaire (DEQ-5). * Indicates statistical significance ($p < 0.05$).

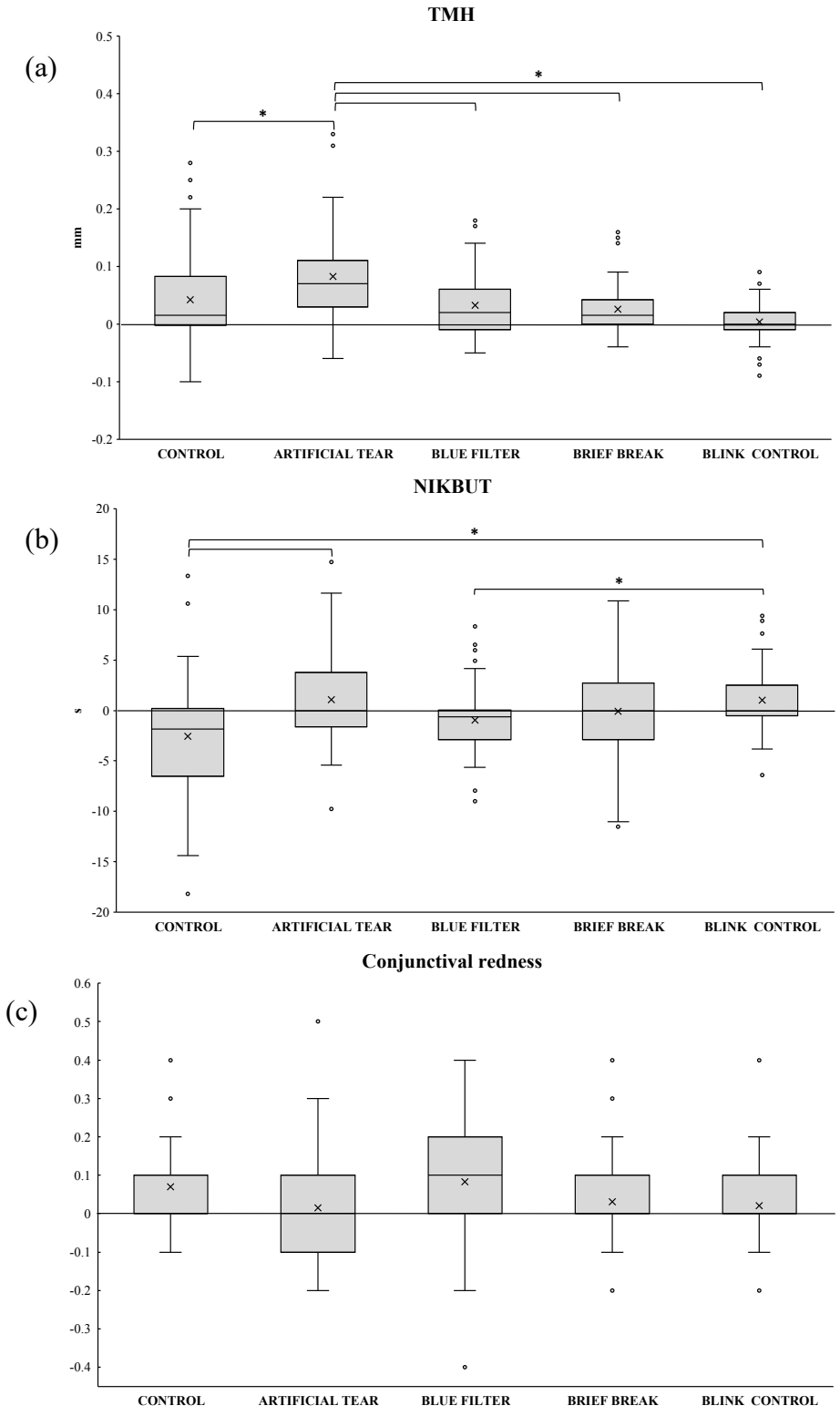


Figure 8.2. Boxplots of the differences in ocular surface and tear film variables obtained before and after the control computer task and the computer task with the different management strategies: (a) tear meniscus heigh (TMH), (b) non-invasive keratograph break-up time (NIKBUT), (c) conjunctival redness. * Indicates statistical significance ($p < 0.05$).

8.4 Discussion

According to the results of this study, artificial tear instillation and blink control were the best management strategies for preventing the short-term effects of computer on dry eye signs and symptoms. Conversely, taking a brief break halfway through the task or using a blue-light blocking filter offered limited benefits.

The results of this study revealed both a statistically and clinically significant increase in dry eye symptoms after reading on the computer for 20 minutes. This is in accordance with the accepted theory of DES, recognized as a health problem for over 30 years (Dain et al., 1988). Likewise, tear stability reduced on average by 2.6 s, whereas conjunctival redness was significantly greater after task performance, indicating tear film destabilization and ocular surface stress with short-term computer use. This is in line with the findings of Chapters 6 (*6. How do different digital displays affect the ocular surface?*; Talens-Estarelles et al., 2020) and 7 (*7. Ocular surface predisposing factors for digital display-induced dry eye*; Talens-Estarelles et al., 2022c) and with previous research (Cardona et al., 2011; Uchino et al., 2013).

Chapter 6 (*6. How do different digital displays affect the ocular surface?*; Talens-Estarelles et al., 2020), as well as other studies (Cardona et al., 2011) found significantly lower TMH and Schirmer test results after computer use. Nevertheless, these studies either carried out the measures in separate sessions or assessed long-term effects in office workers. Conversely, Choi et al. (2018) obtained no difference in tear volume (TMH and Schirmer test), when measurements were taken before and after 1 hour of computer use under controlled conditions. Nielsen et al. (2008) reported a compensatory burst of blinks right after cessation of an active digital display task. The authors attributed this phenomenon to compensation for the oppression of blinking during the digital display task and, therefore, as a wetting process secondary to ocular surface disturbance. As discussed in Chapter 7 (*7. Ocular surface predisposing factors for digital display-induced dry eye*; Talens-Estarelles et al., 2022c), considering the greater dry eye symptoms reported by the participants in the present study, the higher TMH obtained following the non-management computer task could be due to compensatory tearing secondary to ocular surface stress.

In this study, the instillation of artificial tears was capable of completely preventing an increase in dry eye symptoms with computer use. This strategy additionally revealed a significantly lesser worsening of symptoms compared to performing the

reading task with no management strategy or using a blue light filter. Artificial tears are widely acknowledged as an effective approach for ameliorating dry eye symptoms (Craig et al., 2021). High viscosity drops, such as those of this study, have been shown to regularize the interblink interval and relief ocular symptoms during digital display work (Acosta et al., 1999).

Moreover, the instillation of artificial tears proved to be significantly beneficial in preventing a drop in tear stability. In addition, the use of lubricating eye drops led to a significantly greater increase in tear volume compared to the other management strategies. Sodium hyaluronate tears have been shown to have a prolonged residence time and significantly increase TMH and TBUT, even 20 minutes after instillation (Carracedo et al., 2019). Likewise, the use of artificial tears has been shown to be effective in recovering the tear film in individuals with dry eye symptoms associated with extra hours of computer use (Calvão-Santos et al., 2011). Nevertheless, considering that the residence time of artificial tears on the ocular surface is limited, the benefits of initial artificial tear instillation before device use are probably transient and may not be significant after longer durations of display visualization.

Blink control prevented both an increase in dry eye symptoms and a worsening of ocular surface and tear film variables following computer use. In addition, this strategy proved to be significantly more beneficial in preserving tear stability compared to the use of a blue light filter. The use of digital displays has been shown to alter normal blinking by reducing the blink rate and increasing the percentage of incomplete blinks (Chu et al., 2010; Portello et al., 2013). Controlling blinking by means of an acoustic order not only prevented a reduction in blink rate but led to voluntary blinking which has been shown to increase blink amplitude and eliminate incomplete blinking (Sanchis-Jurado et al., 2020).

Accordingly, techniques based on blink control and blink training may be helpful strategies in symptomatic digital display users. Ang et al. (2014) found an increase in post-task tear stability and a reduction in ocular surface symptoms when reading on a computer for 20 minutes when blinking was stimulated every 5 s compared to a control measurement. Conversely, Portello and Rosenfield (2010) did not find a significant reduction in DES symptoms when blinking was controlled during short-term computer reading by means of a metronome, to produce a blink every 4 s. Dry eye symptoms do not account for all the symptoms associated with DES, and the benefits of blink control in their study may have been masked by an increase in other symptoms of DES. Despite

these benefits, many participants in the present study reported that constant conscious blinking made reading difficult.

As previously mentioned, longer periods of display visualization have been associated with greater tear film abnormalities and ocular surface dryness (Choi et al., 2018; Wu et al., 2014). Therefore, regular breaks are generally recommended for screen users. In this study, taking a brief break halfway through the reading prevented a significant increase in OSDI but not in DEQ-5. Nevertheless, this strategy significantly reduced the impact of computer use on dry eye symptoms for both questionnaires. Likewise, taking a brief break prevented a significant increase in conjunctival redness following computer use. Nevertheless, the brief rest period did not prevent a significant increase in TMH, which probably reveals some degree of ocular surface stress. According to the findings of the present study, taking regular breaks may partially reduce the impact of short-term digital display use on dry eye signs and symptoms, although this strategy should be applied in conjunction with others to fully prevent the disruption of the ocular surface.

Recently, the blue light emitted by digital displays has been suggested as contributing factor to dry eye (Zhao et al., 2018). In the present study, the use of a blue light filter did not prevent an increase in dry eye signs or symptoms, and all the variables assessed were significantly worse after completion of the task. Likewise, this management strategy was not significantly better than reading with no filter in preventing an increase in dry eye symptoms or a worsening of signs and was significantly worse in reducing dry eye symptoms and tear instability than artificial tears or blink control, respectively. Similarly, Cheng et al. (2014) showed no improvement in Schirmer test in a group of dry eye and non-dry eye patients after wearing low, medium, and high-density blue light filters.

Nevertheless, despite statistical significance, the use of a blue light filter partially reduced dry eye symptoms and led to a lower decrease in NIKBUT after task performance than the control condition. Screen filters can be useful for reducing screen reflections and luminance and improving contrast (Thomson, 1998). The better image quality on the display screen and the reduced glare can decrease squinting and alter blinking to a lesser extent (Gowrisankaran et al., 2007; Palavets & Rosenfield, 2019; Sheedy et al., 2005). Accordingly, in this study, the blue light filter may have offered some benefits by acting as a conventional filter and reducing screen luminance, thus improving image quality and

participants' comfort. Palavets and Rosenfield (2019) found that a filter that eliminated 99% of the emitted blue light from a tablet computer reduced DES symptoms, although was not more effective than an equivalent neutral density filter.

Finally, this study had some limitations to consider. Owing to the subjective evaluation of symptoms, a nocebo/placebo effect on results cannot be completely ruled out. Moreover, a 20-minute task duration was chosen, which may not be representative of modern durations of device usage. This may have led to fewer signs and symptoms of dryness than expected after longer periods of display use. Nevertheless, task duration was determined based on previous research of similar nature and to prevent fatigue effects and ensure the correct compliance of the participants with the task. In addition, reading on the computer may not represent a typical display task undertaken by most young adults. However, a reading task was chosen to carefully control and adjust study variables and ensure a constant cognitive demand throughout the entire task and between sessions.

All things considered, the instillation of high-viscosity artificial tears and blink control were the best management strategies for preventing short-term effects of digital display use on dry eye signs and symptoms. Techniques based on blink control can be useful management strategies, although they may hinder task performance. Taking regular, brief breaks may partially reduce ocular desiccation, and should not be advised in isolation. Finally, using a blue light filter was not found to be effective in preventing dry eye signs and symptoms during computer use. Further studies are needed to confirm these findings. This study establishes the basis for future works, which would evaluate the benefits of different management strategies to reduce the effects of digital display use on dry eye after longer exposure times and/or under different experimental conditions.

9.

Digital display use and contact lens wear: Effects on dry eye signs and symptoms

9.1 Introduction

CL wear is widely recognised as one of the main risk factors for DED (Stapleton et al., 2017), with data suggesting a prevalence up to four times higher in CL users (Tan et al., 2015). CL wear leads to a thinner and irregular lipid layer with deficient tear spreading and wettability, tear film instability, increased tear evaporation and osmolarity, lower basal tear turnover rate and decreased tear volume (Del Águila-Carrasco et al., 2015; Hori, 2018; Santomingo-Rubido et al., 2006; Yokoi et al., 2008).

Research indicates a greater prevalence of dry eye symptoms and ocular surface abnormalities in CL wearing computer workers as compared to non-CL wearers (González Méijome et al., 2007; Tauste et al., 2016, 2018). Likewise, in Chapter 4 (*4. Dry eye-related risk factors for digital eye strain*; Talens-Estarelles et al., 2022b) it was found that CL wear was independently associated with suffering from DES and that greater symptoms of CL discomfort and dryness were associated with greater symptoms of DES. In parallel, Chapters 5 (*5. Blinking kinematics characterization during digital displays use*; Talens-Estarelles et al., 2022a) and 6 (*6. How do different digital displays affect the ocular surface?*; Talens-Estarelles et al., 2020) showed that different digital displays impact blinking and the ocular surface to different extents, while Chapter 8 (*8. Determining the best management strategy for preventing short-term effects of digital display use on dry eyes*; Talens-Estarelles et al., 2022d) evidenced that the instillation of artificial tears was the best management strategy to prevent the effects of digital display use on the ocular surface and tear film.

All things considered, the present chapter aimed to assess the potential additive effects of computer or smartphone use and CL wear on the ocular surface and tear film in a sample of young, healthy individuals under three different experimental conditions: reading without correction, with CL wear and CL wear with the instillation of artificial tears.

9.2 Methods

9.2.1 Participants

Thirty-four young, current soft CL wearers ranging in age from 18 to 26 years participated in this study. Inclusion criteria were age ≥ 18 and ≤ 35 years, use of soft CLs, maximum spectacle astigmatism of 0.75 D, CDVA better or equal to 20/20 (0.00

logMAR) and normal binocularity. Exclusion criteria were posterior or anterior segment pathologies, eyelid disease and a history of eye surgery. All the participants wore either monthly or daily-disposable CLs.

The study followed the tenets of the Declaration of Helsinki and was approved by the University of Valencia human research ethics committee. All the participants were informed about the nature of the study and gave their written consent.

9.2.2 Experimental design and apparatus

Dry eye signs and symptoms were evaluated before and after executing a 20-minute reading task with a modern laptop computer and a smartphone under three different experimental conditions: with the naked eye, CL wear and CL wear with initial instillation of artificial tears. A 20-minute task was chosen following previous chapters (Chapters 6-8) and research of a similar nature which reported significant tear film changes after similar periods of display use (Bilkhu et al., 2021; Choi et al., 2018; Yazici et al., 2015). The experimental design mirrored that of previous chapters (Chapters 5-8).

Dry eye symptoms were evaluated using the OSDI and DEQ-5. Both questionnaires were included to assess a broader range of dry eye symptoms and provide a detailed study of the effects of CL wear and digital device use on dry eye symptomatology. The participants were instructed to respond to a modified version of the questionnaire to match the aim of the present study. The OSDI includes three subscales: ocular symptoms, vision-related activities of daily living and environmental triggers. Participants were instructed to respond based on their sensation during the visit and only to the ocular symptom subscale (i.e., the first five questions), thus excluding questions that were not applicable to the task (wind, driving at night, watching TV, etc.). The OSDI score ranges from 0 to 100, with higher scores corresponding to the severity of the symptoms. The DEQ-5 score was obtained as in its original version (i.e., the sum of all individual questions). This approach was similar to that adopted in previous chapters (Chapters 7 and 8) and studies (Choi et al., 2018; Yazici et al., 2015).

Tear film and ocular surface parameters, including TMH, conjunctival redness and NIKBUT were assessed using the Keratograph 5M (Oculus Optikgerate, Wetzlar, Germany) (*3.2.2 Oculus Keratograpgh 5M, 3. General methods*). NIKBUT was measured 3 times and an average value was obtained. Detailed information on the questionnaires and measurement procedures can be found in Chapter 3 (*3.2 Measurements and devices, 3. General methods*).

The text material was a compilation book of Edgar Allan Poe's short stories in Spanish. The text was displayed using the Kindle reading app (Amazon Inc., Seattle, WA, USA). Text characteristics were selected from the Kindle app interface and set as equal on the different digital devices in terms of font style (Georgia font with black letters on a white background), angular size (appropriately chosen for each device for a 0.15 logMAR visual acuity), angular line spacing, number of words per line and page, page angular width (appropriately chosen for each device for a 25° width) and text alignment (left-justified). In addition, screen luminance was equalised by modifying the display brightness level in settings.

Digital displays included a MacBook Air Retina laptop computer (Apple Inc., Cupertino, CA, USA), with a 13-inch screen, a resolution of 227 ppi, refresh rate of 60 Hz and a contrast ratio of 1350:1; and an iPhone 6 smartphone (Apple Inc.), with a 4.7-inch screen, 326 ppi, 60-Hz refresh rate and 1000:1 contrast ratio. Each digital display was positioned based on a typical viewing distance and angle of usage: that is, 60 cm and approximately 10° below eye level for the laptop computer and 30 cm and 45° for the smartphone (Bababekova et al., 2011).

Room illuminance was maintained at approximately 220 lux at the plane of the participants' eyes. A Chroma Meter CL-200 (Konica Minolta, Ramsey, NJ, USA) was used to measure photometric values. Room temperature and humidity were constantly monitored and remained stable at 23.3 ± 1.3°C and 43 ± 5%, respectively.

9.2.3 Contact lenses

All the participants were fitted in both eyes with a daily-disposable CL (Dailies Total One., Alcon Laboratories Inc. Fort Worth TX, USA) (Table 9.1). CLs were ordered from the manufacturer according to the refractive error of the participants. The lens fit assessment process was carried out according to the fitting procedure described by Chamberlain et al. (2011). After an adaptation period of 5 minutes, standard high-contrast distance logMAR visual acuity was measured, as well as standard CL assessment of centration, movement and corneal coverage using the 5-point grading system (Morgan & Efron, 2002). Participants were given a total of four identical pairs of lenses, one for each session requiring CL wear, and were instructed to insert them 60 minutes ahead of their visit. Participants were instructed not to wear their CLs for 24 hours before the study visit.

Table 9.1. Technical specifications of the contact lens fitted in this study.

Parameter	Contact Lens
Material	Delefilcon A
Refractive index	1.34
Water content (%)	33 (nucleus), > 80 (surface)
Dk/t (barrer/cm)	156
CT (mm)	0.09
BCOR (mm)	8.5
TD (mm)	14.1
Power range	+6.00 D to -12.00 D
Lens design	Spherical
Manufacturer	Alcon Inc.

BCOR = Back central optic radius; CT = Centre thickness; Dk/t = oxygen transmissibility; TD = Total diameter.

9.2.4 Protocol

The participants completed each of the six experimental conditions in a randomised order: (1) reading on the computer without CLs; (2) reading on the smartphone without CLs; (3) reading on the computer with CLs; (4) reading on the smartphone with CLs; (5) reading on the computer with CLs and instillation of artificial tears; and (6) reading on the smartphone with CLs and instillation of artificial tears. Each condition was tested in separate sessions with a rest period of 7 days between sessions. To minimize day-to-day variability of the tear film, each session was carried out on the same day of the week, at the same time of day and under the same, constant environmental conditions (temperature and humidity). Fifteen minutes before the visit of the participants, the laboratory was acclimatised, and the experimental conditions were set up. To minimise the effects of outdoor conditions on the way to the laboratory, a 15-minute acclimatisation period was allowed between entry into the room and the measurements being obtained.

After the acclimatisation period, dry eye signs and symptoms were evaluated. Measurements were performed in the following order: OSDI, DEQ-5, TMH, conjunctival redness and NIKBUT. NIKBUT was measured three times and an average value obtained. The measurements were performed on the right eye for all the participants.

The participants then received instructions on the reading task. When required, one drop of Systane Ultra (Alcon SL, Geneva, Switzerland) single-dose artificial tears was instilled on each eye, 2 minutes before starting reading.

After the reading task, the battery of standard clinical tests was repeated. The measurements were performed within 3 minutes after the task. The participants were instructed to report symptoms experienced during device use, for a direct comparison with the pre-task score. All the measurements were taken by the same experienced examiner to reduce the variability of data.

9.2.5 Statistical analysis

The results were evaluated using the SPSS software v.26 (IBM Corp, Armonk, NY, USA). The normality of data was assessed using the Shapiro-Wilk test. When normality could be assumed, a paired-sample t test was used to examine differences between pre-and post-task measurements for each variable. The non-parametric Wilcoxon paired signed-rank test was used when parametric test assumptions were not fulfilled. To compare the impact of the different conditions, the difference between the post-and pre-task measurements was calculated for each variable. A repeated-measures ANOVA was used to compare the results for the six task conditions. Please refer to Chapter 3 for more information on repeated-measures ANOVA (*3.3.3.3 Differences between three or more repeated measurements, 3. General methods*). The nonparametric Friedman test for repeated measures with Dunn-Bonferroni post-hoc analysis was used when parametric test assumptions were not fulfilled.

9.3 Results

Thirty-seven Caucasian volunteers were initially recruited, out of which 34 (10 males and 24 females) ranging in age from 18 to 26 years (21 ± 2 years) met the inclusion/exclusion criteria and completed all visits. Table 9.2 shows the results for each variable, both before and after digital display use, with and without CL wear or artificial tear instillation. The table also shows statistical comparisons. Table 9.3 indicates the calculated post-task/pre-task differences for each variable, along with the statistical comparisons. Figures 9.1 and 9.2 illustrate boxplots of dry eye symptomatology and ocular surface pre-task/post-task differences, respectively.

The results indicate that reading on the computer and the smartphone without CLs led to higher post-task symptoms (OSDI and DEQ-5), conjunctival redness and TMH compared to pre-task ($p \leq 0.02$). Likewise, the results showed a significantly shorter NIKBUT after task performance when reading on the computer without CLs ($p = 0.008$), while no difference was obtained for this parameter when reading on the smartphone ($p = 0.11$) (Table 9.2).

When examining the influence of CL wear, participants reported higher post-task dry eye symptoms (OSDI and DEQ-5) when reading on both devices compared with pre-task levels ($p \leq 0.01$). Additionally, reading on the computer during CL wear led to a significantly greater post-task conjunctival redness ($p = 0.02$) and shorter NIKBUT ($p = 0.02$) compared with pre-task, while TMH remained unchanged ($p = 0.23$). Conversely, no significant changes in conjunctival redness ($p = 0.08$) or NIKBUT ($p = 0.73$) were found when reading on the smartphone with CLs, although TMH was significantly higher after the task ($p = 0.001$) (Table 9.2). Lastly, TMH increased significantly less when reading on the computer with CLs compared to without CLs ($p = 0.005$), though no other differences were observed between the CL and non-CL conditions ($p > 0.05$) (Table 9.3, Figures 9.1 and 9.2).

Finally, when examining the influence of artificial tear instillation during CL wear, results revealed no significant change in symptoms when reading on any of the devices ($p \geq 0.68$) (Table 9.2). Reading on the computer or the smartphone with CLs and artificial tear instillation led to a significantly smaller increase in symptoms compared with the non-artificial tear conditions ($p < 0.001$) (Table 9.3, Figure 9.1).

Moreover, no changes in conjunctival redness or NIKBUT were observed when reading on the computer with CLs when artificial tears were instilled ($p \geq 0.55$), while post-task TMH was significantly higher than pre-task ($p = 0.001$). Similarly, conjunctival redness remained unchanged ($p = 0.77$), while TMH was significantly higher ($p < 0.001$) after reading on the smartphone with CLs compared to pre-task when artificial tears were instilled. Nevertheless, contrary to the analogous computer condition, a greater post-task NIKBUT was found after reading on the smartphone with CLs and artificial tears compared to pre-task ($p = 0.04$) (Table 9.2). Lastly, reading on the smartphone with CLs and artificial tears led to a higher increase in TMH in comparison with reading on the computer with CLs but no artificial tear instillation ($p = 0.04$) (Table 9.3, Figure 9.2).

Table 9.2. Ocular surface and tear film variables obtained before (pre-task) and after (post-task) reading on the computer or the smartphone with and without contact lens wear and artificial tear instillation. Data are presented as mean [95% confidence intervals].

		OSDI	p-value	DEQ-5	p-value	TMH (mm)	p-value	Conjunctival redness	p-value	NIKBUT (s)	p-value
Computer	**Pre-Task**	6.3 [3.3 – 9.3]	< 0.001*[2]	4 [3 – 6]	< 0.001*[2]	0.21 [0.19 – 0.24]	< 0.001*[2]	0.5 [0.4 – 0.6]	0.003*[2]	15.2 [12.6 – 17.9]	0.008*[2]
	Post-Task	17.2 [11.0 – 23.4]		8 [6 – 10]		0.28 [0.24 – 0.31]		0.6 [0.5 – 0.8]		12.5 [9.9 – 15.1]	
Computer + CL	**Pre-Task**	8.4 [3.9 – 12.9]	< 0.001*[2]	4 [2 – 5]	< 0.001*[2]	0.19 [0.16 – 0.21]	0.23[2]	0.5 [0.4 – 0.6]	0.02*[2]	8.6 [7.0 – 10.3]	0.02*[2]
	Post-Task	19.6 [12.8 – 26.3]		7 [6 – 9]		0.20 [0.18 – 0.22]		0.6 [0.4 – 0.7]		7.4 [5.8 – 9.1]	
Computer + CL + AT	**Pre-Task**	9.4 [4.6 – 14.2]	0.82[2]	3 [2 – 5]	0.69[2]	0.19 [0.17 – 0.21]	0.001*[2]	0.5 [0.4 – 0.6]	0.97[2]	8.4 [6.6 – 10.2]	0.55[2]
	Post-Task	9.1 [5.0 – 13.3]		3 [2 – 4]		0.23 [0.20 – 0.26]		0.5 [0.4 – 0.6]		9.1 [7.0 – 11.1]	
Smartphone	**Pre-Task**	10.4 [5.4 – 15.5]	< 0.001*[2]	5 [3 – 6]	0.005*[2]	0.22 [0.20 – 0.25]	0.02*[1]	0.5 [0.4 – 0.6]	0.006*[2]	14.0 [11.5 – 16.6]	0.11[2]
	Post-Task	15.2 [9.0 – 21.3]		7 [5 – 8]		0.25 [0.23 – 0.27]		0.6 [0.5 – 0.7]		12.7 [10.1 – 15.2]	
Smartphone + CL	**Pre-Task**	7.4 [3.6 – 11.1]	0.001*[2]	3 [2 – 5]	0.001*[2]	0.18 [0.16 – 0.19]	0.001*[1]	0.4 [0.4 – 0.5]	0.08[2]	8.6 [6.5 – 10.6]	0.73[2]
	Post-Task	12.9 [7.8 – 18.1]		5 [3 – 6]		0.20 [0.19 – 0.22]		0.5 [0.4 – 0.6]		8.9 [6.8 – 11.0]	
Smartphone + CL + AT	**Pre-Task**	6.0 [2.7 – 9.3]	0.68[2]	3 [2 – 4]	0.87[2]	0.19 [0.17 – 0.20]	< 0.001*[1]	0.5 [0.4 – 0.5]	0.77[2]	10.0 [7.8 – 12.1]	0.04*[1]
	Post-Task	6.5 [3.2 – 9.7]		3 [2 – 4]		0.23 [0.21 – 0.24]		0.5 [0.4 – 0.6]		11.4 [9.3 – 13.6]	

AT = Artificial tear; CL = Contact lens; DEQ-5 = 5-item Dry Eye Questionnaire; NIKBUT = Non-invasive keratograph break-up time; OSDI = Ocular Surface Disease Questionnaire; TMH = Tear meniscus height. * Indicates statistically significant values ($p < 0.05$). [1] Paired t-test. [2] Wilcoxon paired signed-rank test.

Table 9.3. Differences between post-task and pre-task ocular surface and tear film variables obtained when reading on the computer or the smartphone with and without contact lens wear and artificial tear instillation. Data are presented as mean [95% confidence intervals].

Variable	Computer (C)	Computer + CL (C-CL)	Computer + CL +AT (C-CL+AT)	Smartphone (S)	Smartphone + CL (S-CL)	Smartphone + CL + AT (S-CL+AT)	p-value	Statistically significant post-hoc differences (p-value)
OSDI	10.9 [6.3 – 15.5]	11.2 [5.6 – 16.7]	-0.3 [-3.0 – 2.4]	4.7 [1.9 – 7.5]	5.6 [2.2 – 9.0]	0.4 [-1.3 – 2.2]	< 0.001*[2]	C / C-CL+AT (0.02) C / S-CL+AT (0.002) C-CL / C-CL+AT (< 0.001) C-CL / S-CL+AT (< 0.001)
DEQ-5	4 [2 – 6]	4 [2 – 5]	0 [-2 – 1]	2 [1 – 3]	2 [1 – 3]	0 [-1 – 1]	< 0.001[2]	C / C-CL+AT (0.004) C / S-CL+AT (0.001) C-CL / C-CL+AT (< 0.001) C-CL / S-CL+AT (< 0.001)
TMH (mm)	0.06 [0.03 – 0.09]	0.01 [-0.01 – 0.03]	0.04 [0.01 – 0.06]	0.03 [0.01 – 0.05]	0.02 [0.01 – 0.04]	0.04 [0.02 – 0.06]	0.004*[2]	C / C-CL (0.005) C-CL / S-CL+AT (0.04)
CR	0.1 [0.0 – 0.2]	0.1 [0.0 – 0.1]	0.0 [0.0 – 0.1]	0.1 [0.0 – 0.1]	0.0 [0.0 – 0.1]	0.0 [-0.1 – 0.0]	0.001*[2]	C / C-CL+AT (0.04) C / S-CL+AT (0.03)

NIKBUT (s)	-2.7 [-4.6 – -0.9]	-1.2 [-2.5 – 0.0]	0.6 [-0.9 – 2.2]	-1.4 [-3.3 – 0.5]	0.3 [-1.4 – 2.1]	1.5 [0.0 – 3.0]	0.01*[2]	C / S-CL+AT (0.02)

AT = Artificial tear; CL = Contact lens; CR = Conjunctival redness; DEQ-5 = 5-item Dry Eye Questionnaire; NIKBUT = Non-invasive keratograph break-up time; OSDI = Ocular Surface Disease Questionnaire; TMH = Tear meniscus height. * Indicates statistically significant values ($p < 0.05$). [1] Repeated-measures ANOVA. [2] Friedman.

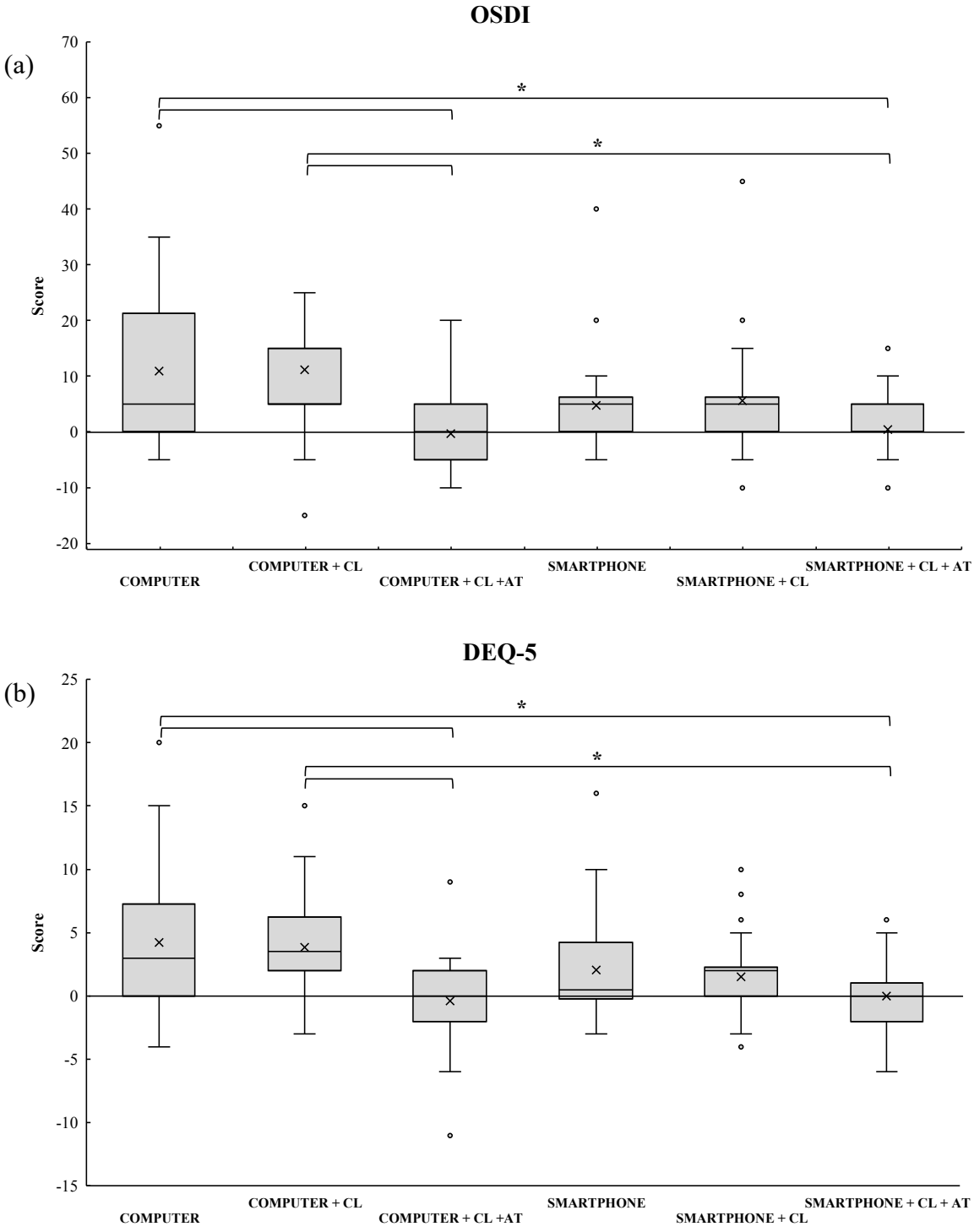


Figure 9.1. Boxplots of the differences between post-task and pre-task (a) Ocular Surface Disease Index (OSDI) and (b) 5-item Dry Eye Questionnaire (DEQ-5) scores obtained when reading on the computer or the smartphone with and without contact lens wear and artificial tear instillation. * Indicates statistical significance ($p < 0.05$).

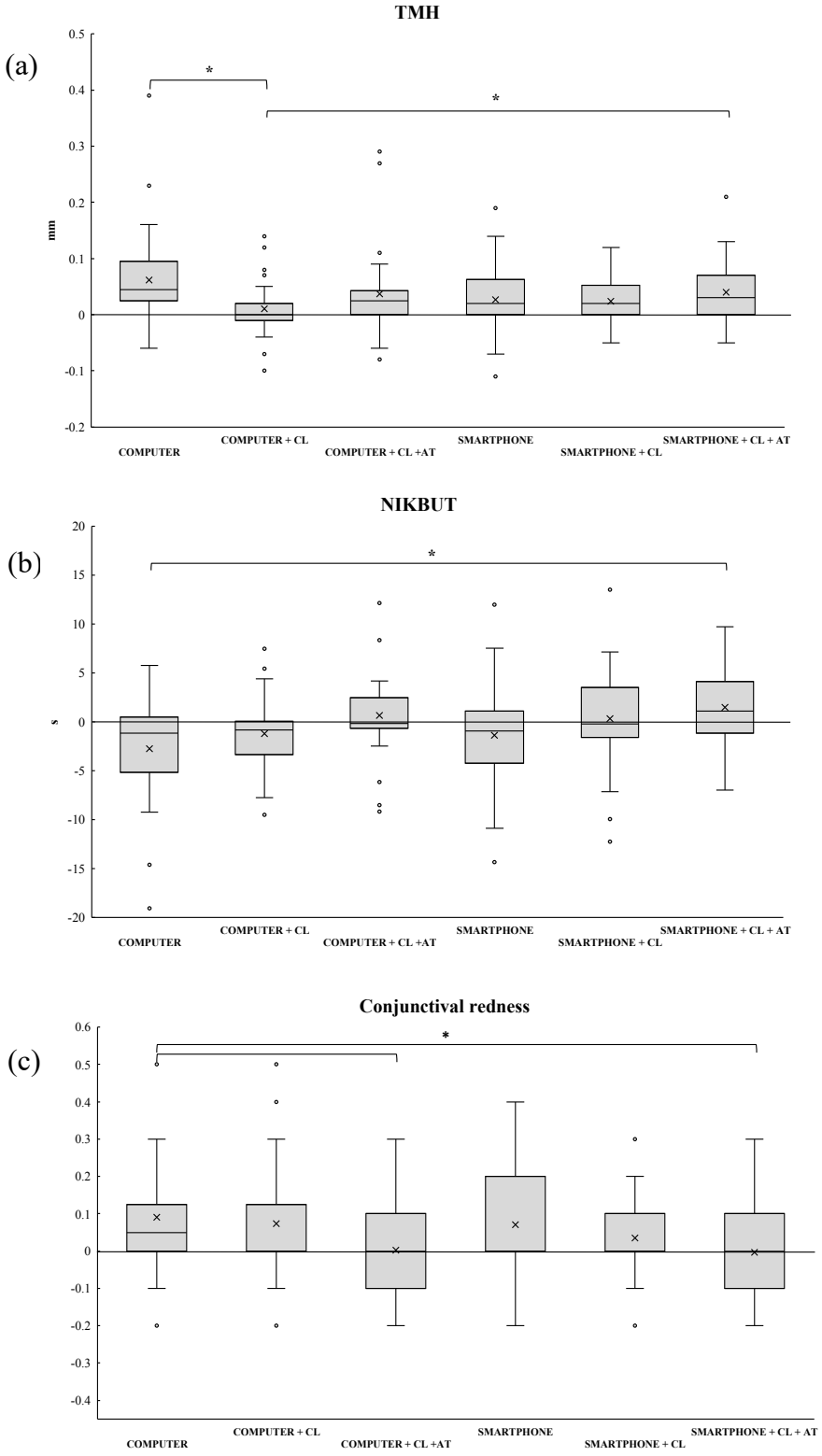


Figure 9.2. Boxplots of the differences between post-task and pre-task (a) tear meniscus height (TMH), (b) conjunctival redness and (c) non-invasive keratograph break-up time (NIKBUT) obtained when reading on the computer or the smartphone with and without contact lens wear and artificial tear instillation. * Indicates statistical significance ($p < 0.05$).

9.4 Discussion

In the present study, reading on the computer or the smartphone for 20 minutes led to an increase in dry eye signs (NIKBUT and conjunctival redness) and symptoms, indicating tear film destabilisation and ocular surface stress. This is in accordance with previous research (Bilkhu et al., 2021; Choi et al., 2018; Uchino et al., 2013; Yazici et al., 2015) and with the findings of previous chapters (Chapters 5-8). Conversely, reading on the smartphone did not significantly reduce tear stability (i.e., NIKBUT). According to the findings of previous chapters (Chapters 4-6), using the smartphone may be less harmful to the ocular surface than the computer, due to a lower gaze angle resulting in a smaller palpebral fissure and reduced ocular surface exposure. The same outcome can be observed in the CL condition, in which reading on the smartphone with CLs did not worsen eye redness or NIKBUT. Based on these findings, device position may play a relevant role in dry eye signs during CL wear, although specific research is needed on the matter before drawing firm conclusions.

As in previous chapters (Chapters 7 and 8), a significant increase in TMH was obtained after reading from each display without CLs. Considering the worsening of dry eye signs and symptoms observed in the present study, the higher TMH found after reading from each display could be due to compensatory tearing acting as a wetting process following ocular surface stress (Nielsen et al., 2008) .

Most importantly, CL wear did not lead to a greater increase in symptoms or signs of dry eye compared to the non-CL condition. Numerous studies have reported an increase in dry eye symptoms in computer workers who wore CLs (González Méijome et al., 2007; Kojima et al., 2011; Tauste et al., 2016, 2018). Contrary to the present study, González-Méijome et al. (2007) found that soft CL wearers who worked with digital displays for longer periods were more likely to develop ocular symptoms such as burning and itching than non-CL wearers. Similarly, Tauste et al. (2016) found that workers who wore CLs and used the computer for more than 6 hours/day were more likely to suffer DES than non-CL wearers who worked on the computer for the same amount of time. In the years following these studies, the authors also found that computer workers who wore CLs were more likely to suffer bulbar, limbal and lid redness, and lid roughness (Tauste et al., 2018).

Differences with previous research may be due to considerable dissimilarities in the experimental design or the smaller sample size of the present study, among other possibilities. For instance, previous research assessed and compared the long-term effects

of computer use in CL and non-CL wearing office workers (Kojima et al., 2011; Tauste et al., 2016), whereas the present study evaluated the impact of CL wear and digital display use under controlled conditions and shorter time frames. Also, given that all the participants in the present study were fitted with the same daily-disposable CL after a washout period of at least 24 hours, alterations associated with CL maintenance or previous CL wear were either not present or unprovable. In addition, in the present study participants were assessed in the mornings; thus, unfavourable effects of long periods of CL wear on dry eye signs and symptoms were unprovable, which may further explain the discrepancies with earlier published results, where dry eye parameters were assessed at the end of the wearing day (Chalmers & Begley, 2006; Vermeltfoort et al., 2006).

Additionally, the delefilcon A daily-disposable water gradient CLs used in the present study have been shown to offer good patient satisfaction along with high oxygen transmissibility with a lubricious surface and a low coefficient of friction (Pérez-Gómez & Giles, 2014; Pruitt et al., 2012). Therefore, while more research is needed on the benefits of this material for DED, the properties of the lenses used in the present study could have helped prevent an additive effect between CL wear and device reading.

Despite a significant increase in TMH after reading on the computer with the naked eye, no significant increase was found when reading with CLs. Similarly, previous research reported no differences in the Schirmer test between CL and non-CL wearing computer workers (Tauste et al., 2018). Based on previous research, the high-water content of the CLs fitted in the present study may have absorbed part of the tear fluid secreted into the CL matrix, subsequently leading to a lower increase in post-task TMH compared to the non-CL condition (Kojima, 2018; Wang et al., 2009).

Lubricating eye drops have been shown to effectively regulate the interblink interval and relieve ocular symptoms during computer work (Acosta et al., 1999). In the present study, reading with CLs without artificial tears caused a greater increase in dry eye symptoms than when artificial tears were instilled, though no differences were observed in dry eye signs. As found in Chapter 8 (*8. Determining the best management strategy for preventing short-term effects of digital display use on dry eyes*; Talens-Estarelles et al., 2022d) and reported in the literature (Calvão-Santos et al., 2011), sodium hyaluronate artificial tears have proven effective in recovering the tear film in individuals with dry eye symptoms associated with computer use. In the present study, Systane Ultra artificial tears containing propylene glycol and polyethylene glycol were instilled. Various studies have shown that these agents are effective in reducing signs and

symptoms associated with dry eye, providing extended ocular surface protection and symptom relief, and that they are well tolerated among individuals who wear CLs (Davitt et al., 2010; Kading, 2010; Srinivasan & Manoj, 2021). Likewise, in several clinical studies comparing this brand of artificial tears with other marketed lubricant eye drops, it was generally superior to the active comparator (Davitt et al., 2010; Ousler et al., 2007; Srinivasan & Manoj, 2021). Therefore, these artificial tears may have been especially beneficial for symptomatic display users who wear CLs.

The present study had some limitations. Modified versions of questionnaires were used to assess the change in symptomatology with display use. This was done in the absence of an appropriate questionnaire to assess the change in symptoms after a short task. Also, due to the subjective evaluation of symptoms, the nocebo/placebo effect on results cannot be ruled out. Additionally, while some symptoms may be clearly associated with dry eye, others, such as blurred or degraded vision, can also be linked with accommodative or vergence stress, which may appear while viewing the device. In the present study, participants were asked to respond to questionnaires based merely on any symptoms of dryness that they experienced. Finally, the present study assessed the impact of CL wear during short test periods, which may not be representative of modern durations of device usage. Consequently, this may have resulted in fewer signs and symptoms of dryness than might be expected after longer periods of work. The present study establishes the basis for future work, which would assess the effects of longer periods of device use in CL wearers under controlled conditions.

In conclusion, the use of CLs during short periods of digital display use significantly increased signs and symptoms of dry eye compared with pre-task levels, although this increase was not greater than when reading on displays without CLs. The instillation of artificial tears is an effective strategy for counteracting the effects of digital display use on dry eye signs and symptoms in both CL wearers and non-wearers. Research is required on larger samples to confirm these findings and to assess the impact of device position and examine the effects of different CL materials and wearing modalities on dry eye during device usage.

10.

Ocular surface changes following computer use in post-LASIK patients

10.1 Introduction

LASIK is the most commonly performed surgery to correct refractive error (Ang et al., 2021) and is especially popular among young adults, generally 20 to 40 years old (López-Montemayor et al., 2016). LASIK remains the gold standard of laser refractive surgery sin it appeared, largely because it is a safe, effective, and well-established procedure that offers many advantages, such as a fast and painless visual rehabilitation, low probability of regression, and the absence of subepithelial corneal haze (Ang et al., 2021; Kim et al., 2019; Wen et al., 2017). While patients are typically satisfied with outcomes after their procedure (Pasquali et al., 2014), side effects in the form of ocular surface dryness are common (Cohen & Spierer, 2018; De Paiva et al., 2006; Lee et al., 2000; Solomon et al., 2004; Toda, 2018). In fact, dry eye is categorized as the most common adverse effect of LASIK (Cohen & Spierer, 2018; Solomon et al., 2004), with this technique having the highest incidence and severity of postoperative DED of all kerato-refractive procedures (Lee et al., 2000; Zhang et al., 2016).

LASIK involves the creation of a superficial flap of corneal epithelium and anterior stroma, which is retracted to allow for the ablation of the uncovered stromal surface using an excimer laser. It is suspected that the transection of corneal nerves that occurs during flap creation leads to a long-term decrease in corneal nerve density, which may affect the lacrimal functional unit (LFU) (Chao et al., 2014; Cohen & Spierer, 2018; Solomon et al., 2004; Toda, 2018; Xie, 2016). Alterations of the lacrimal functional reflex may decrease tear secretion and blinking and ultimately lead to signs and symptoms of dry eye (Stern et al., 2004). Other factors, such as damage to limbal goblet cells or increased tear film evaporation due to alterations of tear film distribution attributed to morphological changes in the cornea, may also contribute to postoperative ocular dryness (Cohen & Spierer, 2018; Rodriguez-Prats et al., 2007; Solomon et al., 2004; Toda, 2018; Xie, 2016). Although symptoms tend to peak in the early postoperative period (50% prevalence in the first week and 40% prevalence in the first month) (De Paiva et al., 2006; Shoja & Besharati, 2007), they persist in approximately 20 to 55% of patients at 6 months or more postoperatively (De Paiva et al., 2006; Levitt et al., 2015; Shoja & Besharati, 2007; Tuisku et al., 2007).

In Chapter 7 (*7. Ocular surface predisposing factors for digital display-induced dry eye*; Talens-Estarelles et al., 2022c) it was found that that individuals with greater symptoms of dry eye and eye redness were susceptible to a greater increase in symptoms

and a reduction in tear stability following computer use. All things considered, the aim of this chapter was to thoroughly assess and compare the effects of short-term computer use on the ocular surface in a group of young, post-LASIK individuals and a group of healthy controls, in order to determine whether post-LASIK patients are at an increased risk of digital display-induced dry eye.

10.2 Methods

10.2.1 Participants

Thirty-six young volunteers, ranging in age from 23 to 35 years, participated in this study. Students and workers of the University of Valencia (Valencia, Spain) were invited to participate by means of email and poster advertisements. Participants were allocated to the LASIK or control group, depending on whether or not they had undergone LASIK surgery. Inclusion criteria were age ≥ 18 and ≤ 35 years, CDVA better or equal to 20/20 (0.00 logMAR) in both eyes and myopic LASIK surgery up to -5.00 D in the LASIK group. Exclusion criteria were health conditions which may affect the eyes, including, but not limited to, Graves disease, diabetes, Sjögren syndrome or multiple sclerosis, current pregnancy or breastfeeding, current use of eye and/or general medications known to affect eye health or comfort, anterior or posterior segment pathologies, current eye infection or inflammation, history of eye surgery (apart from LASIK in the LASIK group), binocular disorders (i.e., strabismus, amblyopia, anisometropia, etc.) and a history of CL wear in the past 7 days. Participants who had undergone LASIK surgery in the past 6 months were also excluded. Additionally, participants were instructed not to use artificial tears within 2 hours before the visit.

The study followed the tenets of the Declaration of Helsinki and was approved by the University of Valencia human research ethics committee. All the participants were informed about the nature of the study and gave their written consent.

10.2.2 Experimental conditions

All the measurements were taken in the same laboratory. The approximate duration of each session was 45 minutes. All sessions were carried out at the same time of the day (first thing in the morning, at 9 am) and under the same, constant environmental conditions (temperature and humidity). In addition, participants were asked not to use other digital displays 30 minutes before the session.

The laboratory was set up 15 minutes prior to each participant's visit. To minimize the effects of outdoor conditions on the way to the laboratory, a 15-minute acclimatization period was left between the entry of the participants into the room and the measurements. The whole experiment was carried out under constant background illumination. The room was free from ambient lighting. Room illuminance was provided by indirect lighting to avoid any glare sources and was maintained at approximately 220 lux on the plane of the eyes of the participants. Chroma Meter CL-200 lux meter (Konica Minolta, Ramsey, NJ, USA) was used to measure photometric values. Room temperature and humidity were constantly monitored and remained stable at 22.6 ± 1.7°C and 42 ± 5%, respectively.

10.2.3 Measurements and procedure

Symptoms of dry eye and DES and ocular surface variables were evaluated before and after executing a 30-minute task using a laptop computer under 2 experimental conditions: without (visit 1) and with (visit 2) initial instillation of artificial tears. Each condition was tested in separate sessions. The study design mirrored that of previous chapters (Chapters 4-9).

One of the authors checked whether or not each volunteer met the inclusion/exclusion criteria before initiating the experiment. Visual acuity and ocular surface health were subsequently assessed. Symptoms of dry eye and DES were evaluated using the OSDI and CVS-Q. Ocular surface and tear film variables were assessed using the Keratograph 5M (Oculus Optikgerate, Wetzlar, Germany) (*3.2.2 Oculus Keratograpgh 5M, 3. General methods*). Measurements were performed in the following order: corneal HOAs, TMH, limbal and bulbar conjunctival redness, spontaneous blinking pattern, LLT and NIKBUT.

NIKBUT was measured 3 times and an average value was obtained. The spontaneous blinking of the participants was assessed in terms of the blink rate (i.e., total number of blinks) and percentage of incomplete blinks through the recording of a 60-s video sequence. LLT was graded using the Guillon grading scale (Guillon, 1998). Aberrations were reconstructed using Zernike polynomials for pupil diameters of 3 and 5 mm. The RMS of HOAs up to the 6th order was calculated. Both study groups underwent the same examination procedures. All measurements were taken on the right eye and by the same experienced examiner.

Next, participants were instructed to watch a predetermined television series on a laptop computer (MacBook Air Retina, 2020, Apple Inc., Cupertino, CA, USA). The

device was placed in accordance with the typical viewing distance and angle of usage: 60-cm distance and approximately 10° below eye level and with an inclination angle of 100° from the surface of the desk. When required (visit 2), one drop of Systane Ultra (Alcon SL, Geneva, Switzerland) single-dose artificial tears were instilled in each eye, 2 minutes before the task. Participants were seated comfortably and instructed to carry out the mentioned task in silence for 30 minutes until the examiner told them to stop.

After the 30-minute computer task, the battery of standard clinical tests was repeated. Measurements were taken in the following order: corneal HOAs, TMH, limbal and bulbar conjunctival redness, LLT, NIKBUT and spontaneous blinking pattern. Measurements were performed within 3-5 minutes after the task. To match the study question, participants were instructed to respond to the CVS-Q based exclusively on the symptoms experienced during the computer task. The OSDI was not used as the majority of its questions could not be extrapolated to the task (windy conditions, driving at night, reading, etc.). Instead, participants responded to the SANDE II, which asked them about the difference in the frequency and severity of dry eye symptoms compared to before computer use. Detailed information on the questionnaires and measurement procedures can be found in Chapter 3 (*3.2 Measurements and devices, 3. General methods*).

Figure 10.1 displays a flowchart of the study design.

10.2.4 Statistical analysis

The results were evaluated using SPSS software v.28 (IBM Corp., Armonk, NY). The normality of data was assessed using the Shapiro-Wilk test. When normality could be assumed, an unpaired t-test was used to compare demographic and baseline variables between both study groups. The chi-square test was used for the comparison of qualitative variables. The non-parametric Mann-Whitney U test was used when parametric test assumptions were not fulfilled.

Furthermore, a paired-sample t-test was used to examine the differences between pre-task and post-task ocular surface variables for each study group and visit. The non-parametric Wilcoxon paired signed-rank test was used when parametric test assumptions were not fulfilled. Additionally, a one-sample Wilcoxon signed-rank test was used to examine if the SANDE II scores were significantly greater than zero.

Finally, the impact of the computer task was calculated for each study variable as the difference between post-task and pre-task results (post-task – pre-task). Either a paired-sample t-test or the Wilcoxon paired signed-rank test, depending on the sample

distribution, was used to compare the impact of computer use and the CVS-Q and SANDE II scores between visits (normal vs artificial tear). In parallel, an unpaired t-test or the Mann-Whitney U test, depending on the sample distribution, was used for the comparisons between study groups (control vs LASIK).

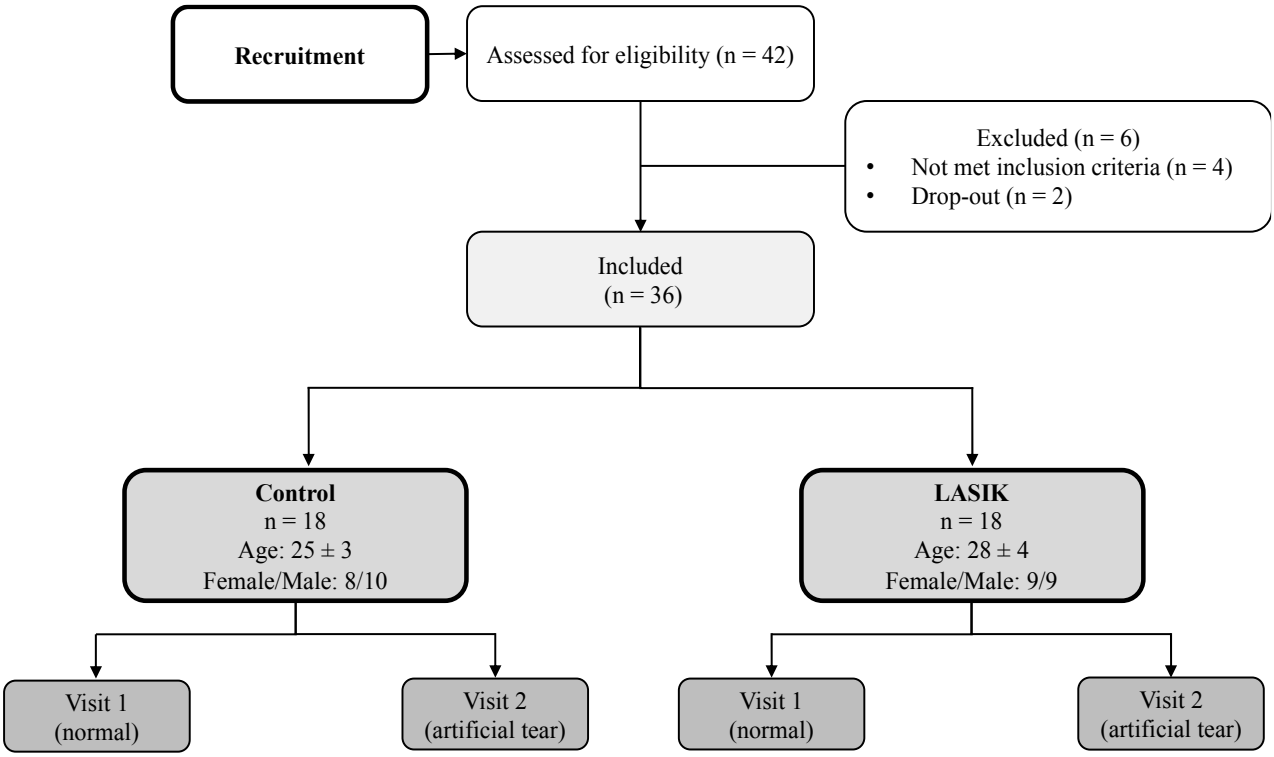


Figure 10.1 Study flowchart

10.3 Results

Forty-two Caucasian volunteers were initially recruited out of which 36 (17 females and 19 males) ranging in age from 23 to 35 years (27 ± 4 years) met the inclusion/exclusion criteria and completed all visits. From the 36 participants, 18 (8 females and 10 males, aged 25 ± 3 years) were divided into the control group and 18 (9 females and 9 males, aged 28 ± 4 years) into the LASIK group. The average time of computer use reported by the participants was 6.7 ± 2.6 hours a day, 6 ± 1 days a week.

Table 10.1 shows the demographics and baseline ocular surface variables of both study groups. The table additionally displays the statistical results of the comparisons. No statistically significant age or sex differences were observed between groups ($p \geq 0.07$). Likewise, no significant differences on any baseline variable were observed between the control and LASIK groups ($p \geq 0.17$), except for a significantly higher OSDI score ($p =$

0.04) and RMS of corneal HOAs ($p = 0.03$ for 3 mm pupil and $p = 0.004$ for 5 mm pupil) in the LASIK group compared to the control.

Table 10.2 displays the ocular surface variables obtained before and after the computer task at both visits and for both study groups. The table additionally displays the statistical results of the comparisons between pre-task and post-task variables. At visit 1, the control group obtained SANDE II frequency and severity scores significantly greater than zero ($p \leq 0.008$). Additionally, LLT increased significantly following the use of the computer ($p < 0.001$) in this group. Conversely, no other significant differences were found between pre-task and post-task variables in the control group ($p \geq 0.20$). Similarly, at visit 1, the LASIK group obtained SANDE II frequency and severity scores significantly greater than zero ($p \leq 0.005$). In addition, participants in this group exhibited a significantly greater TMH ($p = 0.04$), LLT ($p = 0.01$) and redness of the bulbar-temporal conjunctiva ($p = 0.008$) after the computer task compared to before, as well as a significantly shorter NIKBUT ($p = 0.006$).

At visit 2, the control group obtained SANDE II frequency and severity scores significantly lower than zero ($p \leq 0.003$). Furthermore, this group showed a significant increase in TMH following the computer task ($p < 0.001$), while the rest of the variables remained unchanged ($p \geq 0.10$). Analogously, at visit 2, the LASIK group obtained a SANDE II frequency score significantly lower than zero ($p = 0.03$), although the severity score was not significantly different from zero ($p = 0.07$). Also, participants in the LASIK group obtained a significantly greater TMH ($p < 0.001$) and LLT ($p = 0.01$) after the use of the computer when artificial tears were instilled compared to before.

Finally, Table 10.3 shows the symptoms of DES experienced during the computer task and the changes in ocular surface variables following computer use. The table additionally displays the statistical results of the comparisons between visits and between groups. At visit 2, the control group reported a significantly lower CVS-Q score compared to visit 1 ($p = 0.009$). Likewise, participants in this group exhibited a significantly lower increase in the frequency and severity of dry eye symptoms (SANDE II) following computer use at visit 2 compared to visit 1 ($p < 0.001$), as well as a lower increase in bulbar-nasal conjunctival redness ($p = 0.04$). No other statistically significant differences between visits were observed in the control group ($p \geq 0.07$). Similarly, participants in the LASIK group reported a significantly lower CVS-Q score at visit 2 compared to visit 1 ($p = 0.003$), as well as a significantly lower increase in the frequency and severity of dry eye symptoms (SANDE II) following the computer task ($p \leq 0.005$). Additionally,

post-task NIKBUT and blink rate decreased significantly less following computer use at visit 2 compared to visit 1 ($p = 0.008$ for NIKBUT and $p = 0.02$ for the blink rate). Regarding group comparisons, no statistically significant differences were found in the change of any variable following computer use between the control group and the LASIK group at any visit ($p \geq 0.08$).

Table 10.1. Demographics, symptom scores and baseline variables of the study participants and comparisons between study groups (control and LASIK). Data are presented as mean ± SD [min, max].

Variable	Control (n = 18)	LASIK (n = 18)	p-value
Age	26 ± 3 [23, 34]	28 ± 4 [23, 35]	0.067[2]
Sex (female:male)	9:9	8:10	0.732[3]
OSDI	7.7 ± 7.5 [2,1, 22.9]	19.5 ± 20 [0.0, 83.3]	0.041*[2]
CVS-Q	7 ± 4 [2, 17]	8 ± 5 [0, 18]	0.518[2]
Corneal RMS[a] (μm)			
3 mm	0.09 ± 0.04 [0.04, 0.24]	0.11 ± 0.04 [0.05, 0.18]	0.029[2]
5 mm	0.22 ± 0.08 [0.15, 0.48]	0.30 ± 0.08 [0.17, 0.49]	0.004[2]
TMH (mm)	0.23 ± 0.05 [0.16, 0.35]	0.23 ± 0.06 [0.11, 0.31]	0.976[1]
Conjunctival redness			
Bulbar – Temporal	0.6 ± 0.3 [0.1, 1.5]	0.8 ± 0.4 [0.4, 1.8]	0.170[2]
Bulbar – Nasal	0.7 ± 0.4 [0.2, 1.4]	0.8 ± 0.4 [0.2, 1.6]	0.614[1]
Limbal – Temporal	0.3 ± 0.3 [0.0, 1.2]	0.4 ± 0.4 [0.1, 1.3]	0.218[2]
Limbal – Nasal	0.4 ± 0.3 [0.0, 1.1]	0.4 ± 0.4 [0.0, 1.1]	0.579[1]
LLT[b]	2 ± 1 [1, 3]	2 ± 1 [1, 3]	0.540[2]
NIKBUT (s)	10. 9 ± 4.5 [6.1, 25.1]	11.4 ± 5.4 [4.0, 22.2]	0.892[2]
Blink rate (blinks/min)	14 ± 7 [4, 28]	15 ± 12 [2, 46]	0.731[1]

Incomplete blinking (%)	71 ± 30 [0, 100]	60 ± 30 [10, 100]	0.231[2]

CVS-Q = Computer Vision Syndrome Questionnaire; NIKBUT = Non-invasive keratograph break-up time; OSDI = Ocular Surface Disease Index; RMS = Root mean square; TMH = Tear meniscus height. [a] RMS of higher-order aberrations up to the 6th order. [b] Graded as: 1 = open meshwork; 2 = closed meshwork; 3 = wave; 4 = amorphous; 5 = 1st order colours; 6 = 2nd order colours. * Indicates statistically significant values ($p < 0.05$). [1] Unpaired t-test. [2] Mann-Whitney U test. [3] chi-square test.

Table 10.2. Ocular surface variables obtained before (pre-task) and after (post-task) computer use at visit 1 (Normal) and visit 2 (Artificial tear) for both study groups (control and LASIK) and statistical results of the comparisons. Data are presented as mean ± SD. [min – max].

Variable	Control (n = 18)						LASIK (n = 18)					
	Visit 1 (Normal)			Visit 2 (Artificial tear)			Visit 1 (Normal)			Visit 2 (Artificial tear)		
	Pre-task	Post-task	p-value	Pre-task	Post-task	p-value	Pre-task	Post-task	p-value	Pre-task	Post-task	p-value
SANDE II[a]												
Frequency	–	1.1 ± 0.9 [0.0, 2.5]	0.001*[3]	–	-1.1 ± 1.0 [-4.0, 0.0]	< 0.001*[3]	–	1.0 ± 1.1 [-1.5, 2.7]	0.005*[3]	–	-0.7 ± 1.3 [-4.4, 1.3]	0.03*[3]
Severity	–	0.8 ± 0.9 [0.0, 2.5]	0.008*[3]	–	-0.9 ± 1.1 [-4.2, 0.0]	0.003*[3]	–	0.7 ± 0.8 [0.0, 2.5]	0.008*[3]	–	-0.5 ± 1.1 [-3.2, 1.5]	0.07[3]
Corneal RMS[b] (μm)												
3 mm	0.09 ± 0.04 [0.04, 0.24]	0.10 ± 0.04 [0.07, 0.25]	0.31[2]	0.11 ± 0.05 [0.05, 0.26]	0.10 ± 0.04 [0.05, 0.18]	0.88[2]	0.11 ± 0.04 [0.05, 0.18]	0.13 ± 0.05 [0.05, 0.23]	0.10[1]	0.12 ± 0.07 [0.04, 0.34]	0.13 ± 0.07 [0.07, 0.35]	0.21[2]
5 mm	0.22 ± 0.08 [0.15, 0.48]	0.22 ± 0.07 [0.14, 0.47]	0.87[2]	0.23 ± 0.09 [0.15, 0.46]	0.23 ± 0.09 [0.16, 0.48]	0.93[2]	0.30 ± 0.08 [0.17, 0.49]	0.33 ± 0.09 [0.15, 0.51]	0.09[1]	0.32 ± 0.09 [0.17, 0.45]	0.32 ± 0.10 [0.18, 0.54]	0.76[1]
TMH (mm)	0.23 ± 0.05 [0.16, 0.35]	0.25 ± 0.05 [0.18, 0.34]	0.30[1]	0.25 ± 0.06 [0.15, 0.36]	0.30 ± 0.09 [0.19, 0.53]	< 0.001*[1]	0.23 ± 0.06 [0.11, 0.31]	0.26 ± 0.08 [0.17, 0.45]	0.04*[1]	0.24 ± 0.06 [0.14, 0.38]	0.29 ± 0.07 [0.19, 0.46]	< 0.001*[1]
Conjunctival redness												
Bulbar – Temporal	0.6 ± 0.3 [0.1, 1.5]	0.6 ± 0.3 [0.2, 1.5]	0.97[2]	0.6 ± 0.4 [0.1, 1.7]	0.6 ± 0.4 [0.1, 1.7]	0.17[2]	0.8 ± 0.4 [0.4, 1.8]	0.9 ± 0.5 [0.3, 1.9]	0.008*[2]	0.8 ± 0.4 [0.3, 1.6]	0.8 ± 0.4 [0.3, 1.6]	0.36[1]
Bulbar – Nasal	0.7 ± 0.3 [0.2, 1.4]	0.8 ± 0.4 [0.2, 1.6]	0.20[1]	0.7 ± 0.4 [0.2, 1.6]	0.6 ± 0.4 [0.2, 1.6]	0.17[2]	0.9 ± 0.4 [0.2, 1.6]	0.8 ± 0.4 [0.3, 1.8]	0.82[2]	0.8 ± 0.4 [0.3, 1.8]	0.7 ± 0.4 [0.3, 1.6]	0.53[1]
Limbal – Temporal	0.3 ± 0.3 [0.0, 1.2]	0.3 ± 0.3 [0.0, 0.9]	0.39[2]	0.4 ± 0.3 [0.0, 1.0]	0.3 ± 0.2 [0.0, 0.9]	0.57[2]	0.4 ± 0.4 [0.1, 1.3]	0.5 ± 0.4 [0.1, 1.3]	0.63[2]	0.4 ± 0.3 [0.1, 1.1]	0.4 ± 0.2 [0.0, 0.8]	0.75[2]
Limbal – Nasal	0.4 ± 0.3 [0.0, 1.1]	0.4 ± 0.3 [0.0, 0.9]	0.73[1]	0.4 ± 0.3 [0.1, 1.0]	0.4 ± 0.3 [0.0, 0.9]	0.48[2]	0.4 ± 04 [0.0, 1.1]	0.4 ± 0.2 [0.1, 0.9]	0.30[2]	0.4 ± 0.3 [0.1, 1.4]	0.4 ± 0.3 [0.0, 1.0]	0.70[2]

LLT[c]	2 ± 1 [1, 3]	3 ± 1 [2, 4]	< 0.001*[2]	2 ± 1 [1, 3]	3 ± 1 [2, 3]	0.11[2]	2 ± 1 [1, 3]	3 ± 1 [1, 4]	0.01*[2]	2 ± 1 [1, 3]	3 ± 1 [1, 4]	0.01*[2]
NIKBUT (s)	10. 9 ± 4.5 [6.1, 25.1]	10.3 ± 4.1 [4.1, 20.4]	0.55[2]	11.6 ± 5.8 [3.6, 24.9]	11.9 ± 5.8 [3.1, 22.3]	0.80[1]	11.4 ± 5.4 [4.0, 22.2]	9.0 ± 5.3 [2.9, 18.5]	0.006*[2]	11.8 ± 6.1 [3.9, 22.4]	12.6 ± 6.4 [3.1, 25.0]	0.25[1]
Blink rate (blinks/min)	14 ± 7 [4, 28]	14 ± 8 [2, 26]	0.60[1]	14 ± 6 [6, 24]	16 ± 8 [6, 30]	0.52[2]	15 ± 12 [2, 46]	13 ± 14 [1, 46]	0.23[2]	10 ± 9 [0, 36]	13 ± 10 [0, 34]	0.17[2]
Incomplete blinking (%)	71 ± 30 [0, 100]	69 ± 32 [0, 100]	0.51[2]	70 ± 27 [0, 100]	63 ± 28 [0, 100]	0.10[2]	60 ± 30 [10, 100]	65 ± 39 [0, 100]	0.33[2]	63 ± 36 [0, 100]	54 ± 38 [0, 100]	0.18[2]

NIKBUT = Non-invasive keratograph break-up time; RMS = Root mean square; TMH = Tear meniscus height. [a] Frequency and severity of dry eye symptoms compared to before the computer task. [b] RMS of higher-order aberrations up to the 6th order. [c] Graded as: 1 = open meshwork; 2 = closed meshwork; 3 = wave; 4 = amorphous; 5 = 1st order colours; 6 = 2nd order colours. * Indicates statistically significant values ($p < 0.05$). [1] Paired-sample t-test. [2] Wilcoxon paired signed-rank test. [3] One-sample Wilcoxon signed-rank test, comparison with value of 0 (no change).

Table 10.3. Ocular symptoms during the computer task and changes in ocular surface variables following computer use (post-task – pre-task), and statistical results of the comparisons between visits (Normal vs Artificial tear) and between groups (control vs LASIK). Data are presented as mean ± SD [min, max].

Variable	Control (n = 18)			LASIK (n = 18)			Control vs LASIK	
	Visit 1 (Normal)	Visit 2 (Artificial tear)	p-value	Visit 1 (Normal)	Visit 2 (Artificial tear)	p-value	Visit 1 (Normal) p-value	Visit 2 (Artificial tear) p-value
CVS-Q[a]	4 ± 4 [0, 13]	2 ± 3 [0, 10]	0.009*[2]	4 ± 4 [0, 15]	2 ± 4 [0, 13]	0.003*[2]	0.43[4]	0.90[4]
SANDE II[b]								
Frequency	1.1 ± 0.9 [0.0, 2.5]	-1.1 ± 1.0 [-4.0, 0.0]	< 0.001*[2]	1.0 ± 1.1 [-1.5, 2.7]	-0.7 ± 1.3 [-4.4, 1.3]	0.002*[2]	0.97[3]	0.29[4]
Severity	0.8 ± 0.9 [0.0, 2.5]	-0.9 ± 1.1 [-4.2, 0.0]	< 0.001*[2]	0.7 ± 0.8 [0.0, 2.5]	-0.5 ± 1.1 [-3.2, 1.5]	0.005*[2]	0.79[4]	0.15[4]
Corneal RMS[c] (µm)								
3 mm	0.00 ± 0.03 [-0.05, 0.05]	-0.01 ± 0.05 [-0.13, 0.04]	0.08[2]	0.02 ± 0.04 [-0.03, 0.12]	0.01 ± 0.09 [-0.23, 0.17]	0.91[2]	0.74[4]	0.12[4]
5 mm	0.00 ± 0.03 [-0.07, 0.06]	0.00 ± 0.05 [-0.10, 0.08]	0.93[1]	0.03 ± 0.06 [-0.09, 0.13]	0.01 ± 0.08 [-0.14, 0.13]	0.43[1]	0.12[3]	0.49[3]
TMH (mm)	0.02 ± 0.06 [-0.09, 0.14]	0.05 ± 0.05 [-0.03, 0.17]	0.09[1]	0.04 ± 0.06 [-0.06, 0.15]	0.05 ± 0.04 [0.00, 0.12]	0.17[1]	0.49[3]	0.87[3]

Conjunctival redness								
Bulbar – Temporal	0.0 ± 0.2 [-0.5, 0.6]	-0.1 ± 0.1 [-0.5, 0.1]	0.64[2]	0.1 ± 0.1 [-0.1, 0.4]	-0.1 ± 0.3 [-0.7, 0.4]	0.19[2]	0.08[4]	0.82[4]
Bulbar – Nasal	0.1 ± 0.2 [-0.2, 0.6]	-0.1 ± 0.3 [-0.7, 0.6]	0.04*[2]	0.0 ± 0.3 [-0.6, 1.0]	-0.1 ± 0.3 [-0.9, 0.5]	0.86[2]	0.63[4]	0.64[3]
Limbal – Temporal	0.1 ± 0.2 [-0.3, 0.6]	0.0 ± 0.2 [-0.6, 0.2]	0.29[2]	0.0 ± 0.2 [-0.4, 0.7]	0.0 ± 0.2 [-0.5, 0.5]	0.54[2]	0.84[4]	0.93[4]
Limbal – Nasal	0.0 ± 0.2 [-0.3, 0.6]	0.0 ± 0.2 [-0.3, 0.5]	0.75[2]	-0.1 ± 0.3 [-0.8, 0.2]	0.0 ± 0.3 [-0.8, 0.8]	0.84[2]	0.81[4]	0.96[4]
LLT	1 ± 1 [0, 2]	0 ± 1 [-1, 2]	0.07[2]	1 ± 1 [-1, 2]	1 ± 1 [0, 2]	0.16[2]	0.38[4]	0.56[4]
NIKBUT (s)	-0.6 ± 3.7 [-6.0, 4.4]	0.3 ± 4.5 [-8.6, 8.1]	0.54[2]	-2.4 ± 4.0 [-9.8, 8.9]	0.6 ± 2.8 [-5.1, 5.8]	0.008*[1]	0.26[4]	0.85[4]
Blink rate (blinks/min)	-1 ± 5 [-6, 10]	2 ± 7 [-8, 20]	0.28[1]	-1 ± 6 [-10, 10]	2 ± 7 [-4, 20]	0.02*[2]	0.50[3]	0.76[4]
Incomplete blinking (%)	-2 ± 40 [-100, 42]	-7 ± 16 [-28, 33]	0.30[2]	5 ± 31 [-51, 80]	-9 ± 27 [-50, 30]	0.16[1]	0.82[4]	0.70[3]

NIKBUT = Non-invasive keratograph break-up time; RMS = Root mean square; TMH = Tear meniscus height. [a] Symptoms of digital eye strain experienced during the computer task. [b] Frequency and severity of dry eye symptoms compared to before the computer task. [c] RMS of higher-order aberrations up to the 6th order. * Indicates statistically significant values ($p < 0.05$). [1] Paired-sample t-test. [2] Wilcoxon paired signed-rank test. [3] Unpaired t-test. [4] Mann-Whitney U test.

10.4 Discussion

According to the results of the present study, participants in both study groups reported a similar increase in the frequency and severity of dry eye symptoms (SANDE II) following the use of the computer. Analogously, an increase in dry eye symptoms was observed in previous chapters (Chapters 6-9). The results of Chapter 7 (*7. Ocular surface predisposing factors for digital display-induced dry eye*; Talens-Estarelles et al., 2022c) indicate that individuals with greater symptoms of dry eye are prone to a greater increase in symptoms following computer use. Nevertheless, in the present investigation, individuals in the LASIK group did not report a greater increase in symptoms following the computer task compared to controls, despite higher symptoms of dry eye at baseline (OSDI).

Despite the increase in symptoms, participants in the control group did not exhibit an increase in dry eye signs following the computer task. This is in contrast with previous chapters (Chapters 6-9) in non-operated healthy individuals, where an increase in conjunctival redness and a decrease in tear stability after reading on a computer for 20-30 minutes was observed. The impact of computer use on the eye is highly related to the cognitive demand of the task and the accompanying suppression of blinking (Cardona et al., 2011; Rosenfield et al., 2015). In the present study, participants were instructed to watch a television series on the computer, which, despite being more representative of modern patterns of digital device use in younger individuals, may result in a lower cognitive demand compared to reading. Overall, differences in the computer task may explain discrepancies in the results between studies.

Conversely, the results of the present study revealed an increase in dry eye signs (increase in conjunctival redness and decrease in NIKBUT) following computer use in the LASIK group, indicating tear film destabilization and ocular surface stress. Additionally, tear volume (TMH) was significantly greater after the computer task compared to before in these individuals. Similarly, previous chapters (Chapters 7-9) reported an increased tear volume accompanied by increased signs and symptoms of dry eye after digital display use. Blinking keeps the eye surface humid and hydrated by favouring the secretion of tears and spreading them through the ocular surface (Doane, 1981; Holly, 1980). Nielsen et al. (2008) reported a compensatory burst of blinks right after cessation of an active digital display task. Authors attributed this phenomenon to compensation for the oppression of blinking during the digital display task and therefore

as a wetting process secondary to ocular surface disturbance, which may explain the greater post-task tear volume obtained in the present study.

Judging by the results of the present study, despite a similar increase in symptoms, post-LASIK patients may be at greater risk of reduced tear stability and ocular surface stress following computer use than non-operated individuals. Moreover, dry eye symptoms, such as discomfort, burning, dryness and red eye, among others, tend to peak in the first weeks/months after LASIK surgery (De Paiva et al., 2006; Shoja & Besharati, 2007). As reported in Chapter 7 (*7. Ocular surface predisposing factors for digital display-induced dry eye*; Talens-Estarelles et al., 2022c), individuals with greater symptoms of dry eye and eye redness may be susceptible to a greater increase in symptoms and reduction in tear stability following computer use. In the present study, individuals who had undergone LASIK surgery in the past 6 months were excluded as per the exclusion criteria. Therefore, a greater impact of computer use may be obtained in post-LASIK patients in the early postoperative period. Nevertheless, more research is needed in specifically designed studies to examine this postulation and confirm the findings of the present study.

Blinking helps in the expression of lipids from the meibomian glands and spreads tear lipids through the precorneal film (Doane, 1981; Korb et al., 1994). Partial blinking associated with digital device use is suspected to cause thinning of the lipid layer and poor lipid distribution, leading to tear break-up problems (McMonnies, 2007; Portello et al., 2013; Rosenfield et al., 2015). Despite this, a significantly greater LLT was observed in the present study after the computer task compared to before in both study groups. Complete blinks favour the secretion of lipids and lead to an increase in LLT. Therefore, compensatory blinking after the interruption of the task could also be responsible for the increased thickness of the lipid layer observed after computer use. Additionally, a more coloured interference pattern of the lipid layer could not only be due to an increase in the thickness of the lipid layer but also to an alteration in the composition of lipids and their distribution through the precorneal film. Consequently, alteration of lipids, attributable to deficient blinking during the computer task, could explain the higher subjective gradation of the lipid layer after computer use. More studies are needed to objectively evaluate changes in the lipid layer following computer use.

The tear film-air interface is the first refractive structure of the eye that influences the optical light path to the retina. Due to the significant refractive index change from air to tear film, abnormalities to the tear film can impact the optical quality of the retinal

image markedly (Albarrán et al., 1997). In the present study, despite significant changes in tear stability (NIKUT) and tear film lipid layer (LLT), no changes in the optical quality of the anterior surface of the eye (corneal RMS) were observed following computer use in any of the study groups. More studies are needed to assess changes in optical quality in computer users.

As opposed to visit 1, both study groups reported an improvement in the frequency and severity of dry eye symptoms after the computer task when artificial tears were instilled. Likewise, the instillation of artificial tears prior to computer use prevented the worsening of dry eye signs in post-LASIK individuals, especially with regards to tear stability (NIKBUT), and contributed to an increase in tear volume (TMH) in both study groups. Preservative-free artificial tears are the key treatment for both post-LASIK dry eye and digital display-induced dry eye (Cohen & Spierer, 2018; Talens-Estarelles et al., 2022d; Toda, 2018; Xie, 2016). Lubricating eye drops have been shown to effectively regulate the interblink interval and relieve ocular symptoms during computer use (Acosta et al., 1999). More specifically, sodium hyaluronate tears, such as the ones used in the present study, have proven effective in recovering the tear film in individuals with dry eye symptoms associated with computer use (Calvão-Santos et al., 2011). Likewise, in Chapter 8 (*8. Determining the best management strategy for preventing short-term effects of digital display use on dry eyes*; Talens-Estarelles et al., 2022d) it was concluded that the instillation of this type of artificial tears was the best strategy to prevent alterations of the ocular surface following computer use. Considering that computer use had a greater impact on the tear film and ocular surface in the LASIK group, the instillation of artificial tear substitutes may be especially beneficial in post-LASIK symptomatic computer users.

Additionally, the results of the present study revealed a significant increase in LLT following the computer task in both study groups when artificial tears were instilled. Systane Ultra artificial tears contain polyethylene glycol and propylene glycol demulcents with the polymer hydroxypropyl guar as a gelling agent, which results in a gel-matrix with bioadhesive properties (Srinivasan & Manoj, 2021). This may explain the increase in the subjective gradation of LLT observed in the present study at visit 2. Korb et al. (2005b) reported a 16% increase in LLT after the instillation of this brand of artificial tears, although Fogt et al. (2016) did not find significant differences 15 minutes after the instillation of a single drop.

The present study has some limitations to consider. Due to the subjective evaluation of symptoms, the nocebo/placebo effect on results cannot be completely ruled

out. Also, the present study assessed the impact of short periods of computer use, which may not be representative of modern durations of device usage. This may have led to fewer signs and symptoms of dryness than those expected after longer periods of display visualization. In addition, although the sample in the present study allowed for sufficient statistical power for the study's primary endpoint (dry eye symptoms), it was insufficient for the comparisons of ocular surface variables. Even so, the present study establishes the basis for future works which would assess the effects of device use after longer exposure and in larger samples of post-LASIK patients.

In conclusion, using a computer for 30 minutes significantly increased the frequency and severity of dry eye symptoms in normal and post-LASIK individuals. The increase in symptoms of dry eye and the symptoms of DES reported during the computer task were comparable between both study groups. Symptoms were accompanied by a significant worsening of dry eye signs in the LASIK group, while no significant changes were found in the control group. Lastly, the instillation of artificial tears prevented an increase in dry eye symptoms and significantly reduced the symptoms of DES during the computer task. It was also effective in preventing the worsening of dry eye signs in post-LASIK individuals. Further investigation in specifically designed studies with larger samples is needed to confirm these findings. Likewise, future studies are required to assess the impact of longer durations of computer use on the ocular surface of individuals after kerato-refractive procedures, especially during the early postoperative period.

11.

Corneal hypersensitivity to cold stimuli in symptomatic computer users

11.1 Introduction

Increasing reports of ocular discomfort have led to a renewed interest in the relationship between the uncomfortable sensations experienced under symptom-inducing conditions and functional disturbances in the sensory supply to the anterior segment of the eye (Bilgic et al., 2022; Golebiowski et al., 2017; Kovács et al., 2016; Situ et al., 2020a; Vereertbrugghen & Galletti, 2022).

The drying of the ocular surface causes elevated tear osmolarity levels, evaporation-induced cooling and mechanical distortion of epithelium layers and deformation of intercellular spaces, eventually causing the local release of inflammatory agents (Belmonte et al., 2004a; Belmonte et al., 2004b; Belmonte & Gallar, 2011a; Bron et al., 2017; Lemp et al., 2011; Li et al., 2015; Vereertbrugghen & Galletti, 2022). All these physical and chemical disturbances that accompany excessive evaporation may act as stimuli for the distinct functional types of sensory neurons that innervate the ocular surface (mechanonociceptor, polymodal nociceptor, and cold thermoreceptor neurons) thereby becoming a potential source of ocular discomfort (Belmonte et al., 2004a; Belmonte et al., 2004b; Belmonte et al., 2017; Belmonte & Gallar, 2011a; Hirata et al., 2012; Kovács et al., 2016; Labetoulle et al., 2019; Vereertbrugghen & Galletti, 2022).

Evidence has accrued on the existence of changes in nerve morphology caused by dry eye (Belmonte et al., 2017; Labetoulle et al., 2019; Vereertbrugghen & Galletti, 2022), with studies showing a reduction in nerve density which correlates with disease severity as well as reduced nerve thickness, hyperreflectivity and increased tortuosity, among others (Belmonte et al., 2017; Cruzat et al., 2017; Labetoulle et al., 2019; Vereertbrugghen & Galletti, 2022). These morphological alterations of corneal nerves have been associated with a reduction in corneal sensitivity to pure mechanical stimulus and to disease severity (Belmonte et al., 2017; Labbé et al., 2012, 2013; Labetoulle et al., 2019; Vereertbrugghen & Galletti, 2022). Contrastingly, tissue injury and inflammation arising after repeated noxious stimulation of the ocular surface may result in sustained stimulation of the underlying nociceptors which may develop long-lasting changes in their excitability (i.e., sensitization), leading to sustained and spontaneous sensations of dryness and pain, and enhanced sensitivity to new stimuli, often observed in individuals with dry eye (Belmonte, 2019; Belmonte et al., 2004b; Belmonte et al., 2017; Galor et al., 2018; Labetoulle et al., 2019; Vereertbrugghen & Galletti, 2022). Heightened sensory input from cold thermoreceptors also contributes to the unpleasant sensations and blinking and

tearing rate adjustments occurring in patients with dry eye and these neurons may also develop changes in their excitability (Belmonte & Gallar, 2011b; Kovács et al., 2016; Parra et al., 2014; Vereertbrugghen & Galletti, 2022).

Corneal nerve physiology has traditionally been assessed using the Cochet-Bonnet aesthesiometer. However, the Cochet-Bonnet aesthesiometer only effectively activates the Aδ selective mechanonociceptors found among the subbasal nerve plexus (Belmonte et al., 2017; Vereertbrugghen & Galletti, 2022). Additionally, several critical limitations undermine its utility (Chao et al., 2015; Golebiowski et al., 2011). Belmonte et al. (1999) developed the non-contact aesthesiometer using an air jet of modifiable characteristics as the stimulating medium, potentially differentiating between selective mechanonociceptors, polymodal nociceptors, and cold thermoreceptors. Nevertheless, the size of the air stimulus footprint is hard to determine, and it is difficult to eliminate the thermal component from the air-jet mechanical stimulus, thus a true mechanical sensation threshold may not be reachable (Golebiowski et al., 2013; Nosch et al., 2018). To overcome these deficiencies, a more sophisticated liquid-based stimulation method was developed by Ehrmann et al. (2018) (LJA), which was later refined to include active cooling of the liquid (UNSW LJA). It can measure the sensitivity of ocular tissues using small droplets of modifiable characteristics projected onto the target surface under controlled conditions.

The aim of this chapter was to evaluate the relationship between ocular symptoms and central corneal sensitivity to mechanical and cold stimuli in computer users, employing the UNSW LJA. To the authors' knowledge, this is the first study to assess the relationship between ocular symptoms and ocular surface sensitivity in computer users.

11.2 Methods

11.2.1 Participants

Fifty-two young volunteers aged 18 to 44 years participated in this clinical trial. Participants were recruited from the School of Optometry and Vision Science at the UNSW (Sydney, Australia) by means of email and poster advertisements. Inclusion criteria were age ≥ 18 and ≤ 45, CDVA better or equal to 20/30 (0.17 logMAR) in both eyes and computer use of at least 4 hours a day, 4 days a week. Exclusion criteria were history of ocular pathology or systemic disease that could potentially impact the integrity of the ocular surface, including, but not limited to, Graves disease, diabetes, Sjögren

syndrome or multiple sclerosis, current pregnancy or breastfeeding, current eye infections or inflammation, current use of eye and/or general medications known to affect eye health or comfort, history of eye surgery and history of rigid CL wear or use of soft CLs in the past 7 days. Additionally, participants were instructed not to use artificial tears 2 hours before the visit.

The study followed the tenets of the Declaration of Helsinki and was approved by the UNSW human research ethics committee. All the participants were informed about the nature of the study and gave their written consent.

11.2.2 Measurement of sensation threshold

Cold (15°C) and mechanical sensation thresholds at the central cornea were determined using the UNSW LJA (UNSW, Sydney, Australia). The technical details of the UNSW LJA utilised in this investigation have been described elsewhere (Ehrmann et al., 2018). In brief, a microvalve which switches on and off at variable 'on' periods allows a droplet of adjustable volume to be propelled onto the ocular surface to generate a stimulus of variable intensity. The ocular surface sensation threshold is determined based on the participants' 'felt' or 'not felt' subjective feedback, provided via a handheld pushbutton, which feeds into an automated double staircase algorithm. After the high and low starting staircases have converged for the first time, 9 more stimulations were applied, and the sensation threshold was automatically calculated as the mean droplet volume of these last 9 stimulations. The clinical reliability of the instrument to determine corneal sensitivity has previously been verified (Ehrmann et al., 2023). Please refer to Chapter 3 for detailed information on the device and measurement procedure (*3.2.6 UNSW Liquid Jet Aesthesiometer, 3. General methods*).

11.2.3 Protocol and experimental design

Ocular surface symptoms and central corneal mechanical and cold sensation thresholds were assessed in a group of frequent computer users (computer use ≥ 4 hours/day and ≥ 4 days/week), including symptomatic and asymptomatic users.

Fifteen minutes before the entry of the participants, the laboratory was set up and acclimatised. One of the authors checked whether or not each volunteer met the inclusion/exclusion criteria before initiating the experiment. Visual acuity and ocular surface health were subsequently assessed. Symptoms of dry eye, ocular discomfort and

DES were evaluated using the OSDI, OCI, IOSS and CVS-Q. Detailed information on the questionnaires can be found in Chapter 3 (*3.2.1 Symptomatology questionnaires, 3. General methods*). Additionally, participants were surveyed about the average hours of computer and smartphone use per day and average days of computer use per week. Next, careful instructions were recited to the participants via a predetermined script before the measurement of corneal sensitivity.

Prior to the measurement, a brief test run was performed in the non-test eye to familiarise the participant with the instrumentation and procedure. Mechanical and cold sensation thresholds were determined at the central cornea of the randomly selected eye of each participant. The order of the measurements was randomized, and a minimum of 5 minutes was left between measurements. To minimize the effects of outdoor conditions on the way to the laboratory, a minimum acclimatization period of 20 minutes was ensured between the entry of the participants into the room and the determination of corneal sensitivity.

All measurements were taken in the same laboratory and by the same experienced examiner. Visits were carried out in the mornings, between 9 am and 12 pm, and a minimum of 3 hours after waking to account for possible diurnal variation in sensitivity (Millodot, 1972). Room temperature and humidity were constantly monitored and remained stable at 22.5 ± 0.7°C and 41 ± 5%, respectively.

11.2.4 Statistical analysis

Statistical analysis was performed using SPSS software v.28 (IBM Corp., Armonk, NY, USA). Participants were divided into two groups based on the cut-off scores of OSDI (asymptomatic < 13 vs symptomatic ≥ 13) and CVS-Q (asymptomatic < 6 vs symptomatic ≥ 6) and based on the median score of the distribution of OCI (low < 27 vs high ≥ 27) and IOSS (low < 2 vs high ≥ 2). The normality of data was assessed using the Kolmogorov-Smirnov test. Differences in cold and mechanical sensation thresholds between groups were assessed using unpaired T-test or Mann-Whitney U test, depending on the sample distribution.

Pearson (r) correlations were carried out between mechanical and cold sensation thresholds and questionnaire scores, demographic variables and patterns of digital display use. The non-parametric Spearman (ρ) test was used when parametric test assumptions were not fulfilled.

Simple and multiple linear mixed models were used to identify potential predictors of cold and mechanical corneal sensation thresholds. Scatter plots were created to evaluate the relationship between variables and to check for homoscedasticity. Independent variables with a linear relationship with the outcome variable were included in the model. The Durbin-Watson test was used to check the independence of errors. Multicollinearity was tested using variance inflation factors. More information on linear regressions can be found in Chapter 3 (*3.3.3.6 Regression analysis, 3. General methods*).

Statistical analyses were performed for the OSDI total score and for the scores obtained in each of the three questionnaire subscales (visual symptoms, vision-related function and environmental triggers). Similarly, the CVS-Q total score was split into two categories based on the two main DES symptomatology groups (Portello et al., 2012): dry eye (questions 1-10, 13, 15) and accommodative and binocular vision stress (questions 10-16).

11.3 Results

Table 11.1 shows the demographics, digital device use patterns, symptom scores and sensation thresholds of the study participants. Sixty-four volunteers were initially recruited out of which 52 (23 females and 29 males) ranging in age from 18 to 44 years (31 ± 6 years) met the inclusion/exclusion criteria and were included for subsequent analysis. Out of the 52 participants, 36 were Asian, 13 White, 2 Black and 1 Hispanic/Latino. The mean time of computer use reported by the participants was 7.4 ± 2.6 hours a day, 6 ± 1 days a week. The reported time of smartphone use was 3.8 ± 2.7 hours a day. The mean mechanical sensation threshold was 2.1 μl, ranging from 0.3 to 4.6 μl, and the mean cold sensation threshold was 0.04, ranging from 0.02 to 0.09 μl.

Table 11.2 shows the mechanical and cold sensation thresholds obtained by asymptomatic and symptomatic participants for each questionnaire. No significant differences in corneal sensitivity were observed between participants with a negative and positive OSDI score ($p \geq 0.31$), nor between participants with a low and a high OCI or IOSS score ($p \geq 0.16$). In contrast, participants with a positive CVS-Q score exhibited a significantly lower cold sensation threshold compared to those with a negative score ($p = 0.03$), while no significant differences in mechanical sensitivity between groups were observed ($p = 0.11$).

Table 11.3 shows the correlations between corneal sensation thresholds and demographic variables, digital device use patterns and symptom scores. No significant correlations between mechanical sensation threshold and any of the study variables were observed ($p \geq 0.09$), except for a significant positive correlation with cold sensation threshold ($p < 0.001$, $\rho = 0.63$). On the contrary, cold sensation threshold was positively associated with age ($p = 0.04$, $\rho = 0.24$) and negatively associated with CVS-Q score ($p = 0.02$, $\rho = -0.33$) and CVS-Q dry eye score ($p = 0.04$, $\rho = -0.28$). No significant correlations between cold sensitivity and the rest of the variables were found ($p \geq 0.11$).

Tables 11.4 and 11.5 display the simple and multiple linear regression models, respectively, for significant predictors of mechanical and cold sensation thresholds. Age, CVS-Q, CVS-Q dry eye and mechanical sensation threshold were all significant predictors of cold sensation threshold when analysed in isolation (simple linear models, $p \leq 0.04$) (Figure 11.1). Age and mechanical sensation threshold were kept as significant predictors of cold sensitivity in the multiple regression model ($p \leq 0.04$, adjusted $R^2 = 0.46$). Conversely, the regression analysis identified cold sensation threshold as the sole predictor of mechanical sensitivity ($p < 0.001$) (Adjusted $R^2 = 0.44$).

Table 11.1. Demographics, symptom scores and central corneal sensation thresholds of the study participants. Continuous variables are presented as mean ± SD [min, max]. Categorical variables are presented as number (%).

Variable (n = 52)	Value
Demographics	
Age	31 ± 6 [18, 44] years
Sex	
Female	23 (44%)
Male	29 (56%)
Ethnicity	
Asian	36 (69%)
Black	2 (4%)
Latino	1 (2%)
White	13 (25%)
Digital device use	
Hours of computer use per day	7.4 ± 2.6 [4, 15] hours
Days of computer use per week	6 ± 1 [4, 7] days
Hours of smartphone use per day	3.8 ± 2.7 [0.5, 13] hours
Ocular symptoms	
OSDI	12.9 ± 14.0 [0.0, 55.0]
OSDI Symptoms	10.8 ± 11.6 [0.0, 40.0]
OSDI Vision-related function	10.8 ± 18.1 [0.0, 81.3]
OSDI Environmental triggers	16.8 ± 20.1 [0.0, 83.3]
OCI	26.2 ± 13.0 [0.0, 61.2]
IOSS	2 ± 3 [0, 10]
CVS-Q	5 ± 4 [0, 17]
CVS-Q Dry eye	4 ± 4 [0, 15]
CVS-Q A/BV stress	2 ± 2 [0, 8]
Corneal sensitivity	
Mechanical sensation threshold	2.1 ± 1.2 [0.3, 4.6] µl
Cold sensation threshold	0.04 ± 0.02 [0.02, 0.09] µl

A/BV = Accommodative and binocular vision; CVS-Q: Computer Vision Syndrome Questionnaire; IOSS = Instant Ocular Symptoms Survey; OCI = Ocular Comfort Index; OSDI = Ocular Surface Disease Index.

Table 11.2. Comparisons of corneal mechanical and cold sensation thresholds between asymptomatic and symptomatic participants for each symptom questionnaire. Data are presented as mean ± SD [min, max].

Questionnaire		Mechanical sensation threshold (μl)	p-value	Cold sensation threshold (μl)	p-value
OSDI	Asymptomatic (< 13)	2.1 ± 1.3 [0.3, 4.6]	0.98[1]	0.04 ± 0.02 [0.02, 0.09]	0.31[2]
	Symptomatic (≥ 13)	2.1 ± 1.1 [0.3, 4.2]		0.03 ± 0.02 [0.02, 0.07]	
OCI	Low (< 27)	2.3 ± 1.3 [0.3, 4.6]	0.36[1]	0.04 ± 0.02 [0.02, 0.09]	0.24[2]
	High (≥ 27)	2.0 ± 1.0 [0.3, 4.3]		0.04 ± 0.02 [0.02, 0.08]	
IOSS	Low (< 2)	2.4 ± 1.4 [0.3, 4.6]	0.16[1]	0.04 ± 0.02 [0.02, 0.09]	0.29[2]
	High (≥ 2)	1.9 ± 1.0 [0.3, 4.1]		0.04 ± 0.02 [0.02, 0.08]	
CVS-Q	Asymptomatic (< 6)	2.3 ± 1.3 [0.3, 4.6]	0.11[1]	0.05 ± 0.02 [0.02, 0.09]	0.03*[2]
	Symptomatic (≥ 6)	1.8 ± 0.9 [0.5, 4.2]		0.03 ± 0.02 [0.02, 0.07]	

CVS-Q = Computer Vision Syndrome Questionnaire; IOSS = Instant Ocular Symptoms Survey; OCI = Ocular Comfort Index; OSDI = Ocular Surface Disease Index. * Indicates statistically significant values ($p < 0.05$). [1] Unpaired T-test. [2] Mann-Whitney U test.

Table 11.3. Correlations between central corneal sensation thresholds and demographic variables and symptoms scores.

Variable	Mechanical sensation threshold		Cold sensation threshold	
	r/ρ	p-value	ρ	p-value
Age	0.10	0.47	0.24	0.04*
Hours of computer use per day	-0.02	0.88	0.02	0.87
Days of computer use per week	-0.07	0.61	-0.08	0.59
Hours of smartphone use per day	-0.09	0.53	-0.16	0.25
OSDI	0.02	0.92	-0.13	0.37
OSDI Symptoms	-0.04	0.78	-0.14	0.32
OSDI Vision-related function	-0.10	0.48	-0.22	0.11
OSDI Environmental triggers	0.04	0.81	-0.05	0.72
OCI	-0.04	0.78	-0.21	0.15
IOSS	-0.14	0.34	-0.11	0.44
CVS-Q	-0.23	0.09	-0.33	0.02*
CVS-Q Dry eye	-0.21	0.14	-0.28	0.04*
CVS-Q A/BV stress	-0.22	0.12	-0.25	0.07
Cold sensation threshold	0.63	< 0.001*	–	–

A/BV = Accommodative and binocular vision; CVS-Q = Computer Vision Syndrome Questionnaire; IOSS = Instant Ocular Symptoms Survey; OCI = Ocular Comfort Index; OSDI = Ocular Surface Disease Index; r = Pearson correlation coefficient; ρ = Spearman correlation coefficient. * Indicates statistically significant values ($p < 0.05$).

Table 11.4. Simple linear regression models for predictors of corneal mechanical and cold sensation thresholds.

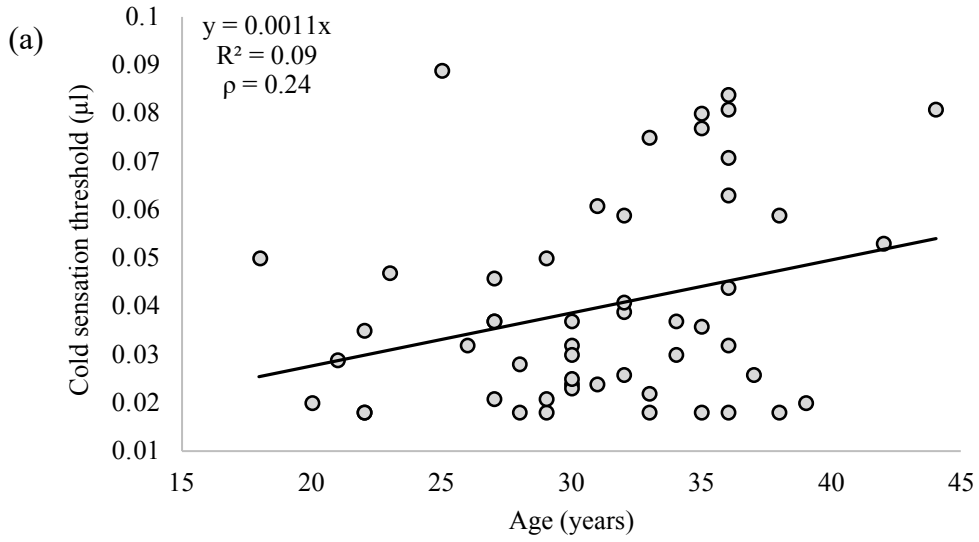
Corneal sensation threshold	Predictive variables	β	SE	Sβ	p-value	R square	Adjusted R square
Mechanical sensation threshold	(Constant)	0.639	0.275	–	0.02*	0.45	0.44
	Cold sensation threshold	39.164	6.232	0.575	< 0.001*		
Cold sensation threshold	Age	0.001	0.001	0.292	0.04*	0.09	0.07
	(Constant)	0.047	0.004	–	< 0.001*	0.09	0.07
	CVS-Q	-0.002	0.001	-0.295	0.03*		
	(Constant)	0.046	0.004	–	< 0.001*	0.08	0.06
	CVS-Q Dry eye	-0.002	0.001	-0.277	0.04*		
	(Constant)	0.014	0.004	–	0.002*	0.45	0.44
	Mechanical sensation threshold	0.011	0.002	0.668	< 0.001*		

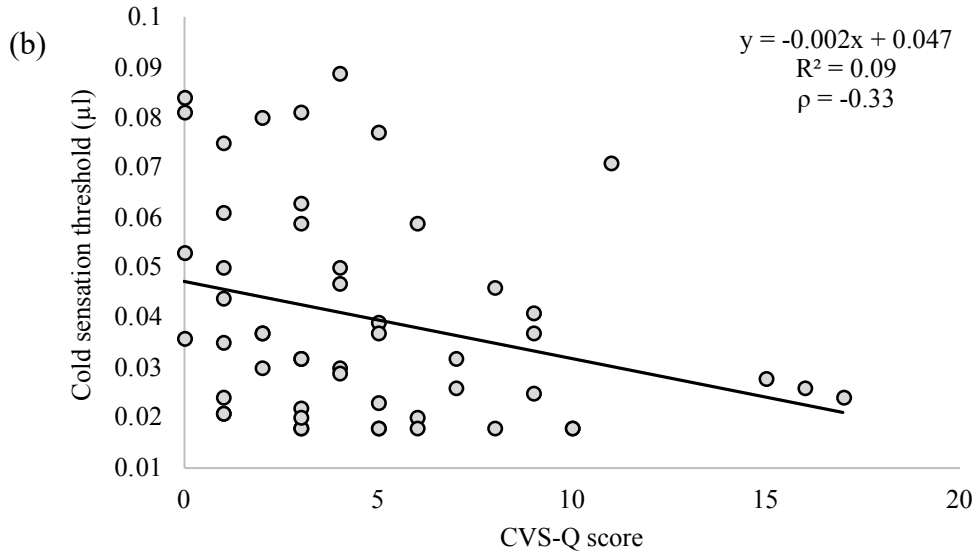
CVS-Q = Computer Vision Syndrome Questionnaire; Sβ = Standardized Coefficient; SE = Standard Error; β = Unstandardized Coefficient. * Indicates statistical significance ($p < 0.05$).

Table 11.5. Multiple linear regression analyses for predictors of corneal cold sensation threshold.

Corneal sensation threshold	Predictive variables	β	SE	Sβ	p-value	R square	Adjusted R square
Cold sensation threshold	Age	0.001	< 0.001	0.235	0.04*	0.48	0.46
	Mechanical sensation threshold	0.011	0.002	0.644	< 0.001*		

Sβ= Standardized Coefficient; SE= Standard Error; β = Unstandardized Coefficient. * Indicates statistical significance ($p < 0.05$).





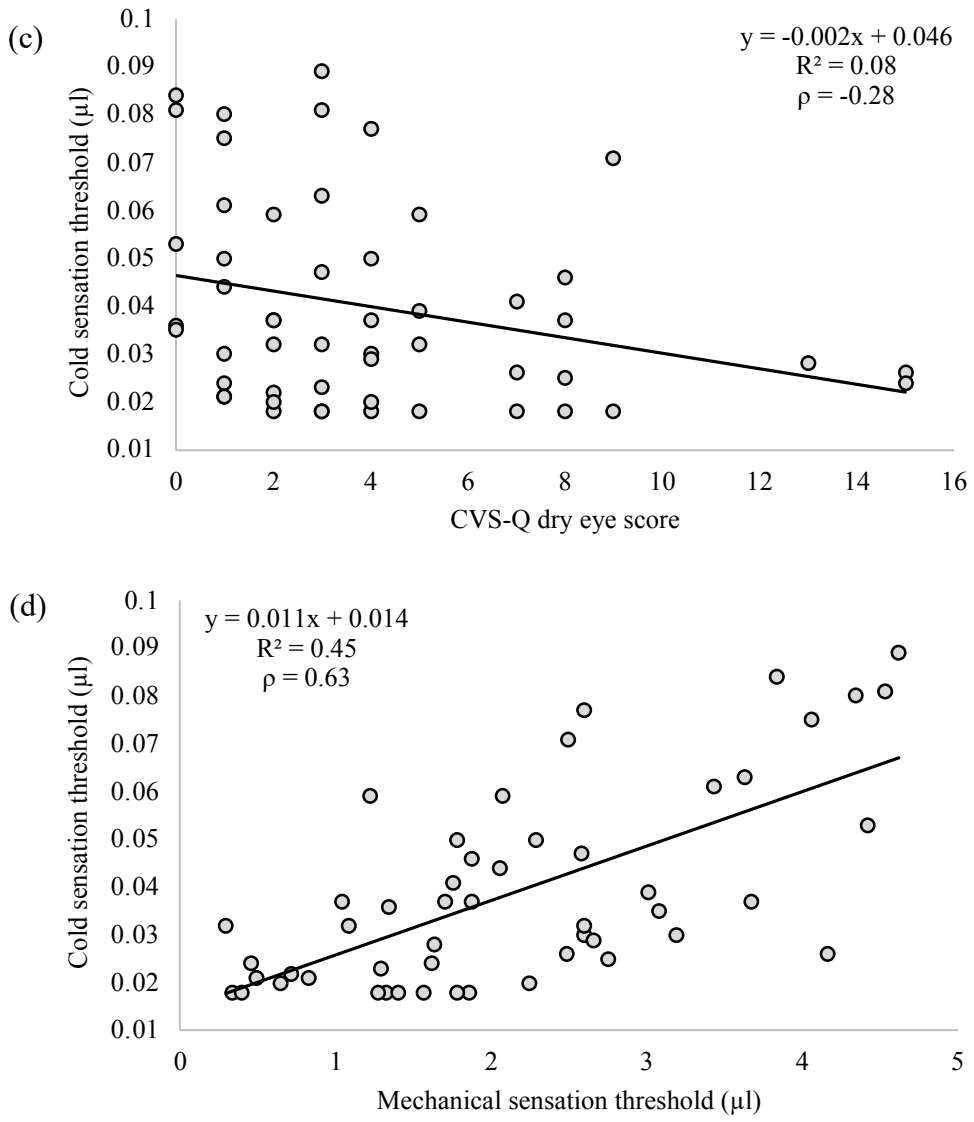


Figure 11.1. Relationship between cold sensation threshold and significant predictors: (a) age, (b) Computer Vision Syndrome Questionnaire (CVS-Q), (c) CVS-Q dry eye and (d) mechanical sensation threshold. R^2 = Adjusted R square; ρ = Spearman correlation coefficient.

11.4 Discussion

As the precorneal tear film thins and evaporates, the induced cooling of the corneal surface leads to increased activation of ion channels in cold thermoreceptors (transient receptor potential melastatin 8, TRPM8) (Belmonte et al., 2017; Parra et al., 2010; Quallo et al., 2015; Vereertbrugghen & Galletti, 2022). This evaporation-induced cooling is accompanied by hyperosmolarity (Bron et al., 2017; Lemp et al., 2011; Vereertbrugghen & Galletti, 2022), which additionally activates the ion channels expressed by polymodal

nociceptors (transient receptor potential vanilloid 1, TRPV1) and probably by high-threshold/low activity cold thermoreceptors (aka., cold nociceptors), especially at noxious osmolarity levels (Belmonte et al., 2017; Guzmán et al., 2020; Parra et al., 2014; Vereertbrugghen & Galletti, 2022).

As addressed in detail in previous chapters (Chapters 1 and 5), digital device use has been associated with decreased blink rate and amplitude and increased ocular surface exposure (Portello et al., 2012; Talens-Estarelles et al., 2022a). Under these drying conditions, TRPM8 and TRPV1 ion channels are activated. The activation of these ion channels leads to an increased firing rate of cold thermoreceptor and polymodal nociceptor neurons which give rise to unpleasant and painful sensations (i.e., burning, itching, feeling of a foreign body, eye pain, etc.) (Belmonte et al., 2004a; Belmonte et al., 2004b; Belmonte & Gallar, 2011b; Hirata & Meng, 2010; Vereertbrugghen & Galletti, 2022), often reported by computer users. At the same time, the response of these neurons activates compensatory mechanisms, through the LFU (Stern et al., 2004), which increases basal tear production and blink rate (Belmonte & Gallar, 2011b; Hirata & Meng, 2010; Kovács et al., 2016; Parra et al., 2010; Vereertbrugghen & Galletti, 2022). This explains the increased reports of tearing and excessive blinking experienced during or immediately after digital device use (Nielsen et al., 2008) and observed in previous chapters (Chapters 5, 7-10).

The present study revealed that computer users with DES (CVS-Q score ≥ 6) had lower cold sensation thresholds (higher sensitivity) at the central cornea than asymptomatic individuals. In parallel, having greater symptoms of DES, particularly dry eye-related symptoms, was predictive of a lower cold sensation threshold. These results suggest alterations in psychophysically assessed corneal sensory function in computer users with DES, particularly those with dry eye-related symptoms, with enhanced cooling sensitivity (i.e., hypersensitivity) and lowered excitation thresholds of the corneal neurons to corneal cooling. Judging by the study results and considering that DES has been acknowledged as a consistent risk factor for dry eye (Stapleton et al., 2017), changes in corneal nerve function in individuals with DES probably resemble the neurophysiological mechanisms leading to nerve dysfunction in DED.

Repetitive drying of the ocular surface may cause the release of endogenous inflammatory mediators originating from injured cells (Belmonte et al., 2004a; Belmonte et al., 2004b; Belmonte et al., 2017; Bron et al., 2017), which activate ion channels in nociceptors (Belmonte, 2019; Belmonte et al., 2004a; Belmonte et al., 2004b;

Vereertbrugghen & Galletti, 2022). Inflammatory mediators modify the normal responsiveness of nociceptors (i.e., sensitization), causing them to exhibit spontaneous activity and lowered excitation thresholds, rendering previously non-noxious stimuli capable of evoking sensation (Belmonte, 2019; Belmonte et al., 2004a; Belmonte et al., 2017; Galor et al., 2018; Labetoulle et al., 2019; Vereertbrugghen & Galletti, 2022).

Changes in cold thermoreceptor responsiveness with prolonged ocular surface dryness have also been reported (Hirata & Rosenblatt, 2014; Kovács et al., 2016; Situ et al., 2016, 2020b). Kováks et al. (2016) reported a progressive increase in excitability of corneal cold trigeminal ganglion neurons in guinea pigs which had their lachrymal glands removed. Similarly, Hirata and Rosenblatt (2014) found that after exposure to hyperosmolar tears, high threshold/low activity corneal neurons became sensitized and began to respond to slight cooling, which could explain the cooling-evoked discomfort in dry eye patients. Moreover, increased cooling sensitivity and suprathreshold sensation have been reported in symptomatic CL wearers (Situ et al., 2016, 2020a). The authors attributed these results to low-grade subclinical inflammation during CL wear, which led to the release of inflammatory mediators, and which modified the activities of nerve endings and the expression of ion channels (Situ et al., 2020a), although animal studies have shown that inflammatory mediators inhibited TRPM8 cold-sensing ion channels (Zhang et al., 2012). The authors argued that sensitization of high threshold/low activity cold thermoreceptors could resemble sensitized polymodal nociceptors and explain the higher cold sensitivity in symptomatic CL wearers (Situ et al., 2020a).

Overall, repetitive drying of the ocular surface due to sustained computer operation, or other causes, may give rise to low-grade inflammation in individuals with DES. As in the reports of CL discomfort, this scenario may lead to the release of inflammatory mediators and cause changes in the excitability of high threshold/low activity thermoreceptors, especially attuned to strong cooling (Situ et al., 2016, 2020a). This might explain the higher sensitivity of symptomatic computer users to the cold stimulus of the present study (15 ºC). Sensitized high threshold/low activity thermoreceptors begin to respond to slight cooling normally encountered between blinks (Hirata & Rosenblatt, 2014). This cooling might be amplified by the reduced blink rate (increased inter-blink interval) during digital device use (Talens-Estarelles al., 2022a), contributing to the increased ocular surface symptoms experienced during computer use by individuals with DES. Although a significant association between DES and cold sensitivity was found, the goodness-of-fit of the simple linear models (i.e., model

accuracy) was considerably small (adjusted $R^2 \leq 0.09$). Consequently, despite a significant trend, there is high variability in data, and these results should be interpreted with caution.

On the contrary, the present study found no associations between mechanical sensitivity and ocular symptoms. Corneal mechanonociceptors are activated exclusively by mechanical forces (Belmonte et al., 2004a; Belmonte et al., 2004b; Belmonte et al., 2017; Belmonte & Gallar, 2011a; González-González et al., 2017). Brief touching of the ocular surface, particularly by a moving object, activates mainly mechanonociceptors and, to a small extent, polymodal nociceptors (Belmonte et al., 2004a; Belmonte et al., 2004b). The fast-moving liquid droplets ejected by the UNSW LJA, with a temperature matching that of the ocular surface, generates a mechanical force that primarily activates corneal mechanonociceptors. Contrarily, according to recent investigations, a true mechanical threshold for corneal sensitivity cannot be established with an air-jet aesthesiometer because its air jet stimulus is likely to have a thermal component, caused by tear film thinning and evaporation due to the airflow (Golebiowski et al., 2013; Nosch et al., 2018). Contradictory findings related to the changes in mechanical sensitivity with DED have been reported, which could stem from differences in the aesthesiometers used and the heterogeneity of DED. According to the results of the present study, the function of corneal mechanonociceptors may remain unaffected, despite the altered response of sensory nerve terminals to corneal cooling in symptomatic computer users. As reported in recent research, prolonged repeated periods of ocular surface stimulation by tear film instability leads to significant changes in suprathreshold scaling and may differently affect mechanical and cooling pathways (Stapleton et al., 2013). More research is warranted on the potential changes in corneal nerve function in individuals with DES and on the mechanisms leading to corneal nerve damage in DED.

In parallel, no associations between sensation thresholds and symptoms of dry eye and ocular discomfort (OSDI, OCI and IOSS) were found in the present study. The relationship between ocular surface symptoms and corneal sensitivity to various stimuli is not consistently reported in the literature and requires further investigation in specifically designed studies (Spierer et al., 2016; Stapleton et al., 2013, 2019). The absence of a relationship between peripheral corneal nerve function and general symptoms of dryness and discomfort in the presence of a relationship with DES, could be due to differences in the symptoms surveyed in the questionnaires and/or to the

contribution of computer use to the symptoms attributable to hyperexcitability of thermoreceptors.

A strong positive correlation between mechanical and cold sensation thresholds was observed in the present study. Boucier et al. (2005) reported a direct correlation between mechanical and thermal (both heat and cold) thresholds in healthy individuals. Nevertheless, other authors observed a correlation between mechanical and heat thresholds, but not between mechanical and cold thresholds (López-de la Rosa et al., 2016). The authors attributed these results to polymodal fibres processing mechanical and heat stimuli, as opposed to cold thermoreceptors being uniquely responsible for the cold thresholds. Recently, González-González et al. (2017) pointed out that the two subtypes of corneal cold thermoreceptor terminals, although preferentially sensitive to cold, also responded to other stimuli such as mechanical forces, which was a prominent characteristic of corneal cold thermoreceptors. This may explain the association between mechanical and cold sensation thresholds obtained in the present study. Nevertheless, further studies are needed to clarify the exact relationship between the different types of corneal sensitivity.

Finally, higher age was associated with increased cold sensation threshold (lower sensitivity) at the central corneal. Previous research observed that corneal thresholds for thermal stimulation, obtained with a gas aesthesiometer, increased with age in individuals with DED (Bourcier et al., 2005), while others found that age was not critical to cooling sensitivity (Corcoran et al., 2017). At the same time, no association between mechanical sensitivity and age was found in the present study, in contrast with studies which utilise the Cochet-Bonnet aesthesiometer and the gas aesthesiometer, and which report significant reductions in corneal mechanical sensitivity with advancing age, mainly in those older than 35 (Acosta et al., 2006; Bourcier et al., 2005; Golebiowski et al., 2008; Mirzajan et al., 2015). However, this is not a universal finding (De Paiva & Pflugfelder, 2004; Ehrmann et al., 2023). The present study included only a small number of participants over 35 years of age, which may explain why no associations with mechanical sensitivity were obtained.

The present study had some limitations to consider. Eight participants reached the lowest possible cold stimulation threshold allowed by the instrument. This floor effect may have affected some associations between variables. Nevertheless, the UNSW LJA offers a significantly wider stimulus intensity range compared to other aesthesiometers and a considerably lower proportion of truncated measurements were obtained in

comparison (Chao et al., 2015; Golebiowski et al., 2011). Additionally, only young to middle-aged participants were recruited, thus the results cannot be extrapolated to older individuals.

In conclusion, symptomatic computer users exhibited lower cold sensation thresholds compared to asymptomatic users, which suggests alterations in the corneal sensory function among computer users with DES. Likewise, greater symptoms of DES, particularly dry eye-related symptoms, were associated with lowered excitation thresholds of the corneal neurons to corneal cooling. Based on previous findings on discomfort and dry eye, the enhanced cooling sensitivity of symptomatic computer users and their increased symptoms of dryness during computer use could be partially attributable to changes in the excitability of high threshold/low activity cold thermoreceptors. Corneal hypersensitivity to cold stimuli as a marker of ocular discomfort during computer use requires further investigation. More research is also warranted on the mechanisms leading to corneal nerve damage in DED.

12.

Changes in corneal mechanical and cold sensitivity following computer use

12.1 Introduction

As addressed in detail in the introduction chapter (*1.3. Tear film and ocular surface, 1. Introduction*; Talens-Estarelles et al., 2021) and reported in several other chapters (Chapters 6-10), ocular surface and tear film abnormalities, including reduced tear stability, alterations in tear volume and tear composition, increased oxidative stress and ocular surface inflammation, have been associated with computer use (Choi et al., 2018; Yazici et al., 2015). All these physical and chemical disturbances that accompany excessive evaporation may act as stimuli for the distinct functional types of sensory neurons that innervate the ocular surface (mechanonociceptor, polymodal nociceptor, and cold thermoreceptor neurons) and give rise to the unpleasant and painful sensations often reported by computer users (Belmonte et al., 2004b; Belmonte et al., 2017; Hirata et al., 2012; Vereertbrugghen & Galletti, 2022). At the same time, the response of these neurons activates compensatory mechanisms, through the LFU (Stern et al., 2004), which may explain the increased reports of tearing and excessive blinking experienced during or immediately after digital device use. (Belmonte & Gallar, 2011a; Parra et al., 2010; Quallo et al., 2015; Vereertbrugghen & Galletti, 2022)

Repetitive drying of the ocular surface may alter the excitability of corneal receptors and their responsiveness to new stimuli (Belmonte, 2019; Belmonte et al., 2004a; Belmonte et al., 2004b; Belmonte et al., 2017; Vereertbrugghen & Galletti, 2022). Evidence has accrued on the existence of changes in peripheral corneal nerve function caused by DED (Belmonte et al., 2017; Labetoulle et al., 2019; Vereertbrugghen & Galletti, 2022), although a unifying model of corneal nerve dysfunction in dry eye has not been reached, probably due to diverse presentations of the disease. More recently, investigations found that prolonged repeated periods of ocular surface stimulation by tear film instability led to significant changes in suprathreshold scaling of polymodal nociceptors and cold thermoreceptors (Situ et al., 2019). Similarly, the results of Chapter 11 (*11. Corneal hypersensitivity to cold stimuli in symptomatic computer users*) indicate that symptomatic computer users might have impaired corneal sensory function, characterized by hypersensitivity to cold stimuli.

Accordingly, the present chapter aimed to evaluate, for the first time, the potential effects of short-term computer use on the sensitivity of the cornea to various stimuli and analyse associations with possible determinants.

12.2 Methods

12.2.1 Participants

Fifty-two young volunteers aged 18 to 44 years participated in this clinical trial. Participants were recruited from the School of Optometry and Vision Science at the UNSW (Sydney, Australia) by means of email and poster advertisements. Inclusion criteria were age ≥ 18 and ≤ 45, CDVA better or equal to 20/30 (0.17 logMAR) in both eyes and computer use of at least 4 hours a day, 4 days a week. Exclusion criteria were history of ocular pathology or systemic disease that could potentially impact the integrity of the ocular surface, including, but not limited to, Graves disease, diabetes, Sjögren syndrome or multiple sclerosis, current pregnancy or breastfeeding, current eye infections or inflammation, current use of eye and/or general medications known to affect eye health or comfort, history of eye surgery and history of rigid CL wear or use of soft CLs in the past 7 days. Additionally, participants were instructed not to use artificial tears within 2 hours of the visit.

The study followed the tenets of the Declaration of Helsinki and was approved by the UNSW human research ethics committee. All the participants were informed about the nature of the study and gave their written consent.

12.2.2 Measurement of sensation threshold

The measurement procedure was like that described in Chapter 11 (*11. Corneal hypersensitivity to cold stimuli in symptomatic computer users*). Cold (15°C) and mechanical sensation thresholds at the central cornea were determined using the UNSW LJA (UNSW, Sydney, Australia). The technical details of the UNSW LJA utilised in this investigation have been described elsewhere (Ehrmann et al., 2018). In brief, a microvalve which switches on and off at variable ‘on’ periods allows a droplet of adjustable volume to be propelled onto the ocular surface to generate a stimulus of variable intensity. The ocular surface sensation threshold is determined based on the participants’ ‘felt’ or ‘not felt’ subjective feedback, provided via a handheld pushbutton, which feeds into an automated double staircase algorithm. After the high and low starting staircases have converged for the first time, 9 more stimulations were applied, and the sensation threshold was automatically calculated as the mean droplet volume of these last 9 stimulations. The clinical reliability of the instrument to determine corneal sensitivity

has previously been verified (Ehrmann et al., 2023). Please refer to Chapter 3 for detailed information on the device and measurement procedure (*3.2.6 UNSW Liquid Jet Aesthesiometer, 3. General methods*).

12.2.3 Protocol and experimental design

Central corneal mechanical and cold sensation thresholds were assessed in a group of frequent computer users (computer use ≥ 4 hours/day and ≥ 4 days/week), before and after working on a computer for one hour.

Fifteen minutes before the entry of the participants, the laboratory was set up and acclimatised. One of the authors checked whether or not each volunteer met the inclusion/exclusion criteria before initiating the experiment. Visual acuity and ocular surface health were subsequently assessed. Symptoms of dry eye, ocular discomfort and DES were evaluated using the OSDI, OCI and CVS-Q. Likewise, the intensity of dry eye symptoms and discomfort at the time of the study visit was evaluated using the IOSS. Detailed information on the questionnaires can be found in Chapter 3 (*3.2.1 Symptomatology questionnaires, 3. General methods*). Additionally, participants were surveyed about the average hours of computer and smartphone use per day and average days of computer use per week. Next, careful instructions were recited to the participants via a predetermined script before the measurement of corneal sensitivity.

Prior to the measurement, a brief test run was performed in the non-test eye to familiarise the participant with the instrumentation and procedure. Mechanical and cold sensation thresholds were determined at the central cornea of the randomly selected eye of each participant. The order of the measurements was randomized, and a minimum of 5 minutes was left between measurements. To minimize the effects of outdoor conditions on the way to the laboratory, a minimum acclimatization period of 20 minutes was ensured between the entry of the participants into the room and the determination of corneal sensitivity.

Next, participants performed a free-choice computer task for 60 minutes using a LCD desktop monitor (Dell P2423DE; Dell Inc., TX, USA). The device was placed in accordance with the typical viewing distance and angle of usage: that is, 60-cm distance, at approximately 10° angle below the eye level of the participants and with an inclination angle of 100° from the surface of the desk. Participants were instructed to carry out the respective task until the examiner told them to stop. The task was carried out under

constant artificial illumination. Room illuminance was provided by indirect lighting to avoid any glare sources.

Corneal sensitivity measurements were then repeated. Additionally, participants responded to the OCI, CVS-Q and IOSS. To match the study question, participants were instructed to respond to the questionnaires based exclusively on the symptoms experienced during the computer task. The OSDI was not administered as the majority of its questions could not be extrapolated to the task (windy conditions, driving at night, reading, etc.).

All the measurements were taken in the same laboratory and by the same experienced examiner. Visits were carried out in the mornings, between 9 am and 12 pm, and a minimum of 3 hours after waking to account for possible diurnal variation in sensitivity (Millodot, 1972). Room temperature and humidity were constantly monitored and remained stable at 22.5 ± 0.7°C and 41 ± 5%, respectively.

12.2.4 Statistical analysis

Statistical analysis was performed using SPSS software v.28 (IBM Corp., Armonk, NY, USA). The normality of data was assessed using the Kolmogorov-Smirnov test. When parametric test assumptions were fulfilled, a paired sample t-test was used to compare the central corneal sensation thresholds obtained before and after the computer task. The non-parametric Wilcoxon paired signed-rank test was used when parametric test assumptions were not fulfilled. Likewise, the IOSS score obtained before and after computer use was compared to assess the differences in symptomatology with the computer task. OCI and CVS-Q scores were not compared, as everyday symptoms reported at the beginning of the visit were not representative of a pre-task state.

Pearson (r) correlations were carried out between changes in corneal sensation thresholds with computer use (post-task – pre-task) and demographic variables, everyday questionnaire scores, and symptoms experienced during the computer task (intra-task), in order to identify possible determinants of changes in corneal sensitivity with computer use. The non-parametric Spearman (ρ) test was used when parametric test assumptions were not fulfilled. Similarly, an unpaired t-test or Mann-Whitney U test, depending on sample distribution, was used to compare demographic variables and symptom scores between participants with an increase vs decrease/no change in sensation thresholds with computer use.

Analyses were performed for the OSDI total score and for the scores obtained in each of the three questionnaire subscales (visual symptoms, vision-related function and environmental triggers). Similarly, the CVS-Q total score was split into two categories based on the two main DES symptomatology groups (Portello et al., 2012): dry eye (questions 1-10, 13, 15) and accommodative and binocular vision stress (questions 10-16).

12.3 Results

Sixty-four volunteers were initially recruited out of which 52 (23 females and 29 males) ranging in age from 18 to 44 years (31 ± 6 years) met the inclusion/exclusion criteria and completed all measurements. Out of the 52 participants, 36 were Asian, 13 White, 2 Black and 1 Hispanic/Latino. The average time of computer use reported by the participants was 7.4 ± 2.6 hours a day, 6 ± 1 days a week. The reported time of smartphone use was 3.8 ± 2.7 hours a day.

Table 12.1 displays the everyday ocular surface symptoms of the study participants and symptoms experienced during the computer task and the central corneal sensation thresholds obtained before and after working on the computer. Additionally, Figure 12.1 represents the ladder plots of the individual changes in corneal sensation thresholds with computer use. No significant differences between the mechanical and cold sensation thresholds obtained before and after one hour of computer use were observed ($p = 0.08$ for mechanical threshold and $p = 0.06$ for cold threshold). Likewise, no change in the IOSS score with the computer task was found ($p = 0.83$).

Table 12.2 shows the correlations between the changes in corneal sensation thresholds with computer use and demographic variables and symptom scores. No significant associations between the changes in corneal sensation thresholds with computer use and demographic variables, everyday symptoms or symptoms experienced during the computer task were observed ($p \geq 0.17$ for mechanical threshold and $p \geq 0.33$ for cold threshold). A significant correlation was found between the change in mechanical threshold with the computer task and the mechanical ($r = -0.51$, $p < 0.001$) and cold ($\rho = -0.30$, $p = 0.03$) thresholds obtained at baseline. Similarly, the change in cold sensation threshold with the computer task was significantly correlated with the cold sensation threshold obtained at baseline ($\rho = -0.31$, $p = 0.03$). Finally, the change in mechanical

sensation threshold with computer use was significantly associated with the change in cold sensation threshold ($\rho = 0.31$, $p = 0.03$).

Table 12.3 shows the comparisons of demographic variables and symptom scores between participants with an increase vs decrease/no change in corneal sensation thresholds with computer use. No significant differences in any demographic variable or symptom score were found between participants with an increase vs decrease/no change in sensation threshold with computer use ($p \geq 0.13$ for mechanical threshold and $p \geq 0.29$ for cold threshold). On the contrary, participants with an increase in cold sensation threshold exhibited a significantly higher increase in mechanical sensation threshold ($p = 0.04$).

Table 12.1. Ocular surface symptoms and symptoms experienced during the computer task (intra-task) and central corneal sensation thresholds obtained before (baseline) and after (post-task) computer use. Data are presented as mean ± SD [min, max].

Variable (n = 52)	Baseline	Intra-task/post-task	p-value
OSDI[a]	12.9 ± 14.0 [0.0, 55.0]	–	–
OSDI Symptoms	10.8 ± 11.6 [0.0, 40.0]	–	–
OSDI Vision-related function	10.8 ± 18.1 [0.0, 81.3]	–	–
OSDI Environmental triggers	16.8 ± 20.1 [0.0, 83.3]	–	–
OCI[b]	26.2 ± 13.0 [0.0, 61.2]	18.3 ± 15.5 [0, 67.1]	–
IOSS	2 ± 3 [0, 10]	2 ± 3 [0, 10]	0.84[2]
CVS-Q[b]	5 ± 4 [0, 17]	2 ± 3 [0, 15]	–
CVS-Q Dry eye	4 ± 4 [0, 15]	2 ± 3 [0, 13]	–
CVS-Q A/BV stress	2 ± 2 [0, 8]	0 ± 1 [0, 6]	–
Mechanical sensation threshold (μl)	2.1 ± 1.2 [0.3, 4.6]	2.4 ± 1.1 [0.3, 4.7]	0.08[1]
Cold sensation threshold (μl)	0.04 ± 0.02 [0.02, 0.09]	0.04 ± 0.02 [0.02, 0.10]	0.06[2]

A/BV = Accommodative and binocular vision; CVS-Q = Computer Vision Syndrome Questionnaire; IOSS = Instant Ocular Symptoms Survey; OCI = Ocular Comfort Index. [a] Intra-task OSDI was not assessed as the majority of its questions could not be extrapolated to the computer task. [b] Everyday and intra-task symptom scores are not comparable. [1] Paired sample t test. [2] Wilcoxon paired signed-rank test.

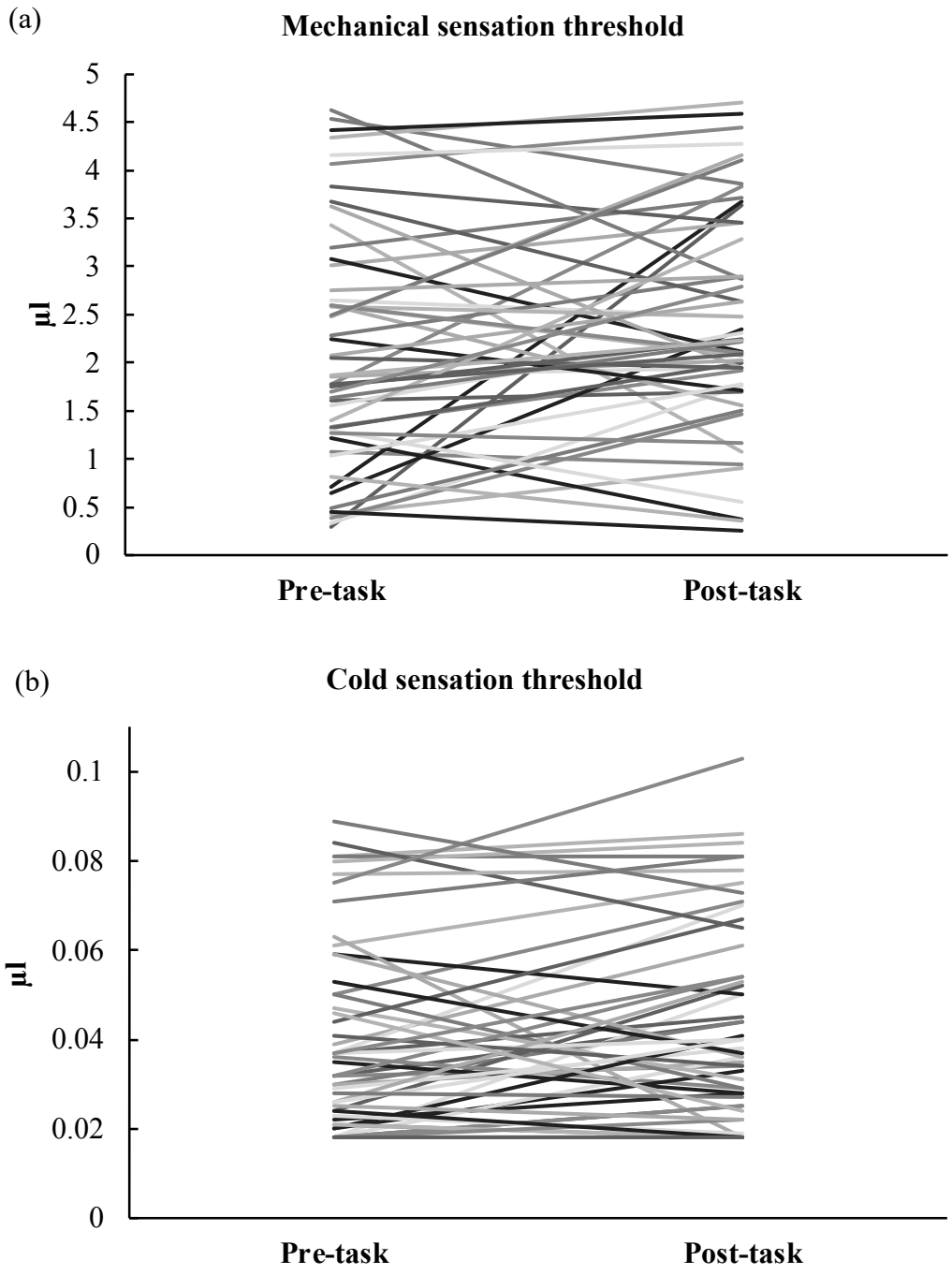


Figure 12.1. Ladder plots of central corneal sensation thresholds obtained before (pre-task) and after (post-task) computer use. (a) mechanical sensation threshold, (b) cold sensation threshold.

Table 12.2. Correlations between changes in corneal sensation thresholds with computer use (post-task – pre-task) and demographic variables and symptom scores.

Variable	Change in mechanical sensation threshold		Change in cold sensation threshold	
	r/ρ	p-value	r/ρ	p-value
Age	0.10	0.50[1]	0.04	0.80[1]
OSDI	-0.02	0.90[2]	0.07	0.62[2]
OSDI Symptoms	-0.06	0.69[2]	-0.06	0.65[2]
OSDI Vision-related function	0.09	0.52[2]	-0.04	0.79[2]
OSDI Environmental triggers	0.06	0.66[2]	0.09	0.52[2]
OCI	0.04	0.79[2]	-0.10	0.48[2]
OCI (intra-task)	0.19	0.17[2]	< 0.005	0.99[2]
IOSS	-0.07	0.62[2]	-0.02	0.92[2]
IOSS (intra-task)	0.18	0.20[2]	-0.03	0.83[2]
CVS-Q	0.17	0.24[2]	0.02	0.91[2]
CVS-Q (intra-task)	0.06	0.67[2]	0.04	0.78[2]
CVS-Q Dry eye	0.15	0.28[2]	0.05	0.72[2]
CVS-Q Dry eye (intra-task)	0.08	0.58[2]	0.03	0.84[2]
CVS-Q A/BV stress	0.12	0.41[2]	-0.14	0.33[2]
CVS-Q A/BV stress (intra-task)	0.06	0.69[2]	0.04	0.76[2]
Mechanical sensation threshold (baseline)	-0.51	< 0.001*[1]	-0.16	0.27[1]
Cold sensation threshold (baseline)	-0.30	0.03*[2]	-0.31	0.03*[2]
Change in mechanical sensation threshold	–	–	0.31	0.03[1]

A/BV = Accommodative and binocular vision; CVS-Q = Computer Vision Syndrome Questionnaire; IOSS = Instant Ocular Symptoms Survey; OCI = Ocular Comfort Index; OSDI = Ocular Surface Disease Index; r = Pearson correlation coefficient; ρ = Spearman correlation coefficient. * Indicates statistically significant values ($p < 0.05$). [1] Pearson correlation coefficient. [2] Spearman correlation coefficient.

Table 12.3. Comparisons of demographic variables and symptom scores between participants with increase vs decrease/no change in corneal sensation thresholds with computer use. Data are presented as mean ± SD [min, max].

Variable	Change in mechanical sensation threshold			Change in cold sensation threshold		
	Decrease/no change (n = 20)	Increase (n = 32)	p-value	Decrease/no change (n = 22)	Increase (n = 30)	p-value
Age (years)	30 ± 6 [20, 44]	32 ± 5 [18, 42]	0.43[1]	31 ± 6 [18, 44]	31 ± 5 [20, 39]	0.81[1]
Sex (female:male)	9:11	14:18	0.93[3]	11/11	12/18	0.47[3]
Ethnicity (Asian:White:Black:Latino)	14:5:0:1	22:8:2:0	0.42[3]	15:7:0:0	21:6:2:1	0.41[3]
OSDI	9.2 ± 7.9 [0.0, 31.8]	15.2 ± 16.4 [0.0, 55.0]	0.68[2]	15.0 ± 15.9 [0.0, 52.3]	11.3 ± 12.3 [0.0, 55.0]	0.76[2]
OSDI Symptoms	9.5 ± 7.9 [0.0, 25.0]	11.6 ± 13.4 [0.0, 40.0]	0.82[2]	13.2 ± 13.1 [0.0, 40.0]	9.0 ± 10.1 [0.0, 40.0]	0.29[2]
OSDI Vision-related function	7.8 ± 10.3 [0.0, 33.3]	12.7 ± 21.6 [0.0, 81.3]	0.88[2]	13.2 ± 20.5 [0.0, 81.3]	9.1 ± 16.3 [0.0, 81.3]	0.56[2]
OSDI Environmental triggers	10.4 ± 12.6 [0.0, 50.0]	20.7 ± 22.9 [0.0, 83.3]	0.13[2]	19.5 ± 22.7 [0.0, 66.7]	14.7 ± 18.1 [0.0, 83.3]	0.70[2]
OCI	26.3 ± 10.0 [0.0, 49.3]	26.2 ± 14.7 [0.0, 61.2]	0.97[1]	28.4 ± 13.6 [0.0, 61.2]	24.7 ± 12.5 [0.0, 49.3]	0.32[1]
OCI (intra-task)	15.1 ± 12.6 [0.0, 36.2]	20.3 ± 17.0 [0.0, 67.1]	0.19[2]	20.1 ± 17.2 [0.0, 67.1]	17.0 ± 14.4 [0.0, 43.6]	0.65[2]
IOSS	2 ± 2	2 ± 3	0.38[2]	2 ± 3	2 ± 2	0.50[2]

	[0, 8]	[0, 10]		[0, 10]	[0, 8]	
IOSS (intra-task)	1 ± 2 [0, 5]	2 ± 3 [0, 10]	0.43[2]	2 ± 3 [0, 10]	2 ± 2 [0, 8]	0.49[2]
CVS-Q	4 ± 4 [0, 17]	5 ± 4 [0, 16]	0.48[2]	5.1 ± 4.9 [0, 17]	4.5 ± 3.4 [1, 16]	0.90[2]
CVS-Q (intra-task)	2 ± 2 [0, 9]	3 ± 4 [0, 15]	0.71[2]	2 ± 3 [0, 14]	2 ± 3 [0, 15]	0.93[2]
CVS-Q Dry eye	3 ± 3 [0, 15]	4 ± 4 [0, 15]	0.45[2]	4 ± 4 [0, 15]	4 ± 3 [1, 15]	0.77[2]
CVS-Q Dry eye (intra-task)	2 ± 2 [0, 6]	2 ± 3 [0, 13]	0.59[2]	2 ± 3 [0, 12]	2 ± 3 [0, 13]	0.98[2]
CVS-Q A/BV stress	2 ± 2 [0, 8]	2 ± 2 [0, 8]	0.94[2]	2 ± 2 [0, 8]	1 ± 2 [0, 8]	0.31[2]
CVS-Q A/BV stress (intra-task)	0 ± 1 [0, 5]	0 ± 1 [0, 6]	0.68[2]	0 ± 1 [0, 5]	0 ± 1 [0, 6]	0.88[2]
Mechanical sensation threshold (baseline) (µl)	2.5 ± 1.2 [0.5, 4.6]	1.9 ± 1.2 [0.3, 4.4]	0.08[2]	2.3 ± 1.3 [0.5, 4.6]	2.1 ± 1.2 [0.3, 4.3]	0.55[1]
Cold sensation threshold (baseline) (µl)	0.05 ± 0.02 [0.02, 0.09]	0.04 ± 0.02 [0.02, 0.08]	0.15[2]	0.04 ± 0.02 [0.02, 0.09]	0.04 ± 0.02 [0.02, 0.08]	0.46[2]
Change in mechanical sensation threshold (µl)	–	–	–	-0.1 ± 0.9 [-1.8, 1.8]	0.7 ± 1.2 [-2.3, 3.3]	0.04*[1]

A/BV = Accommodative and binocular vision; CVS-Q = Computer Vision Syndrome Questionnaire; IOSS = Instant Ocular Symptoms Survey; OCI = Ocular Comfort Index; OSDI = Ocular Surface Disease Index; r = Pearson correlation coefficient; ρ = Spearman correlation coefficient. * Indicates statistically significant values ($p < 0.05$) [1] Unpaired sample t-test. [2] Mann-Whitney U test. [3] chi-square test.

12.4 Discussion

The results of the present study indicate that the sensitivity of the cornea to mechanical and cold stimuli was not affected after one hour of computer work. No relationships were observed between the changes in corneal sensitivity with computer use and demographic variables (age, sex and ethnicity), everyday symptoms of dry eye and discomfort or symptoms experienced during the computer task. In parallel, the intensity of the symptoms of discomfort and dry eye (IOSS score) did not differ between before and after computer work.

As the precorneal tear film thins and evaporates, the induced cooling of the corneal surface leads to increased activation of ion channels in cold thermoreceptors (TRPM8) (Belmonte et al., 2017; Parra et al., 2010; Quallo et al., 2015; Vereertbrugghen & Galletti, 2022). This evaporation-induced cooling is accompanied by hyperosmolarity (Bron et al., 2017; Lemp et al., 2011; Vereertbrugghen & Galletti, 2022), which additionally activates the ion channels expressed by polymodal nociceptors (TRPV1) and probably by high-threshold/low activity cold thermoreceptors (aka., cold nociceptors), especially at noxious osmolarity levels (Belmonte et al., 2017; Guzmán et al., 2020; Parra et al., 2014; Vereertbrugghen & Galletti, 2022).

Digital device use has been associated with a decreased blink rate and amplitude and increased ocular surface exposure (Portello et al., 2012, 2013; Rosenfield et al., 2015; Sheppard & Wolffsohn, 2018; Talens-Estarelles et al., 2022a). Under these drying conditions, TRPM8 and TRPV1 ion channels are activated. The activation of these ion channels leads to an increased firing rate of cold thermoreceptor and polymodal nociceptor neurons which probably gives rise to unpleasant and painful sensations (i.e., burning, itching, feeling of a foreign body, eye pain, etc.) (Belmonte et al., 2004a; Belmonte et al., 2004b; Belmonte et al., 2017; Belmonte & Gallar, 2011b; Vereertbrugghen & Galletti, 2022), often reported by computer users (Seguí et al., 2015). At the same time, the response of these neurons activates compensatory mechanisms, through the LFU (Stern et al., 2004), which increases basal tear production and blink rate (Belmonte & Gallar, 2011a; Kovács et al., 2016; Parra et al., 2010; Vereertbrugghen & Galletti, 2022). This explains the reports of tearing and excessive blinking frequently reported during digital device use.

Repetitive drying of the ocular surface may cause the release of endogenous inflammatory mediators originating from injured cells, which activate ion channels in

nociceptors (Belmonte, 2019; Belmonte et al., 2004a; Belmonte et al., 2004b; Belmonte et al., 2017; Vereertbrugghen & Galletti, 2022). Inflammatory mediators modify the normal responsiveness of nociceptors (i.e., sensitization), causing them to exhibit spontaneous activity and lowered excitation thresholds, rendering previously non-noxious stimuli capable of evoking sensation (Belmonte, 2019; Belmonte et al., 2004a; Belmonte et al., 2017; Labetoulle et al., 2019; Vereertbrugghen & Galletti, 2022). At the same time, changes in cold thermoreceptor responsiveness with prolonged ocular surface dryness have also been reported (Hirata & Rosenblatt, 2014; Kovács et al., 2016; Situ et al., 2016, 2020).

Based on the results of the present study, tear film evaporation associated with sustained gazing and increased ocular surface exposure during the computer task potentially activated ion channels of corneal receptors and triggered compensatory mechanisms through the LFU. This could partially explain the dry eye symptoms and discomfort reported by the study participants during the computer task (intra-task OCI, intra-task CVS-Q and intra-task IOSS).

Conversely, given that DES is highly influenced by the duration of a given task (longer periods of screen visualization have been associated with greater tear film and ocular surface abnormalities) (Jaiswal et al., 2019; Talens-Estarelles et al., 2021), one hour of computer use may not have been enough to cause the release of inflammatory mediators and alter corneal sensory function. According to previous findings of the present work, dry eye symptoms and tear film abnormalities may develop even after as little as 20-30 minutes of computer use. However, physical and chemical alterations of the ocular surface have only been observed after considerably longer periods of digital device use or in long-term computer workers (Bilgic et al., 2022; Choi et al., 2018; Ribelles et al., 2015).

Recently, Situ et al (2019). investigated the effects of tear film instability induced by extended eye opening on the sensory responses to corneal mechanical and cold stimuli. Participants kept one eye open as long as possible for up to 10 trials, with 2 seconds between trials, to induce tear film thinning or tear break-up. Authors found that repeated tear film instability induced by sustained tear exposure significantly altered the neurosensory function of the ocular surface (Situ et al., 2019). Given that the mechanism leading to digital device-induced dry eye resembles that of sustained tear exposure, longer periods of computer visualization may increase the risk of altered nerve function. Likewise, other factors, such as the cognitive demand of the task, which has been shown

to be associated with sustained gazing, could play a relevant role in the impact of digital device use on the sensory function of the cornea.

Although no association was found in the present study between changes in corneal sensitivity with the computer task and symptom scores, participants with a decrease in cold sensation threshold (i.e., increase in cold sensitivity) with computer use showed a trend towards higher symptoms in all questionnaires compared to those who exhibited an increase. This is in line with the findings of Chapter 11 (*11. Corneal hypersensitivity to cold stimuli in symptomatic computer users*), which suggest that symptomatic computer users have enhanced corneal sensitivity to cold stimuli.

On the contrary, participants who exhibited a decrease in mechanical sensation threshold (i.e., increase in mechanical sensitivity) with computer operation showed a trend towards lower symptoms in all questionnaires compared to those with a decrease/no change. These results suggest a potentially different impact of computer use on corneal sensitivity between participants with higher and lower symptoms. Nevertheless, further investigation in specifically designed studies is needed.

Finally, in the present study, changes in corneal mechanical sensitivity with computer use correlated positively with changes in cold sensitivity. Brief touching of the ocular surface, particularly by a moving object, activates mainly mechanonociceptors and, to a small extent, polymodal nociceptors (Belmonte et al., 2004b; Belmonte & Gallar, 2011b; Hirata et al., 2012). The fast-moving liquid droplets ejected by the UNSW LJA during the measurement of mechanical sensitivity, with a temperature matching that of the ocular surface, generated a mechanical force that primarily activated corneal mechanonociceptors. In parallel, high-threshold/low-activity cold thermoreceptors are especially attuned to strong cooling (Hirata et al., 2012; Vereertbrugghen & Galletti, 2022). The cold (15 ºC) droplets ejected by the UNSW LJA during the measurement of cold sensitivity, while keeping the mechanical stimulation at a sub-threshold level, probably activated high-threshold cold thermoreceptors. Based on the findings of the present study, computer use may modify the responsiveness of mechanonociceptors and high-threshold cold thermoreceptors in the same way. Another explanation for this finding could be a direct association between mechanical and cold sensation thresholds. González-González et al. (2017) pointed out that corneal cold thermoreceptor terminals, although preferentially sensitive to cold, also responded to other stimuli such as mechanical forces, which was a prominent characteristic of corneal cold thermoreceptors.

Nevertheless, further studies are needed to clarify the exact relationship between the different types of corneal sensitivity.

The present study had some limitations to consider. The LJA has the disadvantage of the injection of liquid onto the cornea. Although the volumes are in the nano to micro-litre range per stimulus, with up to 40 repeated droplets being propelled onto the eye, it is possible that liquid may accumulate and eventually alter the normal tear environment. This possible confounding factor was mitigated by allowing sufficient recovery time between stimuli and by encouraging participants to blink normally in between. Although methodological choices were made to prevent learning effects, some may have influenced data in the present study. Furthermore, due to the lack of studies assessing the effects of computer use on ocular surface sensitivity, there is a limited comparison of our results to other similar studies. Finally, the present study assessed the impact of short-term computer use on the sensitivity of the eye surface, which may not be representative of modern durations of device usage. This could have resulted in a smaller impact than expected after longer periods of computer visualization.

In conclusion, short-term computer use had no effect on the sensitivity of the central cornea to mechanical and cold stimuli. Additionally, no relationships were found between the changes in corneal sensitivity following computer use and demographic variables, everyday symptoms of dryness and discomfort or the symptoms experienced during the computer task. The present study establishes the basis for future works, which would assess the effects of device use on the sensitivity of the eye surface. Further research is warranted on the impact of longer periods of computer use on ocular surface sensitivity.

13.

Changes in visual function and optical and tear film quality in computer users

13.1 Introduction

Visual disturbance is a fundamental ocular symptom in DED and greatly impacts patient quality of life and interferes with the ability to carry out daily functions (Benítez-del-Castillo et al., 2017; Li et al., 2012). According to previous findings, up to 44% of patients with DED report impaired visual function (Goto et al., 2002).

The tear film-air interface is the first refractive structure of the eye that influences the optical light path to the retina. Due to the significant refractive index change from air to tear film, abnormalities to the tear film can impact visual quality markedly (Albarrán et al., 1997). Additionally, the tear film compensates for the optical irregularity of the corneal epithelium (Albarrán et al., 1997). Accordingly, the optical quality of the retinal image is highly dependent on the homogeneity of the tear film (Albarrán et al., 1997; Montés-Micó, 2007). In DED patients, the deficiencies in tear film quantity or quality lead to tear film irregularities and early break-up which induce aberrations and scattering, thus decreasing the quality of vision (Albarrán et al., 1997; Koh et al., 2002; Tan et al., 2015). Assessment of visual and tear film quality are therefore interconnected.

As made clear throughout this work, computer use induces tear film abnormalities and is categorized as a consistent risk factor for DED (Stapleton et al., 2017). Sustained gazing and increased ocular surface exposure during computer use contribute to the disruption of the tear film, which may eventually degrade image quality – alterations in visual function associated with dry eye are manifestations of tear film instability. In addition, prolonged computer use has been associated with accommodative stress which may impair visual function and contribute to symptoms of blurred vision and difficulties in refocusing often reported by frequent computer users (Sheppard & Wolffsohn, 2018). Previous research indicates a lower visual acuity in daily computer workers compared to those reporting occasional computer use (Abdelaziz et al., 2009).

The aim of this chapter was to thoroughly assess and compare the changes in visual function and optical and tear film quality in a group of computer workers and a group of non-computer workers throughout a normal working day.

13.2 Methods

13.2.1 Participants

Eighty young Caucasian volunteers, ranging in age from 20 to 40 years old, participated in this study. Workers from the School of Sciences of the University of Minho (Braga, Portugal) were invited to participate. Participants were allocated to one of the two study groups depending on their reported time of computer use during a normal working day: computer workers (computer use ≥ 4 hours/day) and controls (occasional computer use ≤ 1 hour/day). Inclusion criteria were age ≥ 18 and ≤ 40 years, CDVA better or equal to 20/20 (0.00 logMAR) in both eyes and a minimum of 4 hours or a maximum of 1 hour of computer use during a normal working day. Exclusion criteria were health conditions which may affect the eyes, including, but not limited to, Graves disease, diabetes, Sjögren syndrome or multiple sclerosis, pregnancy or breastfeeding, anterior or posterior segment pathologies, active eye allergy, history of eye surgery, binocular disorders (i.e., strabismus, amblyopia, anisometropia, etc.) and a history of CL wear in the past 7 days. Additionally, participants receiving treatment for dry eye, actively taking measures to reduce DES (i.e., artificial tear substitutes, planned regular short breaks, screen filters or specialty spectacles) or taking temporary medication known to contribute to dry eye, were excluded.

The study followed the tenets of the Declaration of Helsinki and was approved by the University of Minho human research ethics committee. All the participants were informed about the nature of the study and gave their written consent.

13.2.2 Experimental design and apparatus

Visual function, optical quality and tear film quality were evaluated at the beginning (visit 1, baseline) (8-10 am) and at the end (visit 2) (4-6 pm) of the working day. Additionally, subjective quality of vision and dry eye symptoms experienced during the working day were examined. All participants were indoor occupied. During the study period, the School's central heating system operated at 40% humidity and 23°C temperature. This design was similar to that used in previous studies (Yazici et al., 2015). Visual function was assessed by measuring photopic and mesopic CDVA and CSF using the D 6500 Functional Vision Analyzer (Stereo Optical Inc., Chicago, IL, USA) (*3.2.8*

Optec 6500 Functional Vision Analyzer, 3. General methods). Additionally, light disturbance was assessed using the LDA (CEORLab, Braga, Portugal).

Light disturbance is a phenomenon caused by the light from a central luminous point which forms a halo surrounding the light source (Klyce, 2007). The LDA analyses the size and shape of the halo surrounding a bright light against a dark background under dim illumination conditions. The following metrics related to the size and shape of the light disturbance were assessed: disturbance area, LDI, BFCR, BFCI, and BFCI-SD. Please refer to Chapter 3 for detailed information on the device and measurement procedure (*3.2.9 Light Disturbance Analyzer, 3. General methods*).

In addition, the optical quality of the eye was assessed by measuring ocular aberrations using a Hartmann-Shack aberrometer (irx3^{TM}, Imagine Eyes, Orsay, France) (*3.2.7 irx3^{TM} aberrometer, 3. General methods*). All the measurements were obtained under mesopic conditions. Aberrations were reconstructed using Zernike polynomials for pupil diameters of 3 and 5 mm. The RMS was calculated for LOAs, HOAs up to the 8th order, and total aberrations. Additionally, the Strehl ratio for HOAs obtained by the apparatus was recorded.

Furthermore, tear film quality was assessed by measuring TFSQ, TFSQ area and auto TBUT using the dynamic topography tool of the Medmont E300 corneal topographer (Medmont International Pty Ltd, Melbourne, Australia). Please refer to Chapter 3 for detailed information on the device and measurement procedure (*3.2.5 Medmont E300, 3. General methods*).

Finally, subjective quality of vision and dry eye symptoms were evaluated using validated questionnaires. Subjective quality of vision was assessed using the QoV. The questionnaire is scored on a Rasch scale from 0 to 100 across three subscales – frequency of symptoms, severity of symptoms and bothersomeness of symptoms, with higher scores indicating worse quality of vision. Dry eye symptoms were assessed using the DEQ-5 and SANDE II. Detailed information on the questionnaires can be found in Chapter 3 (*3.2.1 Symptomatology questionnaires, 3. General methods*)

Both study groups underwent the same examination procedures. All the measurements were taken on the same eye (eye with best CDVA), in the same laboratory, and by the same experienced examiner. Room temperature and humidity were constantly monitored and remained stable at 22.5 ± 0.7°C and 41 ± 5%, respectively.

13.2.3 Protocol

Participants were instructed to attend their first visit at the beginning of the working day. Fifteen minutes before the entry of the participants, the laboratory was set up and acclimatized. One of the authors checked whether or not each volunteer met the inclusion/exclusion criteria before initiating the study. The eye with the best photopic CDVA was recorded for subsequent measures. Participants were asked about the number of hours of computer use during a normal working day and were classified according to their responses into one of the two study groups.

Mesopic and photopic CDVA and CSF, light disturbance, ocular aberrations and tear film quality were subsequently assessed in this order. The order of the measurements was chosen from least disturbing to most disturbing. A brief measurement with the LDA was performed before the actual test to familiarize participants with the device and minimize learning effects. During the test run, the room was kept lit to prevent afterimages. For the measurement of ocular aberrations participants were instructed to fixate on the target while maintaining normal blinking. Before each measurement, participants were instructed to blink and then to keep their eyes open. Aberrations were taken approximately 1 second after the final blink (Vasudevan et al., 2015). Ocular aberrations and tear film quality were measured 3 times and an average value was obtained. Tear film quality was measured for 30 seconds, and a one-minute stabilization period was left between consecutive measurements. A minimum acclimatization period of 15 minutes was ensured between the entry of participants into the room and tear film measurements. Finally, the time of the second visit was agreed upon. The participants were instructed to attend the second visit immediately after finishing work. Visit 1 had a duration of 30-40 minutes.

At the second visit, participants were asked how long they had worked on the computer and how much time they had spent in front of other digital screens, including smartphones, tablets, or other devices between visits. Any participant with a computer use between one and four hours was excluded. The measurements were then repeated. Additionally, participants responded to the QoV and DEQ-5. To match the study question, participants were instructed to respond to the questionnaires based exclusively on the symptoms they had experienced during the working day (i.e., between visits). Likewise, participants responded to the SANDE II, which asked them about the difference in the severity and frequency of dry eye symptoms compared to the previous visit. Visit 2 had a

duration of 15-20 minutes. All visits were carried out between the months of May and July.

13.2.4 Statistical analysis

The results were evaluated using SPSS software v.28 (IBM Corp., Armonk, NY, USA). The normality of data was assessed using the Shapiro-Wilk test. When parametric test assumptions were fulfilled, an unpaired t-test was used to compare baseline and demographic characteristics between both study groups. The chi-square test was used for the comparison of qualitative variables. The non-parametric Mann-Whitney U test was used when parametric test assumptions were not fulfilled.

Additionally, a paired-sample t-test was used to examine the differences in visual function and optical and tear film quality before and after the working day (visit 1 and visit 2, respectively) for each study group. The Wilcoxon paired signed-rank test was used as a non-parametric alternative. In parallel, a one-sample Wilcoxon signed-rank test was used to examine if the SANDE II score obtained was significantly greater than zero.

Finally, to quantify the changes experienced throughout the working day, the difference between visits was calculated for each variable (visit 2 – visit 1). An unpaired t-test or the Mann-Whitney U test, depending on the distribution of data, was used to compare the changes experienced throughout the working day, and the DEQ-5 and QoV scores obtained at visit 2, between groups. This analysis mirrored that of previous chapters (Chapters 8-10).

13.3 Results

Eighty-six Caucasian volunteers ranging in age from 20 to 40 years old were initially recruited, out of which 80 (55 females and 25 males) met the inclusion/exclusion criteria and completed both study visits. From the 80 participants, 40 (30 female and 10 males, aged 26 ± 5 years) were divided into the control group, and 40 (25 females and 15 males, aged 28 ± 5 years) into the computer group. The average time between visits was 7.5 ± 1.0 hours (min-max; 6.0-10.0 hours). No significant age ($p = 0.08$) or sex ($p = 0.23$) differences were observed between groups. The average time of computer use between visits reported by computer workers and controls was 7.7 ± 2.4 and 0.1 ± 0.3 hours, respectively ($p < 0.001$). Additionally, the average reported time of digital display use

other than the computer was 1.2 ± 0.6 hours in computer workers and 1.2 ± 0.9 hours in controls ($p = 0.56$).

Table 13.1 shows the mean, SD and range of the optical and tear film quality variables obtained at the beginning and at the end of the working day for both study groups. The table additionally displays the statistical results of the comparisons between visits and baseline variables. No significant differences between groups were observed at baseline for any variable ($p \geq 0.09$). Likewise, no significant differences between visits were observed in any optical or tear film variable in the control group ($p \geq 0.16$) and the SANDE II scores obtained at visit 2 were not significantly different from zero ($p \geq 0.07$). In contrast, TFSQ and TFSQ area were significantly higher at visit 2 compared to visit 1 in computer workers ($p \leq 0.04$), though TBUT and optical quality variables remained unvaried ($p \geq 0.09$). In parallel, the SANDE II frequency and severity scores obtained in the computer group at visit 2 were significantly greater than zero ($p < 0.001$ for both).

Table 13.2 shows the dry eye symptoms reported by participants during the working day and the changes in optical and tear film variables between visits. The table additionally displays the statistical results of the comparisons between groups. As shown, the changes in RMS and Strehl ratio observed throughout the working day did not differ between groups ($p \geq 0.32$). Conversely, the TFSQ and TFSQ area increased significantly more in frequent computer workers compared to controls ($p \leq 0.04$) (Figure 13.1). Additionally, computer workers obtained significantly higher DEQ-5 and SANDE II scores than controls ($p \leq 0.02$) (Figure 13.2).

Table 13.3 shows the mean, SD and range of the visual function variables obtained at the beginning and at the end of the working day for both study groups. The table additionally displays the statistical results of the comparisons between visits and baseline variables. No significant differences were observed at baseline between groups for any variable ($p \geq 0.07$), except for a higher mesopic contrast sensitivity at 3 cpd ($p = 0.004$) in computer workers compared to controls. The control group exhibited a significantly higher photopic contrast sensitivity at 1.5 and 6 cpd and mesopic contrast sensitivity at 1.5, 3 and 6 cpd after the working day compared to visit 1 ($p \leq 0.04$). Likewise, light disturbance area, LDI and light disturbance BFCR were significantly lower at the end of the working day compared to the beginning ($p \leq 0.01$), while no other significant changes were observed in this group ($p \geq 0.06$). In contrast, computer workers exhibited a lower photopic contrast sensitivity at 1.5 cpd and mesopic contrast sensitivity at 3 cpd ($p \leq$

0.04), along with a higher light disturbance area, LDI and light disturbance BFCR ($p \leq 0.04$) after the working day, compared to visit 1.

Finally, Table 13.4 shows the quality of vision reported by participants during the working day and the changes in visual function variables between visits. The table additionally displays the statistical results of the comparisons between groups. Computer workers exhibited a significantly greater decline in photopic contrast sensitivity at 1.5 and 18 cpd, and mesopic contrast sensitivity at 1.5, 3 and 6 cpd ($p \leq 0.03$), along with a significantly greater increase in light disturbance area, LDI and light disturbance BFCR ($p \leq 0.003$) throughout the working day, compared to controls (Figure 13.3). Additionally, significantly higher frequency, severity and bothersome scores of the QoV were obtained in computer workers compared to controls ($p \leq 0.003$) (Figure 13.2).

Table 13.1. Optical and tear film quality variables obtained for both study groups (control and computer workers) and statistical results of the comparisons between visits. Data are presented as mean ± SD [min, max].

Variable			Control (n = 40)			Computer workers (n = 40)			Baseline comparisons
			Visit 1 (baseline)	Visit 2	p-value	Visit 1 (baseline)	Visit 2	p-value	p-value
SANDE II[a]	Frequency		–	0.1 ± 0.6 [-2.5, 2.2]	0.21[5]	–	1.6 ± 1.5 [-1.1, 5.0]	< 0.001*[5]	–
	Severity		–	0.2 ± 0.9 [-3.0, 3.0]	0.07[5]	–	1.5 ± 1.4 [0.0, 5.0]	< 0.001*[5]	–
RMS (μm)	3 mm	LOAs	0.53 ± 0.64 [0.05, 2.42]	0.55 ± 0.66 [0.06, 2.44]	0.47[2]	0.64 ± 0.63 [0.08, 2.76]	0.65 ± 0.66 [0.08, 2.82]	0.46[2]	0.09[4]
		HOAs	0.09 ± 0.02 [0.05, 0.13]	0.08 ± 0.02 [0.05, 0.16]	0.16[2]	0.09 ± 0.03 [0.05, 0.20]	0.09 ± 0.03 [0.06, 0.20]	0.43[2]	0.98[4]
		Total	0.55 ± 0.63 [0.08, 2.42]	0.57 ± 0.65 [0.08, 2.44]	0.46[2]	0.66 ± 0.65 [0.14, 2.77]	0.65 ± 0.64 [0.12, 2.83]	0.76[2]	0.09[4]
	5 mm	LOAs	1.49 ± 1.90 [0.09, 7.13]	1.53 ± 1.94 [0.14, 7.06]	0.20[2]	1.71 ± 1.63 [0.18, 6.19]	1.74 ± 1.66 [0.13, 6.15]	0.97[2]	0.09[4]
		HOAs	0.20 ± 0.08 [0.09, 0.36]	0.20 ± 0.07 [0.09, 0.43]	0.35[2]	0.21 ± 0.06 [0.09, 0.46]	0.20 ± 0.07 [0.12, 0.43]	0.54[2]	0.62[4]
		Total	1.53 ± 1.88 [0.15, 7.14]	1.57 ± 1.90 [0.19, 7.07]	0.25[2]	1.73 ± 1.61 [0.20, 6.20]	1.76 ± 1.64 [0.21, 6.15]	0.92[2]	0.11[4]
Strehl ratio[b]	3 mm		0.45 ± 0.13 [0.17, 0.76]	0.45 ± 0.15 [0.08, 0.73]	0.89[1]	0.42 ± 0.15 [0.09, 0.73]	0.45 ± 0.13 [0.19, 0.69]	0.15[1]	0.48[3]
	5 mm		0.13 ± 0.11 [0.03, 0.63]	0.12 ± 0.07 [0.02, 0.39]	0.58[2]	0.11 ± 0.08 [0.03, 0.48]	0.11 ± 0.05 [0.04, 0.26]	0.09[2]	0.40[4]

TFSQ	0.138 ± 0.058 [0.043, 0.291]	0.135 ± 0.054 [0.069, 0.316]	0.71[2]	0.127 ± 0.067 [0.052, 0.417]	0.148 ± 0.082 [0.046, 0.389]	0.04*[2]	0.21[4]
TFSQ area (%)	6.7 ± 6.5 [0.1, 27.4]	6.9 ± 6.4 [0.6, 26.4]	0.73[2]	6.2 ± 7.0 [0.3, 33.9]	9.0 ± 9.9 [0.1, 38.8]	0.02*[2]	0.30[4]
Auto TBUT (s)	12.8 ± 8.9 [2.5, 30.0]	13.0 ± 8.7 [2.4, 30.0]	0.79[2]	15.9 ± 9.7 [2.4, 30.0]	13.6 ± 9.3 [2.5, 30.0]	0.19[2]	0.14[4]

HOAs = Higher order aberrations up to the 8th order; LOAs = Lower order aberrations; RMS = Root mean square; SANDE II = Symptom Assessment in Dry Eye version 2. TBUT = Tear break-up time; TFSQ = Tear film surface quality. [a] SANDE II was completed at visit 2 and denotes the change in dry eye symptoms between visits. Statistical comparison with value of 0 (no change). [b] Strehl ratio for higher order aberrations. * Indicates statistically significant values ($p < 0.05$). [1] Paired sample t-test. [2] Wilcoxon paired signed-rank test. [3] Unpaired t-test. [4] Mann-Whitney U test. [5] One-sample Wilcoxon signed rank test.

Table 13.2. Dry eye symptoms during the working day and changes in optical and tear film quality between visits (visit 2 – visit 1) and statistical results of the comparisons between groups. Data are presented as mean ± SD [min, max].

Variables			Control (n = 40)	Computer workers (n = 40)	p-value
DEQ-5[a]			2 ± 3 [0, 13]	4 ± 4 [0, 14]	0.02*[1]
SANDE II	Frequency		0.1 ± 0.6 [-2.5, 2.2]	1.6 ± 1.5 [-1.1, 5.0]	< 0.001*[1]
	Severity		0.2 ± 0.9 [-3.0, 3.0]	1.5 ± 1.4 [0.0, 5.0]	< 0.001*[1]
RMS (µm)	3 mm	LOAs	0.02 ± 0.09 [-0.12, 0.26]	0.01 ± 0.10 [-0.22, 0.31]	0.97[1]
		HOAs	0.0 ± 0.02 [-0.04, 0.07]	0.0 ± 0.02 [-0.04, 0.11]	0.34[1]
		Total	0.01± 0.08 [-0.12, 0.23]	0.00 ± 0.09 [-0.28, 0.22]	0.75[1]
	5 mm	LOAs	0.04 ± 0.19 [-0.31, 0.52]	0.03 ± 0.38 [-0.90, 1.65]	0.43[1]
		HOAs	-0.01 ± 0.04 [-0.09, 0.09]	0.00 ± 0.05 [-0.12, 0.20]	0.96[1]
		Total	0.04 ± 0.17 [-0.31, 0.52]	0.03 ± 0.38 [-0.90, 1.65]	0.48[1]
Strehl ratio[b]	3 mm		0.00 ± 0.14 [-0.48, 0.32]	0.03 ± 0.13 [-0.40, 0.27]	0.32[1]
	5 mm		-0.01 ± 0.08 [-0.34, 0.11]	0.00 ± 0.06 [-0.33, 0.06]	0.77[1]
TFSQ			-0.004 ± 0.036 [-0.092, 0.089]	0.021 ± 0.062 [-0.097, 0.250]	0.04*[1]
TFSQ area (%)			-0.7 ± 4.1 [-15.2, 8.2]	2.8 ± 7.0 [-10.4, 29.8]	0.03*[1]
Auto TBUT (s)			0.3 ± 5.7 [-20.9, 13.6]	-2.4 ± 9.4 [-24.0, 15.3]	0.29[1]

DEQ-5 = 5-item Dry Eye Questionnaire; HOAs = Higher order aberrations up to the 8th order; LOAs = Lower order aberrations; RMS = Root mean square; SANDE II = Symptom Assessment in Dry Eye version 2. TBUT = Tear break-up time; TFSQ = Tear film surface quality. [a] Symptoms experienced throughout the working day were assessed at visit 2. [b] Strehl ratio for higher order aberrations. * Indicates statistically significant values ($p < 0.05$). [1] Mann-Whitney U test.

Table 13.3. Visual function variables obtained for both study groups (control and computer workers) and statistical results of the comparisons between visits. Data are presented as mean ± SD [min, max].

Variable		Control (n = 40)			Computer workers (n = 40)			Baseline comparisons
		Visit 1 (baseline)	Visit 2	p-value	Visit 1 (baseline)	Visit 2	p-value	p-value
Photopic CDVA (logMAR)		-0.09 ± 0.05 [-0.20, 0.00]	-0.10 ± 0.05 [-0.20, 0.00]	0.57[1]	-0.07 ± 0.04 [-0.14, 0.00]	-0.07 ± 0.06 [-0.14, 0.10]	0.07[1]	0.07[3]
Mesopic CDVA (logMAR)		0.01± 0.08 [-0.18, 0.14]	-0.01 ± 0.08 [-0.14, 0.14]	0.06[1]	0.03 ± 0.07 [-0.06, 0.20]	0.03 ± 0.09 [-0.10, 0.20]	0.90[2]	0.49[4]
Photopic CSF (dB)	1.5 cpd	47 ± 20 [25, 100]	52 ± 22 [25, 100]	0.04*[2]	47 ± 20 [25, 100]	40 ± 18 [25, 100]	0.04*[2]	0.84[4]
	3 cpd	115 ± 32 [40, 160]	116 ± 27 [80, 160]	0.81[2]	104 ± 31 [40, 160]	104 ± 29 [40, 160]	0.93[2]	0.28[4]
	6 cpd	95 ± 34 [33, 180]	111 ± 39 [23, 180]	0.02*[2]	99 ± 34 [33, 180]	95 ± 43 [12, 180]	0.85[2]	0.59[4]
	12 cpd	52 ± 25 [11, 120]	56 ± 26 [11, 120]	0.19[2]	53 ± 28 [15, 120]	51 ± 29 [0, 120]	0.50[2]	0.92[4]
	18 cpd	19 ± 12 [4, 46]	23 ± 13 [4, 65]	0.06[2]	21 ± 12 [4, 65]	18 ± 10 [0, 33]	0.09[2]	0.64[4]
Mesopic CSF (dB)	1.5 cpd	52 ± 22 [25, 100]	59 ± 21 [25, 100]	0.03*[2]	57 ± 27 [25, 100]	50 ± 20 [18, 100]	0.17[2]	0.52[4]
	3 cpd	96 ± 31 [40, 160]	110 ± 30 [57, 160]	0.006*[2]	116 ± 29 [40, 160]	102 ± 30 [40, 160]	0.005*[2]	0.004*[4]
	6 cpd	63 ± 30 [16, 128]	71 ± 34 [16, 128]	0.02*[2]	70 ± 29 [12, 128]	67 ± 38 [0, 180]	0.45[2]	0.20[4]

	12 cpd	25 ± 15 [0, 60]	26 ± 15 [0, 60]	0.48[2]	22 ± 14 [0, 60]	22 ± 14 [0, 43]	0.98[2]	0.56[4]
	18 cpd	9 ± 8 [0, 46]	9 ± 5 [0, 17]	0.41[2]	7 ± 6 [0, 23]	7 ± 5 [0, 17]	0.82[2]	0.31[4]
Light disturbance	Disturbance area (mm^2)	2040 ± 1107 [752, 5184]	1860 ± 869 [768, 4672]	0.01*[2]	2182 ± 1393 [768, 8336	2429 ± 1370 [768, 6928]	0.04*[2]	0.74[4]
	LDI (%)	10.15 ± 5.50 [3.74, 25.78]	9.25 ± 4.32 [3.82, 23.24]	0.01*[2]	10.85 ± 6.93 [3.82, 41.46]	12.09 ± 6.82 [3.82, 34.46]	0.04*[2]	0.74[4]
	BFCR (mm)	25.1 ± 6.7 [16.0, 41.3]	24.2 ± 5.4 [16.0, 39.3]	0.02*[1]	26.0 ± 7.2 [16.0, 52.7]	27.5 ± 7.2 [16.9, 48.0]	0.02*[2]	0.70[4]
	BFCI (mm)	0.58 ± 0.59 [0.00, 1.80]	0.65 ± 0.70 [0.00, 2.91]	0.46[2]	0.51 ± 0.34 [0.00, 1.41]	0.47 ± 0.38 [0.00, 1.66]	0.48[2]	0.55[4]
	BFCI-SD (mm)	3.76 ± 2.20 [0.00, 9.48]	3.47 ± 1.57 [0.00, 7.52]	0.59[2]	3.91 ± 1.70 [0.00, 9.84]	4.21 ± 1.61 [0.00, 8.91]	0.25[2]	0.95[4]

BFCI = Best-fit circle irregularity; BFCI-SD = Standard deviation of best-fit circle irregularity; BFCR = Best-fit circle radius; CDVA = Corrected distance visual acuity; CSF = Contrast sensitivity function; LDI = Light disturbance index. * Indicates statistically significant values ($p < 0.05$). [1] Paired sample t-test. [2] Wilcoxon paired signed-rank test. [3] Unpaired t-test. [4] Mann-Whitney U test.

Table 13.4. Quality of vision (QoV) during the working day and changes in visual function between visits (visit 2 – visit 1) and statistical results of the comparisons between groups. Data are presented as mean ± SD [min, max].

Variables		Control (n = 40)	Computer workers (n = 40)	p-value
QoV[a]	Frequency	14 ± 20 [0, 67]	27 ± 19 [0, 64]	0.003*[2]
	Severity	11 ± 16 [0, 54]	23 ± 17 [0, 54]	0.002*[2]
	Bothersome	9 ± 16 [0, 63]	21 ± 19 [0, 65]	0.001*[2]
Photopic CDVA (logMAR)		0.00 ± 0.03 [-0.10, 0.04]	0.02 ± 0.05 [-0.06, 0.14]	0.19[2]
Mesopic CDVA (logMAR)		-0.02 ± 0.06 [-0.20, 0.10]	0.00 ± 0.09 [-0.22, 0.18]	0.18[2]
Photopic CSF (dB)	1.5 cpd	5 ± 15 [-29, 35]	-7 ± 19 [-64, 29]	0.003*[2]
	3 cpd	1 ± 29 [-46, 120]	-1 ± 30 [-80, 57]	0.98[2]
	6 cpd	16 ± 38 [-64, 116]	-1 ± 32 [-64, 64]	0.06[2]
	12 cpd	4 ± 22 [-55, 60]	-2 ± 20 [-77, 42]	0.26[2]
	18 cpd	3 ± 10 [-21, 32]	-2 ± 10 [-42, 21]	0.02*[2]
Mesopic CSF (dB)	1.5 cpd	7 ± 17 [-35, 50]	-7 ± 26 [-64, 35]	0.03*[2]
	3 cpd	14 ± 26 [-46, 80]	-14 ± 25 [-57, 46]	< 0.001*[2]
	6 cpd	8 ± 21 [-64, 64]	-3 ± 30 [-67, 64]	0.03*[2]
	12 cpd	1 ± 11 [-28, 32]	0 ± 10 [-28, 15]	0.83[2]
	18 cpd	-1 ± 7 [-34, 9]	1 ± 5 [-15, 13]	0.56[2]
Light disturbance	Disturbance area (mm^2)	-180 ± 404 [-1136, 400]	247 ± 725 [-1408, 2736]	0.002*[2]
	LDI (%)	-0.89 ± 2.00 [-5.65, 1.99]	1.23 ± 3.61 [-7.00, 13.60]	0.002*[2]
	BFCR (mm)	-0.9 ± 2.5 [-6.0, 3.3]	1.5 ± 3.9 [-5.3, 14.0]	0.003*[2]
	BFCI (mm)	0.07 ± 0.73 [-1.51, 1.87]	-0.04 ± 0.45 [-0.99, 0.89]	0.42[1]

BFCI-SD (mm)	-0.29 ± 1.78 [-5.15, 3.00]	0.30 ± 1.78 [-5.46, 5.09]	0.24[2]

BFCI = Best-fit circle irregularity; BFCI-SD = Standard deviation of best-fit circle irregularity; BFCR = Best-fit circle radius; CDVA = Corrected distance visual acuity; CSF = Contrast sensitivity function; LDI = Light disturbance index. QoV = Quality of Vision questionnaire. [a] Symptoms experienced throughout the working day were assessed at visit 2. * Indicates statistically significant values ($p < 0.05$). [1] Unpaired t-test. [2] Mann-Whitney U test.

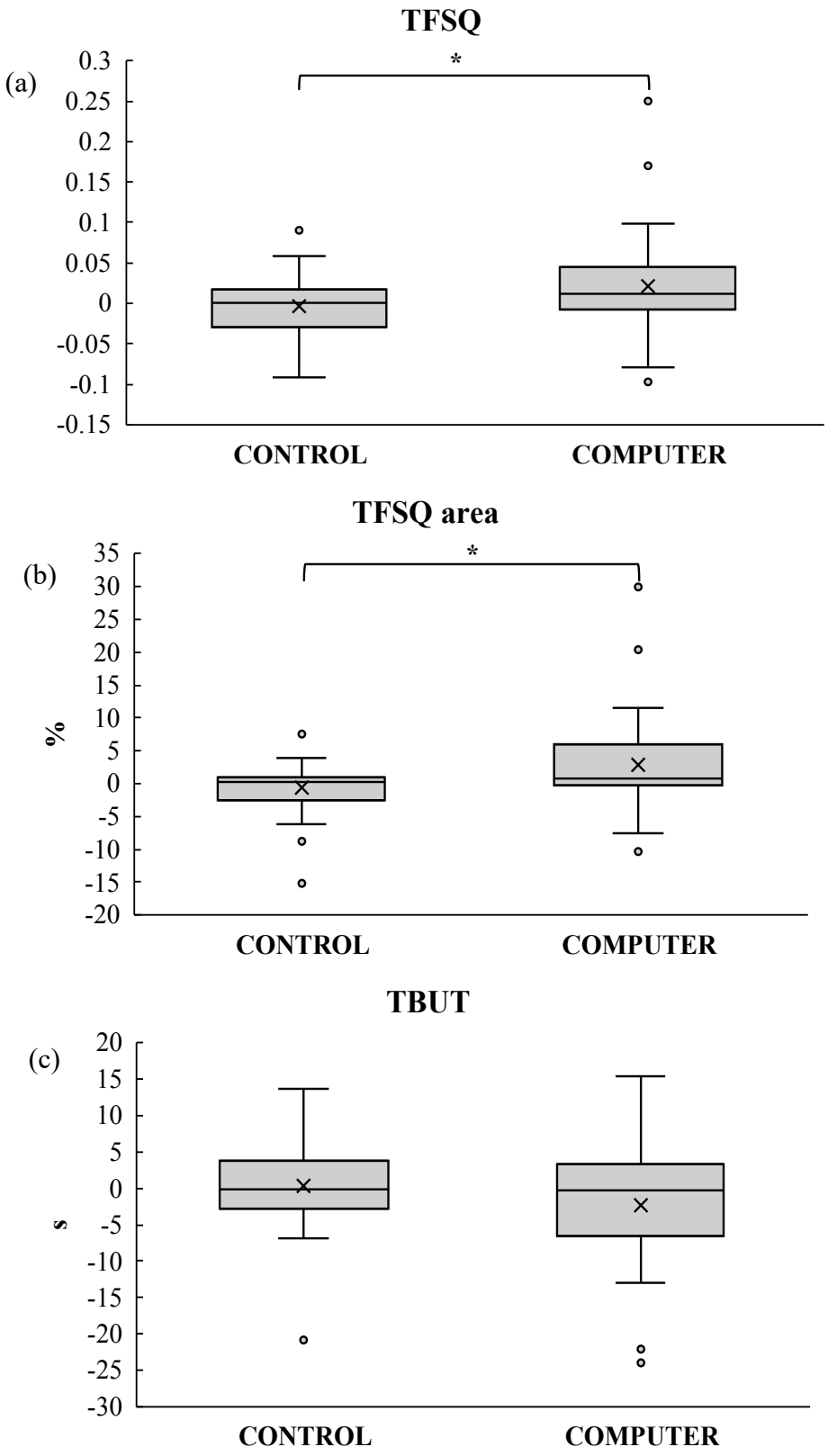


Figure 13.1. Boxplots of the changes in tear film quality between visits (visit 2 – visit 1) in both study groups (control and computer workers). (a) tear film surface quality (TFSQ), (b) tear film surface quality area and (c) tear break-up time (TBUT). * Indicates statistical significance ($p < 0.05$).

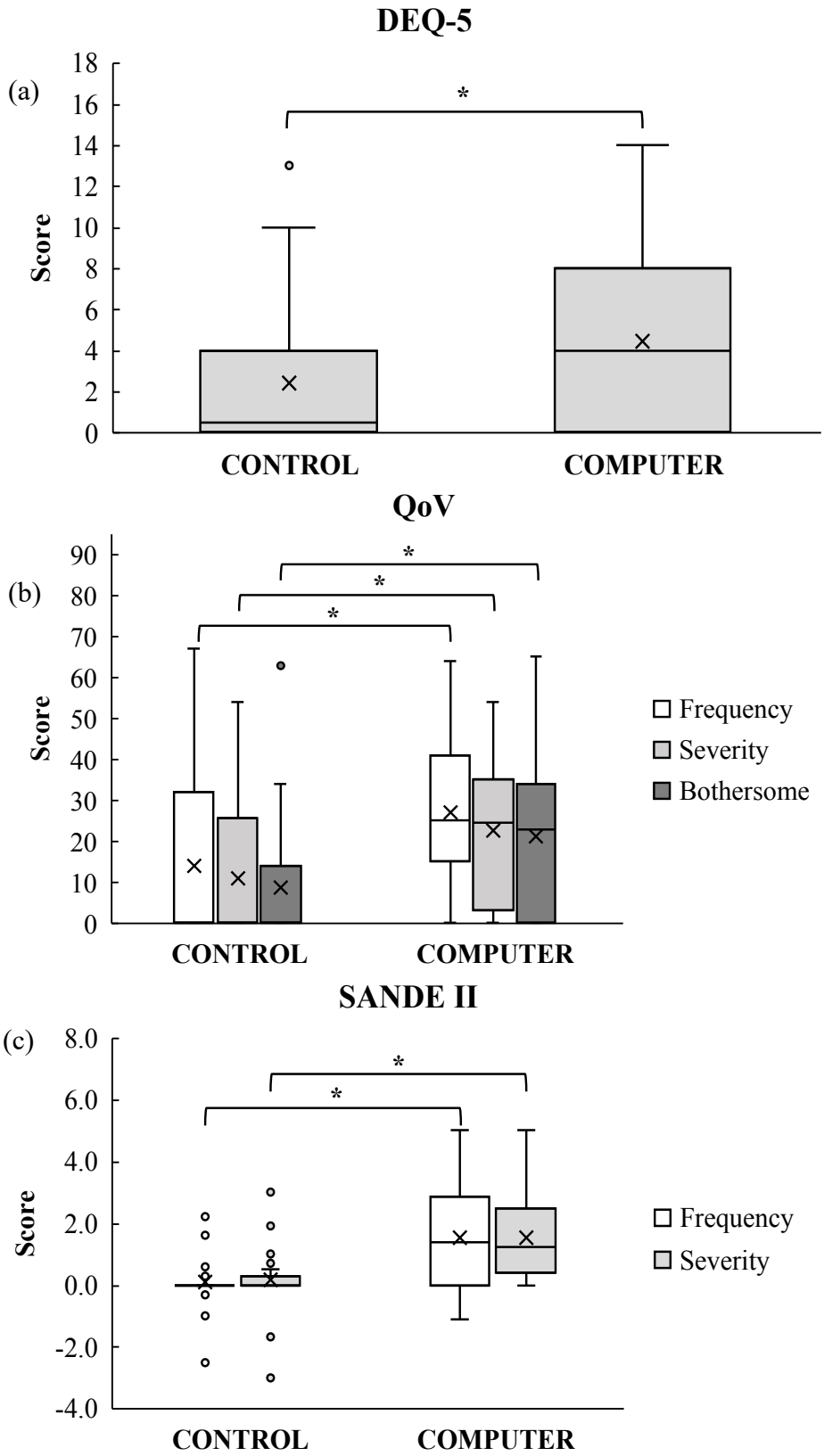


Figure 13.2. Boxplots of the symptoms experienced during the working day in both study groups (control and computer workers). (a) 5-item Dry Eye Questionnaire (DEQ-5), (b) Symptom Assessment in Dry Eye version II (SANDE II), (c) Quality of Vision questionnaire (QoV). * Indicates statistical significance ($p < 0.05$).

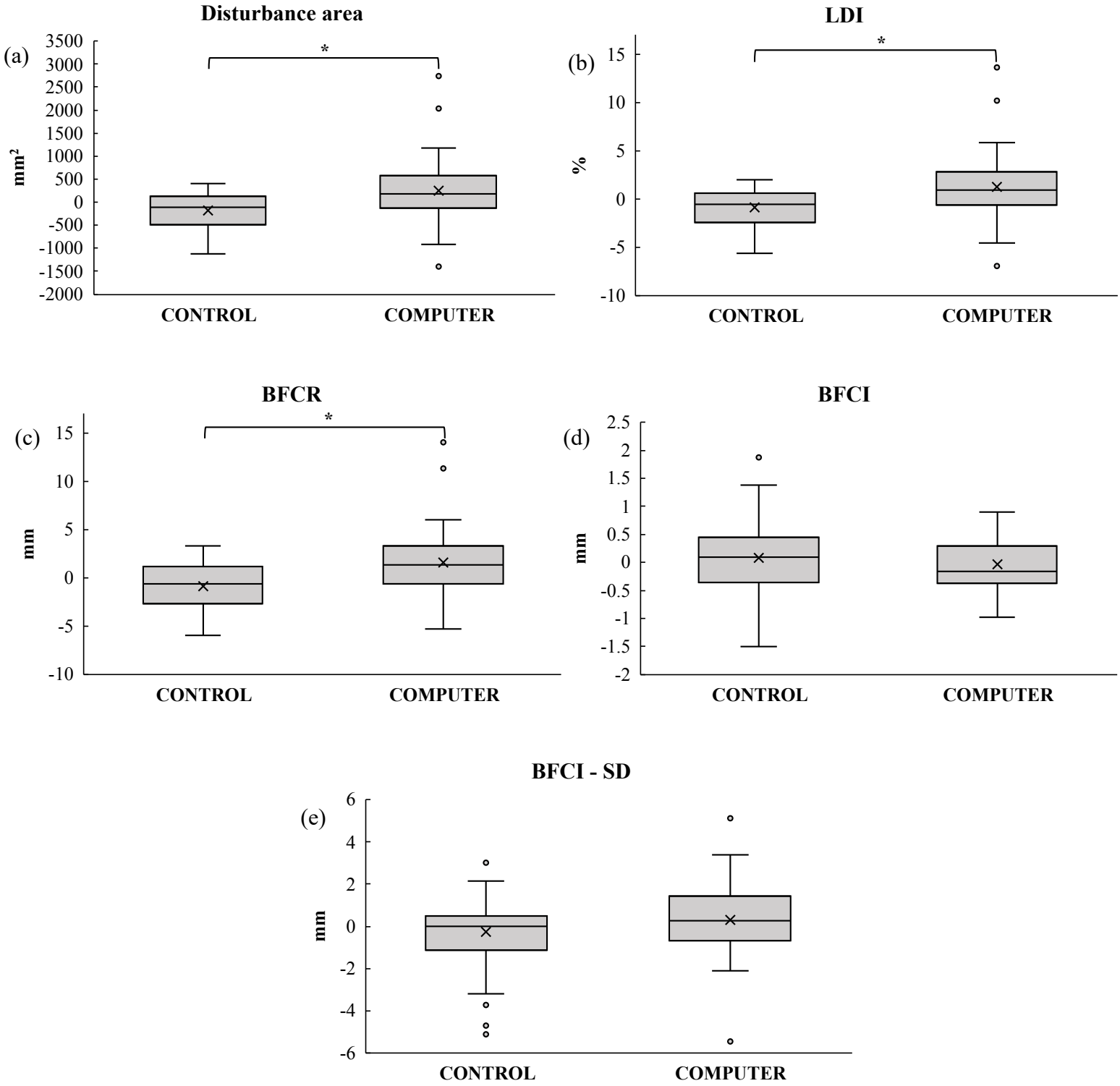


Figure 13.3. Boxplots of the changes in light disturbance between visits (visit 2 – visit 1) in both study groups (control and computer workers). (a) disturbance area, (b) light disturbance index (LDI), (c) best-fit circle radius (BFCR), (d) best-fit circle irregularity (BFCI) and (e) standard deviation (SD) of best-fit circle irregularity. * Indicates statistical significance ($p < 0.05$).

13.4 Discussion

13.4.1 Tear film quality

In the present study, computer workers reported higher dry eye symptoms (DEQ-5) throughout the working day, along with a greater increase in the frequency and severity of their symptoms (SANDE II) compared to controls. Moreover, the tear film quality of computer workers worsened significantly more (16.5% increase in TFSQ and 45.2% increase in TFSQ area) throughout the working day than that of controls (2.2% decrease in TFSQ and 3.0% increase in TFSQ area), indicating greater distortion and destabilization. In a similar study, Yazici et al. (2015) observed a significant worsening of dry eye signs and symptoms in computer workers throughout the working day as opposed to no significant changes in controls. In contrast, despite the changes in TFSQ and TFSQ area, the change in TBUT in computer workers was not statistically significant. TBUT decreased, on average, by more than 2 seconds (14.5% decrease) throughout the working day, which could be considered clinically relevant.

In patients with DED, the loss of homeostasis of the tear film creates an irregularity which diminishes optical and visual quality (Albarrán et al., 1997; Koh et al., 2002; Montés-Micó, 2007; Tan et al., 2015). In the present study, computer workers reported lower quality of vision throughout the working day compared to controls, with a higher frequency, severity and bother of symptoms (QoV). Overall, the disruption of the tear film resulting from sustained gazing associated with computer use may have degraded subjective visual quality in computer users.

Nevertheless, it should be noted that the ocular symptoms associated with DES are often split into two main categories. The first group, termed external symptoms, is related to dry eye, while the second group, termed internal symptoms, is linked to accommodative and/or binocular vision stress (Portello et al., 2012; Sheedy et al., 2003a). Among these symptoms there are vision-related symptoms such as blur, double vision, halos, difficulty in refocusing or sensitivity to bright lights which are associated with one or both categories simultaneously. Accordingly, the lower quality of vision reported throughout the day by frequent computer users in the present study was not unanticipated and may be attributable not only to a decline in tear film quality but also to accommodative stress (Rosenfield, 2011). Equally, it should be noted that, as opposed to controls, computer workers spent most of their working day performing visually demanding vision tasks. This may have increased their awareness of symptoms.

13.4.2 Optical quality

There is evidence demonstrating that dry eyes and HOAs are associated, and that tear film metrics are correlated with HOAs (Rhee et al., 2022). However, in the present study, the reduction in tear film quality observed in computer workers throughout the working day was not accompanied by significant changes in ocular HOAs or Strehl ratio. Previous research revealed that the retinal image quality of individuals with aqueous tear-deficient dry eye and ocular surface damage is impaired immediately after blinking (Koh et al., 2008a). In contrast, in patients with dry eye associated with short tear stability but an absence of tear deficiency, image quality deteriorates over time as the tear film stability decreases, but remains good just after the blink, leading to fluctuations in vision (Koh, 2016; Koh, et al., 2008b). As addressed in detail in Chapter 5 (*5. Blinking kinematics characterization during digital displays use*; Talens-Estarelles et al., 2022a), digital devices induce tear film instability through alterations in the blinking pattern, resulting in evaporative dry eye. In the present study, ocular aberrations were measured shortly after blinking. Therefore, despite mild tear film abnormalities caused by using a computer, the tear film of computer workers was probably stable at the time of measuring ocular aberrations. This could explain why no changes in optical quality were observed with computer use. Future studies are required to confirm these findings and to assess dynamic changes in optical quality in computer users.

Blurred vision is a symptom commonly associated with DES which could result from an inaccurate accommodative response during a computer task or a failure to relax accommodation fully following near vision demands (Rosenfield, 2011). This temporal accommodative spasm results from the overstimulation of the eye's accommodative mechanism and leads to an increase in ocular refractive power known as near-work induced transient myopia (a.k.a., pseudomyopia) (García-Montero et al., 2022). Refractive errors are in essence LOAs. Also, total ocular aberrations and HOAs have been shown to change significantly with changes in accommodation (Zhou et al., 2015). In the present study, no significant changes in total aberrations, LOAs and HOAs were observed throughout the working day in computer workers, thus changes in refraction or accommodative response were unlikely.

13.4.3 Visual function

Computer workers in the present study exhibited a significant increase in light disturbance throughout the working day. More specifically, an average increase in the size of the disturbance halo of 11.3% was observed (disturbance area, LDI and BFCR), though not in its shape or regularity (BFCI and BFCI-SD). Previous research reported a greater forward light scattering in dry eyes than in normal eyes, which explains the symptoms of glare often reported by individuals with DED (Diaz-Valle et al., 2012). Likewise, Himebaugh et al. (2012) described the formation of scatter-producing microaberrations associated with areas of tear break-up which contribute to image degradation. Accordingly, the degradation of the tear film with computer use might have increased light scattering in the group of computer workers without observable changes in ocular aberrations, leading to a greater disturbance of the central glare source in the LDA. This increase in light disturbance probably contributed to the decline in the quality of vision reported by computer workers at the end of the working day. On the contrary, light disturbance significantly improved in non-computer workers. This could be attributed to unavoidable learning effects, although the differences (< 1%) are within the sensitivity of the device. This is particularly relevant since it implies that the true increase in light disturbance in computer workers might be greater than that observed in our data.

Tear instability can also precipitate significant reductions in visual acuity and contrast sensitivity (Liu et al., 2010; Toda et al., 2009). In the present study, both photopic and mesopic contrast sensitivity decreased more at several spatial frequencies in computer workers compared to controls. This decrease could be related to the increase in light scattering observed in computer workers which produces a veiling luminance on the retina and reduces the contrast of the retinal image. Toda et al. (2009) observed that visual performance significantly declined during concentrated visual work and concluded that under conditions in which blinking is restricted, such as computer work, visual performance could be compromised. More specifically, the decline in contrast sensitivity observed in the present study was mainly noticeable at lower spatial frequencies. This is in line with previous research which demonstrated low spatial-contrast sensitivity in dry eyes (Rolando et al., 1998). In parallel, recent findings have suggested that visual fatigue is associated with clinical visual measures and basic visual functions, including contrast sensitivity (Zheng et al., 2021). Conversely, in the present study, photopic and mesopic visual acuity remained unvaried in both groups. This is in contrast with previous research

which reported a significantly lower visual acuity in daily computer workers compared to those with occasional computer use (Abdelaziz et al., 2009).

The present study had some limitations to consider. The study was carried out in the same centre, which may have introduced selection bias. Also, recruitment by means of advertisement could have induced a higher prevalence of symptomatic individuals than expected in the general population. Due to the subjective evaluation of symptoms, a nocebo effect on the results cannot be completely ruled out. Additionally, although methodological choices were made to prevent learning effects, some may have influenced data in the present study. Nevertheless, potential learning effects are not expected to differ between groups and comparisons should not be affected. Moreover, dynamic changes in ocular aberrations over the interblink interval were not assessed. Therefore, ocular aberrations are only representative of participants' optical quality at a particular time after blinking. However, the present study establishes the basis for future work which would assess dynamic aberrations in computer users. Although participants were instructed to attend the second visit immediately after finishing work, it is possible that transient changes may have reduced on their way to the laboratory, prior to the measurements. Nevertheless, all the participants were workers of the School of Sciences and measurements were taken as soon as they arrived at the laboratory, thus the washout period was minimal. Also, the study was non-blinded. Consequently, the examiner was not masked as to which group the participant was in and observer bias cannot be completely ruled out. Finally, due to the lack of studies assessing the effects of computer use on visual function and quality, there is a limited comparison of our results to other similar studies.

In conclusion, computer workers exhibited greater dry eye symptoms, along with a decline in perceived quality of vision, tear film quality, and contrast sensitivity throughout the working day, while no worsening was observed in any variable in workers who only occasionally used the computer. Similarly, computer workers exhibited an increase in light disturbance throughout the working day as opposed to no change in non-computer workers. In contrast, optical aberrations remained unchanged in both groups of participants. Further studies are needed to confirm these findings and to deepen the understanding of the effects of digital screens on visual performance and quality of vision. Likewise, the effects of accommodative and binocular vision stress, as well as workstation design, on the quality of vision and visual function of computer workers requires investigation in specifically designed studies. This study provides insight into

new metrics that can be used to objectively and quantitatively measure changes in visual quality through the analysis of light disturbance.

14.

The effects of breaks on digital eye strain, dry eye and binocular vision: Testing the 20-20-20 rule

14.1 Introduction

Ocular symptoms associated with DES are often split into two main and distinct categories based on the type of sensation and perceived location (Portello et al., 2012; Sheedy et al., 2003a). The first group, termed external symptoms, is related to dry eye and includes symptoms of burning, irritation, dryness, tearing, foreign body sensation, sensitivity to bright lights and discomfort. The second group, termed internal symptoms, encompasses symptoms of eyestrain, eye ache, headache, diplopia, blurred vision and difficulty in refocusing, and is linked to accommodative and/or binocular vision stress.

DES is highly influenced by the visual demand and the duration of a given task (Rosenfield, 2011). For instance, Portello et al. (2012) observed a positive correlation between the symptom score and the time spent working on a computer. Longer periods of screen visualization have been associated with greater tear film and ocular surface abnormalities, and accommodative and vergence disturbances (Jaiswal et al., 2019; Rosenfield, 2011; Talens-Estarelles et al., 2021). Accordingly, as addressed in Chapter 1 (*1.6 Managament strategies, 1. Introduction*; Talens-Estarelles et al., 2021) and evidenced in Chapter 8 (*8. Determining the best management strategy for preventing the short-term effects of computer use on dry eyes*; Talens-Estarelles et al., 2022d), limiting the amount of time spent in front of a digital display is expected to have a positive impact on DES. Based on this principle, frequent screen users are often advised to follow the 20-20-20 rule which instructs them to briefly look away from the screen for at least 20 s to a distant scene at least 20 feet (6 m) away after every 20 minutes of continuous work (Anshel, 2005; Tribley et al., 2011). With the rise of display use, this general rule of visual ergonomics has become increasingly popular and is widely recommended by specialists in the field of vision, although only one study has examined this approach, reporting a benefit but with no evidence of compliance (Alghamdi & Alrasheed, 2020).

In this chapter, a computer software was developed using the laptop webcam to assess user breaks, eye gaze and blinking and could emit personalized regular reminders of rest based on the 20-20-20 rule in order to evaluate, for the first time, the potential benefits of this rule on DES, dry eye and the accommodative and binocular vision systems in a sample of young, symptomatic, regular computer users.

14.2 Methods

14.2.1 Participants

Twenty-nine symptomatic volunteers participated in this prospective, longitudinal, controlled clinical study. Inclusion criteria were DES (CVS-Q score ≥ 6 at baseline), CDVA greater or equal to 20/30 (0.17 logMAR) in both eyes, and reported computer use for a minimum of 4 h a day, at least 5 days per week. Exclusion criteria included anterior or posterior segment pathologies, history of eye surgery in the past 6 months, binocular disorders (i.e., strabismus, amblyopia, anisometropia, etc.) and stereopsis lower than 120 arc seconds. Participants receiving treatment for dry eye, actively taking measures to reduce DES (i.e., artificial tear substitutes, planned regular short breaks, screen filters or specialty spectacles), taking temporary medication known to contribute to dry eye or those who made changes in CL wear during the study period were excluded.

The study followed the tenets of the Declaration of Helsinki and a favourable opinion from the ethical committee of Aston University was obtained. All the participants were informed about the nature of the study and gave their written consent.

14.2.2 Study software

A downloadable computer software (eyeblink, https://www.blinkingmatters.com/) was modified for the study as a tool for the 20-20-20 reminders. Using the built-in camera of the participant's laptop computer the software checked user presence and gaze direction every 10 s. The software considered the user as looking at the screen if they were within range of the camera and their gaze angle (angle of gaze with respect to the centre of the screen) was equal to or less than that of the screen (maximum angle of gaze determined by looking at the corners of the screen) (Figure 14.1). Two consecutive readings with either an absence or a gaze angle greater than the screen angle were considered a break. In case a natural break was detected the timer was reset to 0. After 20 minutes of continuous screen viewing the software issued a message asking the user to rest for 20 s while looking at a distant target located at least 20 feet away (Figure 14.2). The break reminder was accompanied by an acoustic signal (beeping signal) if enabled by the user to ensure it did not go unnoticed. The reminder could not be manually removed by the user and disappeared automatically from the screen once the task was correctly

performed. Additionally, the tool app measured the average blink rate and blink length every 20 minutes for 3 minutes. If the 20-20-20 rule reminder was active the blink measurement was performed in between the rule reminders. The tool app used the motion-based blink detection algorithm to gather blink data (Fogelton & Benesova, 2016).

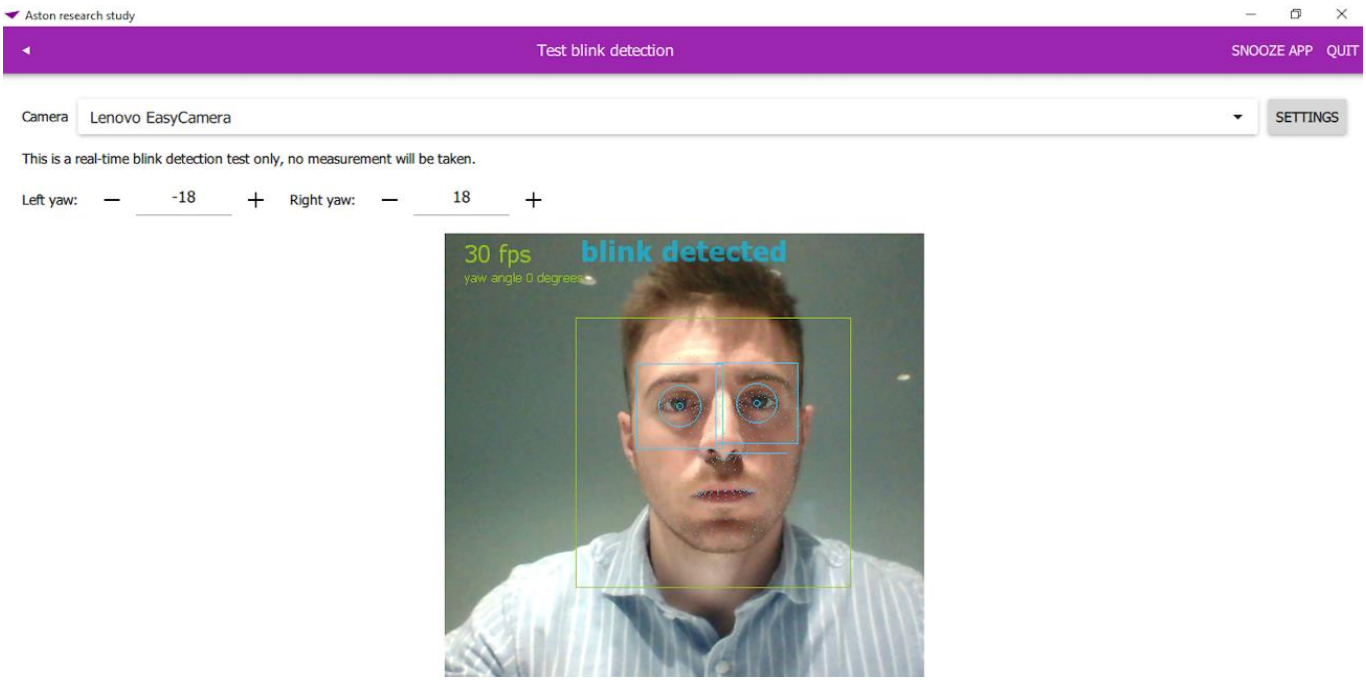


Figure 14.1. Eye blink and gaze detection software testing. The green square indicates that the user is looking at the screen.

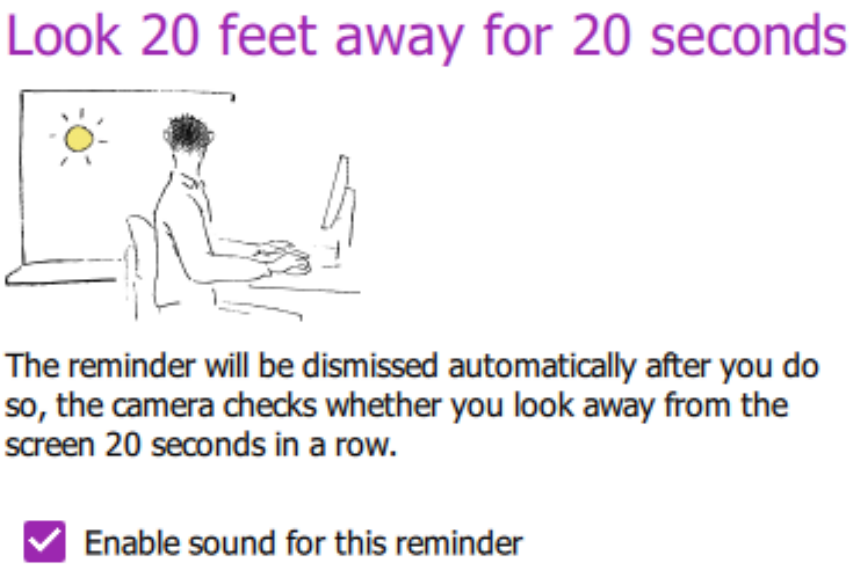


Figure 14.2. 20-20-20 rule break reminder issued by the software.

14.2.3 Experimental conditions

All measurements were taken in the same laboratory. The approximate duration of each session was 45 minutes. All the sessions were carried out on the same day of the week, at the same time of day (mornings from 9 to 11 am) and under the same, constant environmental conditions (temperature and humidity). In addition, participants were asked not to use other digital displays 30 minutes before the session. Likewise, CL wearers were instructed to remove their CLs at least 24 hours before the visit. The laboratory was set up 15 minutes before each visit. To minimize the effects of outdoor conditions on the way to the laboratory, a 20-minute acclimatization period was left between the entry of the participants into the room and tear film measurements. The whole experiment was carried out under constant background illumination. The room was free from ambient lighting. Room temperature and humidity were constantly monitored and remained stable at 21.5 ± 0.7°C and 41 ± 6%, respectively.

14.2.4 Measurements and procedure

Potential participants were sought from the university and advertisements to see if they were likely to meet the study criteria. Each participant made a total of 4 visits: 3 on-site and 1 online, with a period of two weeks between visits for visits 1-2 and 2-3 and of one week for visits 3-4. At visit 1, one of the authors checked whether or not each volunteer met the inclusion/exclusion criteria before initiating the experiment. Next, participants were instructed to simulate their workstation design by placing themselves in front of their laptop as they normally would while considering variables such as the tilt angle of the screen and the height of the chair and the table. Then, their working distance (WD) was measured using a millimetre incremented ruler as the distance from the centre of the screen to their eyes.

Following this, baseline measurements were taken. DES, dry eye signs and symptoms, accommodation and binocular vision were assessed. DES was evaluated using the CVS-Q questionnaire. Dry eye symptoms were evaluated using the OSDI, DEQ-5 and SANDE I. Please refer to Chapter 3 for detailed information on these questionnaires (*3.2.1 Symptomatology questionnaires, 3. General methods*).

Accommodation and vision were subsequently assessed by measuring monocular CDVA and corrected near visual acuity (CNVA), accommodative posture (i.e., lag/lead), stereopsis, fixation disparity, ocular alignment, binocular accommodative facility,

horizontal fusional reserves and near point of convergence (NPC). The order of the measurements was chosen to minimize the effects of fatigue. Measurements were either taken at the participants' WD or both distance (6 m) and WD, depending on the parameter. Due to the higher variability of data, fusional reserves and NPC were measured three times and an average value was obtained. Participants were instructed to rest for 30 s by looking at a distance visual acuity chart between repeated measurements. Also, a rest period of approximately one minute was left between measurements. Measurements were undertaken with the participants' distance spectacle correction.

Finally, the ocular surface and tear film were examined using the Keratograph 5 M (Oculus Optikgerate, Wetzlar, Germany) (*3.2.2 Oculus Keratograpgh 5M, 3. General methods*). The measurement procedures were performed in the following order, based on the guidelines of the TFOS DEWS II Diagnostic Methodology report (Wolffsohn et al., 2017): TMH, limbal and bulbar conjunctival redness, spontaneous blinking pattern, LLT, NIKBUT, corneal and conjunctival staining, LWE and upper and lower eyelid meibography. NIKBUT was measured 3 times and an average value was obtained. For the assessment of blinking, participants were instructed to look at the fixation target with no need to stare at the stimulus and were not actively told that their blink movements were being recorded. Small twitches of the upper eyelid with particularly small amplitudes were not counted as a blink. Detailed information on the measurement procedures can be found in Chapter 3 (*3.2.2 Oculus Keratograpgh 5M, 3. General methods*).

A summary of the clinical tests and measurement procedures performed in the present study can be found in Table 14.1.

Finally, the study software was downloaded and installed onto the participants' laptops and the software settings were set. An identification number was assigned to each participant on the software. Then, the correct functioning of the software was checked, and the maximum screen angle was set by asking the participant to simulate their workstation design and to look at the top-right and top-left corners of the screen. For the first two weeks (visits 1-2) the participants were only instructed to use their laptops as usual while the 20-20-20 rule reminders were turned off. Participants were informed that the software would be collecting data about computer usage statistics and measuring their blink rate every 20 minutes.

At visits 2 and 3 the measurements were repeated, except for the measurement of DEQ-5, WD and eyelid miebography. The DEQ-5 questionnaire was not administered due to its lack of appropriateness to assess symptoms in the past two weeks. To further assess the change in dry eye symptomatology as compared to the previous visit, participants responded to the SANDE II, asking them about the difference in the severity and frequency of symptoms compared to the previous visit. At the end of visit 2, the 20-20-20 rule reminders were enabled, and the participants were informed about the breaks. Two weeks later (visit 3), the software was uninstalled. Finally, one week after the discontinuation of the management strategy (visit 4), an online survey containing the CVS-Q, OSDI, SANDE I and SANDE II was sent to the participants as a follow-up of symptoms. Figure 14.3 displays a flowchart of the study design.

Cross-over and masking were not possible in the study design as it was unknown how long the effects would last for. However, objective measures and real-time monitoring was used to minimize any placebo effect or researcher bias.

Table 14.1. Summary of the clinical tests and measurement procedures performed in the present study.

Parameter	Test
DES	CVS-Q
Working distance[a]	Distance from screen to eyes; mm ruler
Visual acuity (D and N)[a]	ETDRS LogMar chart; R, L.
Accommodative posture[a]	Difference between accommodative demand at WD and change between distance Rx and WD Rx; Open field autorefractor (Grand Seiko WAM-5500 autorefractor, Grand Seiko Co. Ltd., Hiroshima, Japan).
Stereopsis (WD)[a]	TNO test (random dot stereotest) (Laméris Ooctech BV, Nieuwegein, Netherlands).
Fixation disparity (WD)[a]	Minimum prism to eliminate disparity; Mallet unit (Mallett, 1964).
Ocular alignment (D and WD)[a]	Cover test (Pediatric Eye Disease Investigator Group, 2009).
Binocular accommodative facility (WD)[a]	± 2.00 flippers, whilst viewing near target.
Horizontal near fusional reserves (WD)[a]	Prism bar; blur/break/recovery (values at the test ceiling, > 40, were scored as 45) (Wesson, 1982).
Near point of convergence[a]	RAF rule push-up (Neely, 1956).
Dry eye symptomatology	OSDI, DEQ-5, SANDE I and SANDE II.
Tear meniscus height	Oculus K5M.
Conjunctival redness	Oculus K5M.
Blinking pattern	Blink rate and % of incomplete blinks; Oculus K5M; 60 s video recording, hight frame rate option selected; Manually counted while played at 0.25 original speed.
Lipid layer thickness	Oculus K5M; Guillon grading scale (Guillon, 1998).
Tear break-up time	Non-invasive keratograph break-up time; Oculus K5M.
Corneal staining	Oculus K5M; fluorescein, blue light; Oxford grading scale.
Conjunctival staining	Oculus K5M; lissamine green, white light; Oxford grading scale.
Lid wiper epitheliopathy	Horizontal length and sagittal width; Oculus K5M; Lissamine green and fluorescein, white light.
Meibomian glands dropout	Upper and lower infrared meibography; Oculus K5M; Ratio between eyelid area and gland loss area. Image J tool (Wayne Rasband; National Institutes of Health, Bethesda, MD).

CVS-Q = Computer Vision Syndrome Questionnaire; D = Distance (6 m); DEQ-5 = 5-item Dry Eye Questionnaire; DES = Digital eye strain; ETDRS = Early treatment diabetic retinopathy study; L = Left eye; N = Near (40 cm); Oculus K5M = Oculus Keratograph 5M; OSDI = Ocular Surface Disease Index; R = Right eye; RAF = Royal air force rule; Rx = Refraction; SANDE I = Symptom Assessment in Dry Eye, version 1; SANDE II = Symptom Assessment in Dry Eye, version 2; WD = Working distance. [a] Test undertaken with the participant's distance refraction.

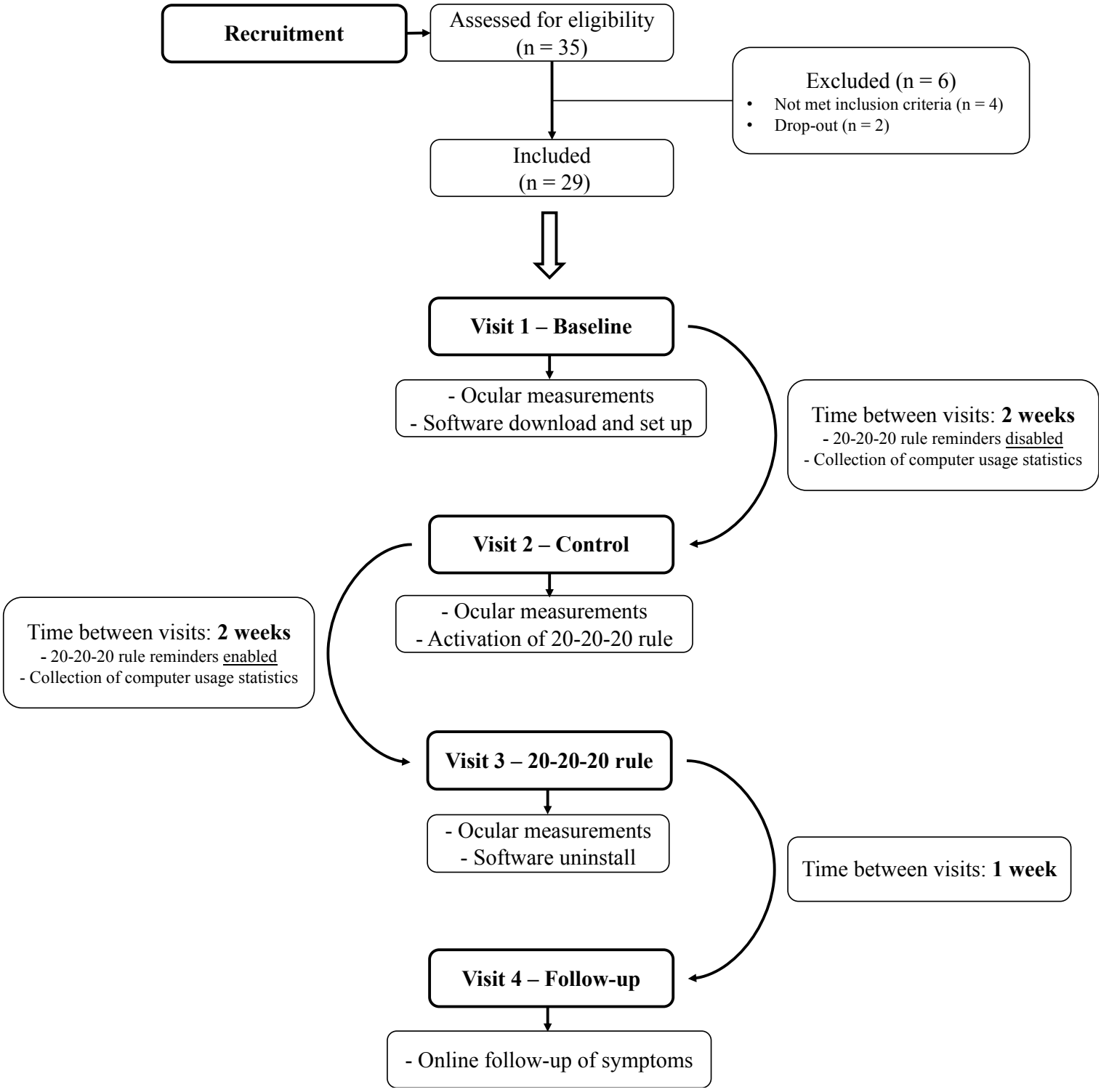


Figure 14.3. Study flowchart.

14.2.5 Statistical analysis

Data on user presence and blink data gathered by the software were downloaded and transferred into Microsoft Excel (Microsoft, Redmond, WA, USA) spreadsheets. Relevant computer usage statistics were then calculated for each participant, before and after the activation of the 20- 20-20 rule reminders, including the average blink rate, average blink duration, average duration of computer use per day (i.e., sum of the time spent in front of the computer per day), number of days of computer use, average duration of continuous (uninterrupted) computer work (i.e., average time looking at the computer screen without taking a break longer than 20 s), average duration of breaks and average number of natural, rule and total breaks taken per day.

The results were then evaluated using SPSS software v.26 (IBM Corp., Armonk, NY). The normality of data was assessed using the Shapiro-Wilk test. When normality could be assumed, a paired-sample t-test was used to examine the differences in computer usage before and after the activation of the 20-20-20 rule reminders. The non-parametric Wilcoxon paired signed-rank test was used when parametric test assumptions were not fulfilled. Additionally, the one-sample Wilcoxon signed-rank test was used to examine if the average number of rule reminder breaks taken per day was significantly greater than zero.

A repeated-measures ANOVA was used to examine the statistical differences of the binocular vision and ocular surface results obtained for the different study visits. Please refer to Chapter 3 for more information on repeated-measures ANOVA (*3.3.3.3 Differences between three or more repeated measurements, 3. General methods*). The non-parametric Friedman test for repeated measures with Dunn-Bonferroni post-hoc analysis was used when parametric test assumptions were not fulfilled. In parallel, a one-sample t-test or a one-sample Wilcoxon signed-rank test, depending on the distribution of data, was used to examine if the SANDE II score obtained during each visit was significantly greater than zero.

Finally, two-way mixed ANOVA were used to examine the influence of several variables on the effectiveness of the 20-20-20 rule in reducing DES. Between-subjects variables included: (1) duration of computer use as detected by the software (moderate $<$ 4 hours/day vs high $\geq$ 4 hours/day), (2) number of natural breaks taken per day (few $<$ 26 breaks/day vs many $\geq$ 26 breaks/day) and (3) severity of DES (CVS-Q score; mild $<$ 10 vs moderate $\geq$ 10). Cut-off values were selected based on the median value of each

distribution. Please refer to Chapter 3 for more information on mixed ANOVA (*3.3.3.4 Interaction between variables, 3. General methods*).

14.3 Results

Thirty-five volunteers were initially recruited out of which 29 (9 males and 20 females) ranging in age from 18 to 43 years (27 ± 7) met the inclusion/exclusion criteria and completed all study visits. Out of the 29 participants, 22 were White, 5 Asian and 2 Hispanic/Latino. The average time of computer use reported by the participants was 7 ± 2 h a day, 6 ± 1 days a week.

Table 14.2 shows the data collected by the study software before and after enabling the 20-20-20 rule reminders along with the statistical results of the comparison. No statistically significant changes in the average blink rate or blink duration during computer use were found before and after the activation of the rule reminders ($p = 0.82$ and $p = 0.40$, respectively). Likewise, no significant differences in the average duration of computer use per day and the total number of days of computer use were observed between the two study periods ($p = 0.85$ and $p = 0.79$, respectively). On the contrary, the average duration of continuous computer use and the average duration of breaks were significantly shorter when the rule reminders were on compared to when they were off ($p = 0.006$ and $p = 0.02$). Finally, the total number of breaks taken per day was significantly higher after the activation of the rule reminders compared to before ($p = 0.003$), while the number of 20-20-20 rule reminder breaks taken per day during weeks 3-4 was significantly higher than zero ($p < 0.001$). Conversely, the number of natural breaks taken did not vary significantly between both study periods ($p = 0.07$).

Table 14.3 shows the visual, accommodative and vergence results obtained before (visits 1 and 2) and after two weeks of compliance with the 20-20-20 rule reminders (visit 3), along with the statistical results of the comparison. No statistically significant differences in CDVA, CNVA, accommodative posture, stereopsis, fixation disparity, ocular alignment, fusional vergences (positive and negative) and near point of convergence were obtained between visits ($p \geq 0.07$). Conversely, binocular accommodative facility was significantly greater at visit 3 compared to visits 1 and 2 ($p = 0.01$ for both).

Table 14.4 displays the dry eye signs and symptomatology scores obtained before (visits 1 and 2) and after two weeks of compliance with the 20-20-20 rule reminders (visit

3), along with the symptoms reported one week after the discontinuation of the management strategy (visit 4). Statistically significant differences in dry eye symptoms and DES were obtained between visits ($p \leq 0.04$). The CVS-Q and the SANDE I severity score obtained at visit 3 were significantly lower than at visit 1 ($p = 0.008$ and $p = 0.04$, respectively). Likewise, a significantly lower CVS-Q, OSDI and SANDE I total score were obtained at visit 3 compared to visit 2 ($p = 0.008$, $p = 0.02$ and $p = 0.04$, respectively). In parallel, the SANDE II frequency and severity scores obtained at visit 3 were significantly lower than zero ($p < 0.001$ for both), while no significant differences with zero were observed at visit 2 ($p = 0.36$ and $p = 0.90$, respectively). Also, a SANDE II frequency score significantly greater than zero was obtained at visit 4 ($p = 0.005$), however, no significant difference was obtained in the severity score during the same visit ($p = 0.22$).

In parallel, no statistically significant differences between visits were obtained on any ocular surface or tear film parameter (TMH, conjunctival redness, percentage of incomplete blinks, LLT, NIKBUT, and ocular surface staining) ($p \geq 0.09$) except for the blink rate, which was significantly lower at visit 3 compared to visit 1 ($p = 0.04$).

Finally, the two-way mixed ANOVA did not reveal an influence of the duration of computer use ($p = 0.92$), the number of natural breaks taken per day ($p = 0.21$) or the severity of DES symptoms (i.e., CVS-Q score) ($p = 0.42$) on the effectiveness of the 20-20-20 rule in reducing DES.

Table 14.2. Data collected by the study software before (weeks 1 to 2) and after (weeks 3 to 4) the activation of the 20-20-20 rule reminders and statistical results of the comparison. Data are presented as mean ± SD [min, max].

Variable	Rule break reminders turned off (weeks 1-2) (n = 29)	Rule break reminders tuned on (weeks 3-4) (n = 29)	p-value
Blink rate[a] (blinks/min)	8 ± 4 [4, 16]	9 ± 5 [3, 19]	0.82[1]
Blink duration[a] (ms)	363 ± 44 [302, 427]	356 ± 36 [292, 412]	0.40[1]
Duration of computer use[a] (hours/day)	5 ± 3 [2, 13]	5 ± 3 [2, 12]	0.85[2]
Days of computer use	12 ± 2 [10, 15]	12 ± 3 [9, 14]	0.79[2]
Continuous computer use[a] (min)	11 ± 4 [4, 21]	7 ± 3 [4, 20]	0.006*[2]
Duration of breaks[a] (min)	5 ± 3 [1, 14]	4 ± 2 [2, 7]	0.02*[2]
Number of natural breaks[a] (breaks/day)	26 ± 13 [10, 52]	31 ± 18 [7, 69]	0.07[1]
Number of rule breaks[a,b] (breaks/day)	–	3 ± 2 [1, 9]	< 0.001*[3]
Total number of breaks[a] (breaks/day)	26 ± 13 [10, 52]	34 ± 18 [9, 73]	0.003*[1]

min = minutes. [a] Intra-average values. [b] Statistical comparison with value of 0. * Indicates statistically significant values ($p < 0.05$). [1] Paired-sample t-test. [2] Wilcoxon paired signed-rank test. [3] One-sample Wilcoxon signed-rank test.

Table 14.3. Visual, accommodative and vergence functions obtained before (visits 1 and 2) and after two weeks of compliance with the 20-20-20 rule reminders (visit 3) and statistical results of the comparison. Data are presented as mean ± SD [min, max].

Variable		Visit 1 (Baseline) (n = 29)	Visit 2 (n = 29)	Visit 3 (20-20-20 rule) (n = 29)	p-value	Statistically significant post-hoc differences (p-value)
CDVA	Right Eye	-0.08 ± 0,09 [-0.24, 0.12]	-0.08 ± 0,09 [-0.26, 0.16]	-0.09 ± 0,09 [-0.30, 0.18]	0.44[2]	—
	Left Eye	-0.09 ± 0,09 [-0.20, 0.12]	-0.10 ± 0,10 [-0.26, 0.12]	-0.09 ± 0,10 [-0.28, 0.15]	0.50[2]	—
CNVA	Right Eye	-0.04 ± 0.11 [-0.20, 0.20]	-0.03 ± 0.08 [-0.16, 0.10]	-0.04 ± 0.08 [-0.20, 0.08]	0.64[1]	—
	Left Eye	-0.05 ± 0.11 [-0.20, 0.18]	-0.03 ± 0.07 [-0.18, 0.12]	-0.04 ± 0.09 [-0.20, 0.18]	0.89[1]	—
Accommodative posture (D)		0.65 ± 0.43 [-0.24, 1.39]	0.65 ± 0.36 [0.05, 1.33]	0.65 ± 0.45 [-0.03, 1.50]	0.99[1]	—
Stereopsis (arc sec)		60 ± 30 [15, 120]	60 ± 27 [15, 120]	30 ± 18 [15, 60]	0.05[2]	—
Fixation disparity (ΔD)		0 ± 1 [-2, 1]	0 ± 1 [-2, 12]	0 ± 1 [-3, 2]	0.84[2]	—
Ocular alignment (ΔD)	Distance	-1 ± 1 [-4, 2]	-1 ± 1 [-4, 1]	-1 ± 1 [-4, 1]	0.46[2]	—
	Working Distance	-2 ± 3 [-10, 5]	-2 ± 3 [-10, 4]	-2 ± 3 [-10, 2]	0.07[2]	—
Binocular accommodative facility (cpm)		6 ± 5 [0, 17]	5 ± 5 [0, 17]	7 ± 5 [1, 20]	< 0.001*[2]	Visit 1 – Visit 3 (0.010) Visit 2 – Visit 3 (0.010)

Positive fusional vergences (ΔD)	Blur	12 ± 2 [9, 18]	13 ± 3 [6, 18]	14 ± 5 [6, 25]	0.71[1]	—
	Break	21 ± 9 [4, 40]	23 ± 10 [5, 40]	23 ± 11 [9, 40]	0.23[2]	—
	Recovery	17 ± 9 [2, 40]	19 ± 11 [2, 40]	19 ± 11 [5, 40]	0.26[2]	—
Negative fusional vergences (ΔD)	Blur	11 ± 3 [6, 16]	10 ± 3 [6,15]	9 ± 3 [4, 15]	0.18[1]	—
	Break	15 ± 4 [9, 22]	14 ± 4 [8, 20]	13 ± 4 [7, 20]	0.07[1]	—
	Recovery	11 ± 4 [5, 20]	10 ± 3 [5, 17]	9 ± 3 [5, 17]	0.06[1]	—
Near point of convergence (cm)	Break	6 ± 3 [4, 14]	6 ± 3 [4, 17]	6 ± 3 [4, 15]	0.70[2]	—
	Recovery	7 ± 3 [4, 15]	7 ± 3 [4, 19]	7 ± 3 [4, 17]	0.30[2]	—

CDVA = Corrected distance visual acuity; CNVA = Corrected near visual acuity. * Indicates statistically significant values ($p < 0.05$). † Repeated-measures ANOVA. ‡ Friedman.

Table 14.4. Dry eye signs and symptoms obtained before (visits 1 and 2) and after two weeks of compliance with the 20-20-20 rule reminders (visit 3) and symptoms reported one week after the interruption of the management strategy (visit 4) and statistical results of the comparison. Data are presented as mean ± SD [min, max].

Variable		Visit 1 (Baseline) (n = 29)	Visit 2 (n = 29)	Visit 3 (20-20-20 rule) (n = 29)	Visit 4 (Online follow-up) (n = 29)	p-value	Statistically significant post-hoc differences (p-value)
CVS-Q		10 ± 4 [6, 20]	11 ± 4 [6, 25]	8 ± 4 [3, 22]	9 ± 4 [4, 21]	p = 0.001[2]	Visit 1 – Visit 3 (0.008) Visit 2 – Visit 3 (0.008)
OSDI		22.9 ± 12.5 [0.0, 45.5]	24.6 ± 16.1 [0.0, 62.5]	19.0 ± 13.6 [0.0, 60.4]	20.0 ± 13.8 [0.0, 50.0]	p = 0.02[2]	Visit 2 – Visit 3 (0.02)
DEQ-5		10 ± 4 [3, 17]	/	/	/	/	
SANDE I	Frequency	40 ± 26 [4, 90]	37 ± 23 [4, 90]	31 ± 21 [0, 85]	37 ± 24 [0, 80]	p = 0.12[2]	—
	Severity	33 ± 22 [4, 81]	32 ± 20 [4, 90]	26 ± 19 [0, 73]	33 ± 23 [0, 90]	p = 0.04*[2]	Visit 1 – Visit 3 (0.04)
	Total score	35 ± 21 [4, 75]	34 ± 20 [4, 90]	28 ± 19 [0, 78]	34 ± 22 [0, 80]	p = 0.02*[1]	Visit 2 – Visit 3 (0.04)
SANDE II[a]	Frequency	/	1 ± 6 [-15, 14]; p = 0.358[4]	-11 ± 10 [-40, 12]; p < 0.001*[3]	8 ± 13 [-10, 40]; p = 0.005*[4]	/	
	Severity	/	0 ± 6 [-17, 16]; p = 0.904[4]	-12 ± 12 [-37, 10]; p < 0.001*[3]	4 ± 17 [-40, 40]; p = 0.222[4]	/	

TMH (mm)		0.23 ± 0.13 [0.11, 0.73]	0.23 ± 0.11 [0.09, 0.64]	0.24 ± 0.10 [0.11, 0.51]	/	p = 0.54[1]	—
Conjunctival redness	Bulbar - Temporal	0.8 ± 0.4 [0.2, 1.8]	0.8 ± 0.5 [0.2, 1.9]	0.8 ± 0.4 [0.2, 1.8]	/	p = 0.68[1]	—
	Bulbar - Nasal	1.1 ± 0.6 [0.2, 2.7]	1.1 ± 0.6 [0.1, 2.9]	1.1 ± 0.7 [0.3, 2.5]	/	p = 0.97[1]	—
	Limbal - Temporal	0.4 ± 0.4 [0.0, 1.6]	0.4 ± 0.4 [0.0, 1.7]	0.4 ± 0.3 [0.1, 1.3]	/	p = 0.81[2]	—
	Limbal - Nasal	0.6 ± 0.5 [0.1, 1.8]	0.6 ± 0.5 [0.0, 1.7]	0.7 ± 0.5 [0.1, 2.2]	/	p = 0.50[2]	—
Blink rate (blinks/min)		23 ± 14 [0, 64]	22 ± 16 [4, 64]	17 ± 12 [1, 54]	/	p = 0.03*[2]	Visit 1 – Visit 3 (0.04)
Incomplete blinking (%)		56 ± 31 [0, 100]	53 ± 31 [0, 100]	49 ± 31 [0, 100]	/	p = 0.09[2]	—
Lipid layer thickness[b]		3 ± 1 [1, 5]	3 ± 1 [1, 5]	3 ± 1 [1, 5]	/	p = 0.18[2]	—
NIKBUT (s)		11.0 ± 6.2 [4.3, 24.2]	10.8 ± 5.9 [3.5, 23.4]	10.8 ± 6.2 [3.7, 23.6]	/	p = 0.99[2]	—
Corneal staining		1 ± 1 [0, 3]	1 ± 1 [0, 4]	1 ± 1 [0, 3]	/	p = 0.92[2]	—
Conjunctival staining		1 ± 1 [0, 4]	1 ± 1 [0, 3]	1 ± 1 [0, 4]	/	p = 0.69[2]	—
LWE	Horizontal length	1 ± 1 [0, 3]	1 ± 1 [0, 3]	1 ± 1 [0, 3]	/	p = 0.58[2]	—
	Sagittal width	0 ± 1	0 ± 1	0 ± 1	/	p = 0.36[2]	—

		[0, 4]	[0, 3]	[0, 3]		
MGD (%)	Upper eyelid	24 ± 14. [3, 69]	/	/	/	/
	Lower eyelid	41 ± 18 [10, 70]	/	/	/	/

CVS-Q = Computer Vision Syndrome Questionnaire; OSDI = Ocular Surface Disease Index; DEQ-5 = 5-item Dry Eye Questionnaire; SANDE I = Symptom Assessment in Dry Eye, version 1; SANDE II = Symptom Assessment in Dry Eye, version 2; TMH = Tear meniscus height; NIKBUT = Non-invasive keratograph break-up time; LWE = Lid wiper epitheliopathy; MGD = Meibomian gland dysfunction. [a] Statistical comparison with value of 0 (no change). [b] Graded as: 1 = open meshwork; 2 = closed meshwork; 3 = wave; 4 = amorphous; 5 = 1st order colours; 6 = 2nd order colours. * Indicates statistically significant values ($p < 0.05$). [1] Repeated-measures ANOVA. [2] Friedman [3] One-sample t-test. [4] One-sample Wilcoxon signed rank test.

14.4 Discussion

14.4.1 Computer use

According to the results of the present study, enabling the 20-20-20 rule reminders had a significant impact on how participants used their computers. Participants took more breaks per day in total when the 20- 20-20 rule reminders were on compared to when they were off (34 with reminders on vs 27 with reminders off), which was partially attributed to the breaks taken following the instructions of the reminders. Conversely, the average number of natural (spontaneous) breaks taken per day did not change significantly, although a slight increase of 5 breaks per day, on average, was observed when the rule reminders were activated. This may be due to an increased consciousness of computer usage which some participants reported during their visits.

Additionally, the participants worked on their computers continuously for shorter periods when they followed the 20-20-20 rule than when they did not, probably due to the increase in the number of breaks taken per day which caused the gap between breaks to shorten. Likewise, the average duration of breaks was significantly reduced when the rule reminders were enabled. This may be attributed to the fact that the reminders instructed participants to rest for a brief period (20 s).

Furthermore, despite a significant change in computer usage between the two study periods, the average number of rule breaks taken per day, although significantly greater than zero, was clinically small (i.e., 3 rule breaks per day on average). Considering that the participants' average natural duration of continuous computer use was of 11 minutes and that the 20-20-20 rule instructs individuals to rest after 20 minutes of continuous work, the rule did not require a clinically significant number of breaks.

Finally, it should be noted that the average duration of computer use per day recorded by the software, although noticeably high, was considerably smaller than the one reported by the participants during the recruitment phase of the study (4 hours per day vs 7 hours per day reported by the participants). Individuals tend to subjectively overestimate their duration of computer use, probably because they do not always consider the time spent on short breaks. This should be taken into consideration in future studies on digital display users.

14.4.2 Binocular vision

According to previous research, the symptoms experienced with computer use may be associated with alterations in the accommodative and vergence systems (Hue et al., 2014; Kwon et al., 2012; Park et al., 2012; Piccoli et al., 1996; Seo, 2012). For instance, Kwon et al. (2012) found an increase in lag in a sample of young individuals after they played a computer game for 90 minutes. Similarly, Seo (2012) observed an increase in lag, along with a decrease in accommodative facility, after two hours of computer use. Also, there are reports that fusional convergence and divergence decline over 6 hours of computer use per day (Piccoli et al., 1996), that NPC recedes after only 20 minutes of device use (Piccoli et al., 1996) and that there is a greater tendency for phoria to shift toward greater exophoria after using a computer for as little as 20 minutes (Park et al., 2012; Piccoli et al., 1996). Nevertheless, despite these findings, other research found no changes in these parameters with computer visualization, which could be due to differences in methodology (Collier & Rosenfield, 2011; Rosenfield et al., 2010; Yammouni & Evans, 2021).

In the present study, following the 20-20-20 rule significantly improved binocular accommodative facility compared to before (i.e., visits 1 and 2). Iribarren et al. (2001) found that the cumulative duration of near work over months showed a significant negative correlation with binocular accommodative facility. Accordingly, the 20-20-20 rule may improve accommodative facility in regular computer users by reducing screen time, thus preventing cumulative effects of prolonged near work, although more research is required to confirm these findings.

Conversely, the 20-20-20 rule had no significant effect on any other visual, accommodative or vergence parameter. Based on the available evidence, the impact of computer use on accommodation and vergence is inconclusive and has yet to be clarified. Participants in the present study were young and took, on average, a considerable number of natural breaks per day. Overall, it is possible that there were no alterations in accommodation and vergence consequent to computer use in the first place, which would have prevented observing any benefits associated with the 20-20-20 rule. Future research is required to assess the benefits of the 20-20-20 rule in computer users with a tendency to stare at the screen for long periods and/or with binocular disorders arising from computer use.

14.4.3 Symptoms and dry eye

The results of the present study indicate a noticeable reduction in the blink rate while using the computer (16-22 blinks/min when looking in primary gaze vs 8-9 blinks/min when using the computer). This is closely in line with the findings of Chapter 5 (*5. Blinking kinematics characterization during digital displays use*; Talens-Estarelles et al., 2022a). Most importantly, following the 20-20-20 rule had no effects on the blink rate and blink duration of the participants while using the computer. Therefore, the 20-20-20 rule reminders are likely to have no beneficial effect on the blinking pattern during device use.

Furthermore, there was a significant improvement in dry eye symptoms after the management period. Following the 20-20-20 rule led to a lower OSDI compared to previous visits, although this was not enough to prevent a positive symptom score (OSDI $\geq$ 13). Likewise, the severity of dry eye symptoms reported in SANDE I was lower after the management period compared to before, leading to a lower total SANDE I score, although no change in the frequency of dry eye symptoms was observed between visits. In parallel, the SANDE II scores after the management period were significantly smaller than 0, meaning that both the severity and frequency of symptoms reported by the participants were lower compared to the previous visit (visit 2).

Symptoms of dry eye (OSDI and SANDE I) reported one week after the discontinuation of the 20-20-20 rule (visit 4) were not different from those reported before the management strategy (visits 1 and 2), yet they were not greater than those observed at visit 3, thus some of the improvement was maintained one week after discontinuation. Similarly, the frequency score in SANDE II obtained one week after the discontinuation of the rule reminders was significantly greater than zero, although the severity score revealed no difference. Consequently, the frequency of dry eye symptoms increased one week after the interruption of the strategy, yet the perceived severity of dry eye was maintained.

Conversely, no differences in dry eye signs were observed between visits for any of the parameters, except for the blink rate which was significantly lower after the management period with the 20-20-20 rule compared to baseline (visit 1). One of the main factors responsible for normal spontaneous blinks is the imminent break-up of the tear film which is sensed by the cornea (Collins et al., 2009). Consequently, excessive blinking has been associated with reduced tear stability and may occur as a wetting

process (Rahman et al., 2015). The reduction in the spontaneous blink rate observed in the present study after the management period might reveal an improvement in tear function, though this was not accompanied by an improvement in any tear film parameter.

As aforementioned, participants naturally looked away from the screen or moved away from their workstation frequently even before the activation of the rule reminders. Therefore, although the 20-20-20 rule prevented exposure times higher than 20 minutes, it did not request a considerable number of rule breaks for most individuals, which may explain why, despite an improvement in symptoms, most parameters remained unchanged.

Finally, the CVS-Q score was significantly lower after the management period compared to before, thus DES significantly decreased as a result of the 20-20-20 rule reminders. Particularly, the CVS-Q score of some participants fell below 6 (positive CVS-Q score) after two-weeks compliance with the 20-20-20 rule, thus excluding them from a positive DES diagnosis after the management period. Nevertheless, no difference with pre-management values was observed one week after the discontinuation of the reminders, although, as with dry eye symptoms, DES was not greater than at visit 3 and therefore some improvement was maintained at the follow-up visit. These results are in accordance with previous research (Alghamdi & Alrasheed, 2020; Anggrainy et al., 2020). Anggrainy et al. (2020) found a significant difference in the incidence of DES between a treatment group taking breaks every 20 minutes during 5 working days and a control group. Similarly, Alghamdi and Alrasheed (2020) found a reduction in DES in a group of symptomatic individuals 20 days after they were given a structured advice booklet with instructions on the 20-20-20 rule. Nevertheless, despite the improvement observed in the present study, the 20-20-20 rule did not prevent DES (average CVS-Q $\geq$ 6).

The present study had some limitations to consider. Due to the subjective evaluation of symptoms, a placebo effect on the results cannot be completely ruled out. Additionally, the developed software was downloaded onto the participants' laptops only, and therefore did not take into account the use of other digital displays. Finally, due to the large volume of tests performed, fatigue effects may have influenced binocular vision measurements to some extent. Nevertheless, as aforementioned, rest periods were left between repeated measurements and between measurement procedures. Additionally, the order of the measurements was chosen to minimize the effects of fatigue on the results.

Overall, following the 20-20-20 rule significantly changed the way the participants used their computers by increasing the total number of breaks taken per day, and by reducing the duration of breaks as well as the time spent looking at the computer screen without rest. However, the blinking pattern exhibited during device use was not different and the blink rate remained low. The 20-20-20 rule improved binocular accommodative facility, although it had no effects on any other accommodative or vergence parameters. Furthermore, the 20-20-20 rule was effective in reducing DES and dry eye symptoms, although it was not sufficient to prevent DES or a positive OSDI score. Moreover, the improvement in symptoms was barely sustained one week after discontinuation; the frequency of dry eye symptoms was no longer different from baseline, although the severity remained slightly better. Conversely, no improvement in dry eye signs was observed during the study period. Further reducing the time interval between breaks or offering personalized rule breaks based on the natural habits of computer users, may prove more beneficial. Future research in larger samples is required to confirm these findings. Also, specific research on the matter is needed to assess and compare the effectiveness of the 20-20-20 rule in different population groups, especially in individuals with different durations of computer usage.

15.

Online vs in-person education: Evaluating the potential influence of teaching modality on dry eye symptoms and risk factors during the COVID-19 pandemic

15.1 Introduction

In January 2020, the World Health Organization declared the COVID-19 outbreak a "public health emergency of international concern" and just a few months later a pandemic (World Health Organization, 2020). The rapid spread of the disease and high death rate challenged society worldwide, with governments, advised by scientists, being enforced to take drastic measures to protect the lives of their fellow citizens. These restrictive measures were essentially aimed at ensuring physical distancing through mobility restrictions and reduction of outdoor activities and social gatherings, ultimately resulting in the closing of centres, such as schools and universities. According to the United Nations Educational, Scientific and Cultural Organization, the overnight closing of educational centres affected more than 1.57 billion students in 191 countries, impacting in some countries over 60% of the student population (UNESCO., 2020).

Fortunately, the restrictions in educational centres did not entirely halt education, although they changed it. To comply with these preventive measures, as well as to ensure the continuity of students' education, society favoured and promoted the most unusual educational arrangement of this generation: online education. Before the COVID-19 pandemic, only a small fraction of educational institutions was implementing online learning methods (a mere 10% of European countries had robust digital learning capabilities) (European Comission, 2020). However, as COVID-19 infections spread around the world, countries instructed their centres to reduce or close operations and switch to online learning modes, triggering a reconceptualization of education provision at all levels. In this regard, online education will become an integral component of education after the pandemic fully resolves.

Nevertheless, the intense use of technological resources to ensure learning continuity may jeopardize students' ocular and visual health. More specifically, as addressed throughout this work, digital display use has been implicated as a contributing factor to DED (Stapleton et al., 2017). DED, as defined by the TFOS DEWS II, is a "multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles" (Craig et al., 2017).

Given the multifactorial nature of DED, not only computer use but multiple other factors such as the use of CLs, environmental exposure, diet, or lifestyle factors such as

smoking, alcohol consumption or caffeine intake, to name a few, have consistently shown to influence the disease (Stapleton et al., 2017). In this regard, remote education, during this unprecedented situation, has not only changed the patterns of digital display usage but has had a far-reaching impact on students' lifestyles.

Accordingly, the aim of this chapter was to assess the potential effects of switching to an online lecture format on dry eye symptoms and DED risk factors, through an in-depth survey based on several validated questionnaires and risk factor-related inquiries in a large sample of university students.

15.2 Methods

15.2.1 Participants

An anonymous cross-sectional online survey was carried out among university students in November 2020. The invitation to the survey was sent to all undergraduate and postgraduate students of the Science Campus of the University of Valencia. The survey was completed by a total of 872 respondents, out of which 812 were finally selected and analysed (282 males and 530 females). The students were carrying out their studies in 56 different university programs. At the time of the survey, the University of Valencia contemplated three modalities of academic teaching: 100% online lectures, in which students attended all their theory lectures online; 100% in-person lectures, in which students attended all their lectures face to face; and 50% online-50% in-person (mixed modality), in which students carried out some of their lectures online and others in-person. These three teaching modalities varied among the different degrees and academic years and were dependent on the number of students and space available, to ensure physical distancing.

The study followed the tenets of the Declaration of Helsinki, and a favourable opinion from the ethical committee of the University of Valencia was obtained. All the participants were informed about the nature of the study and gave their consent.

15.2.2 Procedure

The survey was created using the Google forms platform and distributed to potential participants through a web link sent through the institutional e-mail of the University of Valencia. The survey was sent on the first week of December 2020 and was

left open for 1 week. At the time the email was sent, the participants had received lectures for a total of 11 weeks (78 days) under their respective teaching modalities. The survey had no time limit, although the time spent by the participants to answer all the questions in the survey was recorded, without the participants being aware. This study design was like that of Chapter 4 (*4. Dry eye-related risk factors for digital eye strain*; Talens-Estarelles et al., 2022b).

15.2.3 Questionnaires and risk factors

The survey comprised a total of three dry eye questionnaires included in the TFOS DEWS II diagnostic methodology report (Wolffsohn et al., 2017): (1) OSDI, (2) DEQ-5 and (3) CLDEQ-8. Please refer to Chapter 3 for detailed information on the questionnaires (*3.2.1 Symptomatology questionnaires, 3. General methods*). Additionally, participants answered several questions on DED risk factors contemplated in the TFOS DEWS II epidemiology report (Stapleton et al., 2017), including questions about age, sex, ethnicity, smoking, alcohol consumption, caffeine intake, water intake, hours of sleep, environmental exposures including outdoor activity and exposure to air conditioning or central heating, exercise, stress levels, diet, general health, pathologies, medication, ocular surgery and CL wear. Participants graded the quality of their diet as good (excellent or good quality) if the participants had a balanced intake of protein, carbohydrates, fruits, and vegetables or poor (poor or fair quality) if their diet was unbalanced, associated with the intake of ultra-processed foods, ready-to-eat products, and sugars. Additionally, the participants were surveyed about other relevant information potentially related to dry eye, such as teaching modality, hours of online lectures per week, use of face masks, and use of digital displays.

The participants were instructed to read all questions carefully and respond with the utmost sincerity. In those questions related to their lecture attendance, the participants were asked about their actual attendance and not the one specified in their academic schedule. The survey sequence was as follows: (1) demographic questions, (2) questions on digital display use, (3) DED risk factors, (4) CLDEQ-8, (5) OSDI, and (6) DEQ-5.

15.2.4 Statistical analysis

First, the results from the survey were downloaded and transferred into Microsoft Excel spreadsheets (Microsoft, Redmond, WA, USA). Every answer was double-checked,

and illogical or irrational answers were excluded. To ensure the reliability of the data analysed, the participants who answered the survey in less than 7 minutes (10th percentile of the response time distribution) were excluded from the analysis.

Statistical analysis was carried out using SPSS software v.26 (IBM Corp, Armonk, NY). Participants were classified according to the number of hours during which they attended online lectures: online group (≥ 3 hours of online lectures per week) or in-person group (< 3 hours of online lectures per week). The cut-off value of 3 hours was chosen based on the 10th percentile of the distribution of the hours of online lectures per week that students attended within the 100% online teaching modality.

The normality of data for each group was assessed using the Kolmogorov-Smirnov test. Significant differences between the online and the in-person group for each questionnaire score and every demographic and DED risk factor were assessed using the Mann-Whitney U test, chi-square analysis, or unpaired t-test, depending on the sample distribution.

Preliminary univariate logistic regression was used to identify potential factors associated with the online group. Multivariate logistic regression for these factors was then performed, incorporating variables with a univariate association threshold of $p \leq 0.15$ (Wang et al., 2020). Please refer to Chapter 3 for more information on regression analysis (*3.3.3.6 Regression analysis, 3. General methods*). To properly perform logistic regression analysis, dichotomous variables exclusively related to a particular group of individuals (i.e., pelvic pain in female participants, oral contraceptive therapy, and hormone replacement therapy) were binary coded to 1 if the participant met the condition or to 0 if the participant did not meet the condition or did not apply to him. Likewise, CL-related variables were given a value of 0 if the participant was not a CL wearer.

Finally, a second multivariate logistic regression analysis was performed for the dry eye questionnaires whose score was statistically different between the groups (online vs in-person), to identify the factors that lead to greater dry eye symptoms. To assess this, the entire sample was divided depending on the cut-off values of the questionnaires.8 No adjustment for multiple comparisons was deliberately performed after previous research, to prevent a significant increase in type II error (Armstrong, 2014).

15.3 Results

Eight hundred seventy-two students completed the survey, out of which 812 (282 males and 530 females) ranging in age from 17 to 59 years (22 ± 4 years) were finally included for subsequent analysis. The average response time was 15 ± 7 minutes.

15.3.1 Online vs in-person attendance to lectures

From the total sample, 523 participants (64.4%) were classified into the online group and 289 (35.6%) into the in-person group. Table 15.1 shows the comparison between the online and in-person groups for each questionnaire score and every demographic and DED risk factor. Compared to the in-person group, students in the online group attended significantly more hours of online lessons per week, used the computer for more hours a day and more days a week, spent less time outdoors, practised more exercise per day, wore a face mask for less time, experienced fewer allergic and psoriasis episodes ($p \leq 0.02$), and obtained a higher OSDI score ($p = 0.03$).

Table 15.2 shows the results for the univariate and multivariate-adjusted logistic regression analysis, along with the ORs of the online group. This regression analysis was performed to assess which factors were independently associated with attending online classes. The multivariate logistic regression revealed that the following factors were independently associated with the online group: more hours of computer use per day, fewer hours of face mask use per day, fewer allergies, and a higher OSDI score ($p \leq 0.02$).

15.3.2 Risk factors for dry eye symptoms

Given the significantly higher OSDI score obtained by the online group compared to the in-person group ($p = 0.03$) and its association as an independent factor with attending online lectures ($p = 0.02$), potential factors associated with a positive score were evaluated. Four hundred sixteen subjects (51.2%) were classified into the asymptomatic group (OSDI < 13) and 396 (48.8%) into the symptomatic group (OSDI ≥ 13). Table 15.3 shows the comparison between both groups for each questionnaire score and every demographic and DED risk factor assessed. Compared to asymptomatic participants, participants with dry eye symptoms attended more hours of online lectures per week ($p = 0.04$), drank more caffeinated beverages ($p = 0.01$), spent more hours indoors with central heating ($p = 0.001$), wore CLs for more hours ($p < 0.001$), used the computer and tablet

for longer periods ($p = 0.04$ and $p = 0.006$, respectively), were more stressed, reported poorer health quality and obtained a significantly higher score on all other dry eye questionnaires (DEQ-5 and CLDEQ-8) ($p < 0.001$). Moreover, the dry eye group had significantly more females ($p < 0.001$), CL wearers ($p < 0.001$), and participants suffering from eczema, allergies, depression, vitamin deficiency, rosacea, migraine headaches, anxiety, pelvic pain, asthma, and irritable bowel syndrome ($p \leq 0.04$). Likewise, a higher percentage of participants with dry eye symptoms took oral contraceptive therapy, antihistamines, and anxiolytics compared to asymptomatic participants ($p \leq 0.001$).

Table 15.4 shows the results of the univariate and multivariate-adjusted logistic regression, along with the ORs of the group with positive OSDI score (OSDI $\geq$ 13). Multivariate logistic regression revealed that being female, attending more online lectures per week, using more electronic devices simultaneously, wearing CLs for longer periods, having higher stress levels, suffering from depression, eczema, migraine headaches, pelvic pain in females, or asthma, or obtaining a higher DEQ-5 and CLDEQ-8 score was independently associated with having dry eye symptoms ($p \leq 0.04$).

Table 15.1. Comparison between the online and in-person groups for each DED questionnaire and risk factor evaluated.

Characteristic	Online group (n = 523)	In-person group (n = 289)	p-value
Demographics			
Age *(median; IQR)*	21; 19-22 years	21; 18-23 years	0.27[1]
Female sex *(N of subjects; percentage of subjects)*	347; 66.3%	183; 63.3%	0.42[2]
East Asian ethnicity *(N of subjects; percentage of subjects)*	9; 1.7%	2; 0.7%	0.23[2]
Hours of online lectures per week *(median; IQR)*	12; 8-20 hours	0; 0-2 hours	< 0.001*[1]
Digital displays			
Hours of computer use per day *(median; IQR)*	7; 5-8 hours	5; 3-7 hours	< 0.001*[1]
Days of computer use per week *(median; IQR)*	7; 6-7 days	7; 6-7 days	0.001*[1]
Hours of computer use per week *(median; IQR)*	45; 35-56 hours	35; 21-48 hours	< 0.001*[1]
Hours of mobile phone use per day *(median; IQR)*	4; 3-5 hours	4; 3-6 hours	0.75[1]
Hours of tablet use per day *(median; IQR)*	0; 0-1 hours	0; 0-0 hours	0.28[1]
Hours watching television per day *(median; IQR)*	1; 0-1 hours	1; 0-2 hours	0.07[1]
N of devices used simultaneously *(median; IQR)*	3; 2-3 devices	3; 2-3 devices	0.90[1]
Dry eye risk factors			
Lifestyle factors			
Smokers *(N of subjects; percentage of subjects)*	61; 11.7%	36; 12.5%	0.73[2]
Days smoked per week *(median; IQR)*	0; 0-0 days	0; 0-0 days	0.65[1]
Cigarettes per day *(median; IQR)*	0; 0-0 cigarettes	0; 0-0 cigarettes	0.56[1]
Cigarettes per week *(median; IQR)*	0; 0-0 cigarettes	0; 0-0 cigarettes	0.64[1]
Alcohol consumers *(N of subjects; percentage of subjects)*	333; 63.7%	175; 60.6%	0.36[2]
Units of alcohol per week *(median; IQR)*	1; 0-3 units	1; 0-2 units	0.57[1]
Not caffeine drinkers *(N of subjects; percentage of subjects)*	175; 33.4%	104; 36.0%	0.41[2]
Units of caffeinated drinks per day *(median; IQR)*	1; 0-2 units	1; 0-2 units	0.23[1]
Litres of water per day *(median; IQR)*	1.5; 1.25-2 litres	1.75; 1-2 litres	0.88[1]
Hours of sleep per day *(median; IQR)*	7; 7-8 hours	7; 7-8 hours	0.80[1]
Hours outdoors per day *(median; IQR)*	1.5; 1-2 hours	2; 1-3 hours	< 0.001*[1]
Hours indoors with central heating per day *(median; IQR)*	25; 5-42 hours	24; 7-40 hours	0.64[1]
Hours of exercise per week *(median; IQR)*	3; 2-5 hours	2; 1-5 hours	0.03*[1]
Poor diet quality *(N of subjects; percentage of subjects)*	125; 2.9%	75; 26.0%	0.46[2]
High use of face mask *(N of subjects; percentage of subjects)*	401; 76.7%	258; 89.3%	< 0.001*[2]
Hours of face mask wear per day *(median; IQR)*	5; 3-7 hours	7; 5-8 hours	< 0.001*[1]
Contact lenses			
Contact lens wear *(N of subjects; percentage of subjects)*	141; 27.0%	87; 30.1%	0.18[2]
Soft contact lens wear *(N of subjects; percentage of subjects)*	120; 22.9%	77; 26.6%	0.18[2]
Days of contact lens wear per week *(median; IQR)*	0; 0-1 days	0; 0-1.5 days	0.28[1]
Hours of contact lens wear per week *(median; IQR)*	0; 0-2 hours	0; 0-5 hours	0.41[1]
Health conditions			
Poor health quality *(N of subjects; percentage of subjects)*	95; 18.2%	48; 16.6%	0.52[2]
Stress *(N of subjects; percentage of subjects)*	68; 13.0%	48; 16.6%	0.17[2]
Refractive surgery *(N of subjects; percentage of subjects)*	13; 2.5%	4; 1.4%	0.94[2]
Acne *(N of subjects; percentage of subjects)*	93; 17.8%	50; 17.3%	0.93[2]
Allergies *(N of subjects; percentage of subjects)*	96; 18.4%	78; 27.0%	0.005*[2]
Anxiety *(N of subjects; percentage of subjects)*	110; 21.0%	53; 18.3%	0.07[2]
Migraine headaches *(N of subjects; percentage of subjects)*	80; 15.3%	32; 11.1%	0.23[2]
Eczema *(N of subjects; percentage of subjects)*	34; 6.5%	17; 5.9%	0.74[2]

Asthma *(N of subjects; percentage of subjects)*	32; 6.1%	21; 7.3%	0.61[2]
Psoriasis *(N of subjects; percentage of subjects)*	4; 0.8%	8; 2.8%	0.02*[2]
Depression *(N of subjects; percentage of subjects)*	23; 4.4%	14; 4.8%	0.46[2]
Vitamin deficiency *(N of subjects; percentage of subjects)*	22; 4.2%	10; 3.5%	0.76[2]
Rosacea *(N of subjects; percentage of subjects)*	9; 1.7%	2; 0.7%	0.61[2]
Pelvic pain in females *(N of subjects; percentage of subjects)*	22; 4.2%	11; 3.8%	0.34[2]
Diabetes *(N of subjects; percentage of subjects)*	4; 0.8%	3; 1.0%	0.54[2]
Fertility problems *(N of subjects; percentage of subjects)*	4; 0.8%	3; 1.0%	0.68[2]
Thyroid disease *(N of subjects; percentage of subjects)*	13; 2.5%	7; 2.4%	0.68[2]
Irritable bowel syndrome *(N of subjects; percentage of subjects)*	12; 2.3%	6; 2.1%	0.29[2]
Sclerosis *(N of subjects; percentage of subjects)*	3; 0.6%	4; 1.4%	0.53[2]
Liver disease *(N of subjects; percentage of subjects)*	2; 0.4%	1; 0.3%	0.85[2]
Medication			
Oral contraceptive therapy *(N of subjects; percentage of subjects)*	79; 15.1%	39; 13.5%	0.46[2]
Antihistamines *(N of subjects; percentage of subjects)*	57; 10.9%	35; 12.1%	0.46[2]
Anxiolytics *(N of subjects; percentage of subjects)*	16; 3.1%	12; 4.2%	0.18[2]
Antidepressants *(N of subjects; percentage of subjects)*	7; 1.3%	5; 1.7%	0.18[2]
Hormone replacement therapy *(N of subjects; percentage of subjects)*	8; 2.5%	8; 2.8%	0.45[2]
Anti-inflammatories *(N of subjects; percentage of subjects)*	9; 1.7%	4; 1.4%	0.71[2]
Analgesics *(N of subjects; percentage of subjects)*	2; 0.4%	1; 0.3%	0.30[2]
Dry eye questionnaires			
OSDI *(median; IQR)*	14.2; 6.3-22.7	11.5; 4.6-16.8	0.03*[1]
DEQ-5 *(median; IQR)*	8; 4.5-12	8; 4-11	0.23[1]
CLDEQ-8 *(mean ± SD)*	15 ± 7	15 ± 7	0.74[3]

CLDEQ-8 = 8-item Contact Lens Dry Eye Questionnaire; DEQ-5 = 5-item Dry Eye Questionnaire; IQR = Interquartile range; OSDI = Ocular Surface Disease Index; N = Number. * Indicates statistically significant values ($p < 0.05$). [1] Mann-Whitney U test. [2] chi-square test. [3] Unpaired T-test.

Table 15.2. Univariate and multivariate logistic regressions analysis and odds ratios of the online group.

Characteristic	Unadjusted univariate logistic regression		Multivariate-adjusted logistic regression	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
Demographics				
Age	0.973 (0.940–1.008)	0.128	-	-
Digital displays				
Hours of computer use per day	1.222 (1.152–1.295)	< 0.001*	1.200 (1.129–1.277)	< 0.001*
Days of computer use per week	1.346 (1.161–1.526)	< 0.001*	-	-
Hours of computer use per week	1.029 (1.020–1.037)	< 0.001*	-	-
Dry eye risk factors				
Hours outdoors per day	0.847 (0.771–0.931)	0.001*	-	-
High use of face mask	0.388 (0.253–0.596)	< 0.001*	-	-
Hours of face mask wear per day	0.805 (0.761–0.850)	< 0.001*	0.802 (0.756–0.851)	< 0.001*
Psoriasis	0.270 (0.081–0.904)	0.034*		
Allergies	0.616 (0.437–0.868)	0.006*	0.504 (0.345–0.736)	< 0.001*
Migraine headaches	1.498 (0.963–2.331)	0.073	-	-
Dry eye questionnaires				
OSDI	1.014 (1.002–1.026)	0.023*	1.117 (1.013–1.030)	0.013*

CI = Confidence interval; OR = Odds ratio; OSDI = Ocular Surface Disease Index. *Indicates statistically significant values ($p < 0.05$).

Table 15.3. Comparison between the groups with positive (OSDI ≥ 13) and negative (OSDI < 13) OSDI score for each DED questionnaire and risk factor evaluated.

Characteristic	OSDI < 13 (n = 416)	OSDI ≥ 13 (n = 396)	p-value
Demographics			
Age (*median; IQR*)	21; 19-22 years	21; 19-23 years	0.82[1]
Female sex *(N of subjects; percentage of subjects)*	221; 53.1%	309; 78.0%	< 0.001*[2]
East Asian ethnicity *(N of subjects; percentage of subjects)*	4; 1.0%	7; 1.8%	0.32[2]
Hours of online lectures per week *(median; IQR)*	6; 0-15 hours	8; 2-15 hours	0.04*[1]
Digital displays			
Hours of computer use per day *(median; IQR)*	6; 4-7 hours	7; 5-8 hours	0.04*[1]
Days of computer use per week *(median; IQR)*	7; 6-7 days	7; 6-7 days	0.26[1]
Hours of computer use per week *(median; IQR)*	42; 28-56 hours	42; 30-56 hours	0.06[1]
Hours of mobile phone use per day *(median; IQR)*	4; 3-5 hours	4; 3-5 hours	0.20[1]
Hours of tablet use per day *(median; IQR)*	0; 0-0 hours	0; 0-1 hours	0.006*[1]
Hours watching television per day *(median; IQR)*	1; 0-2 hours	1; 0-1 hours	0.54[1]
N of devices used simultaneously *(median; IQR)*	3; 2-3 devices	3; 2-3 devices	0.06[1]
Dry eye risk factors			
Lifestyle factors			

Smokers *(N of subjects; percentage of subjects)*	43; 10.3%	54; 13.6%	0.15[2]
Days smoked per week *(median; IQR)*	0; 0 days	0; 0 days	0.18[1]
Cigarettes per day *(median; IQR)*	0; 0 cigarettes	0; 0 cigarettes	0.28[1]
Cigarettes per week *(median; IQR)*	0; 0 cigarettes	0; 0 cigarettes	0.22[1]
Alcohol consumers *(N of subjects; percentage of subjects)*	263; 63.2%	245; 61.9%	0.69[2]
Units of alcohol per week *(median; IQR)*	1; 0-2 units	1; 0-3 units	0.94[1]
Not caffeine drinkers *(N of subjects; percentage of subjects)*	155; 37.3%	124; 31.3%	0.07[2]
Units of caffeinated drinks per day *(median; IQR)*	1; 0-2 units	1; 0-2 units	0.01*[1]
Litres of water per day *(median; IQR)*	1.5; 1-2 litres	1.5; 1-2 litres	0.66[1]
Hours of sleep per day *(median; IQR)*	7; 7-8 hours	7; 7-8 hours	0.24[1]
Hours outdoors per day *(median; IQR)*	2; 1-3 hours	2; 1-2 hours	0.18[1]
Hours indoors with central heating per day *(median; IQR)*	20; 0-41 hours	28; 12-42 hours	0.001*[1]
Hours of exercise per week *(median; IQR)*	3; 1-5 hours	3; 2-4 hours	0.43[1]
Poor diet quality *(N of subjects; percentage of subjects)*	106; 25.5%	94; 23.8%	0.57[2]
High use of face mask *(N of subjects; percentage of subjects)*	331; 79.6%	328; 82.8%	0.18[2]
Hours of face mask wear per day *(median; IQR)*	5.5; 4-7 hours	6; 4-8 hours	0.18[1]
Contact lenses			
Contact lens wear *(N of subjects; percentage of subjects)*	85; 20.4%	143; 36.1%	< 0.001*[2]
Soft contact lens wear *(N of subjects; percentage of subjects)*	76; 18.3%	121; 30.6%	< 0.001*[2]
Days of contact lens wear per week *(median; IQR)*	0; 0-0 days	0; 0-3 days	< 0.001*[1]
Hours of contact lens wear per week *(median; IQR)*	0; 0-0 hours	0; 0-8 hours	< 0.001*[1]
Health conditions			
Poor health quality *(N of subjects; percentage of subjects)*	48; 11.5%	95; 24.0%	< 0.001*[2]
Stress *(N of subjects; percentage of subjects)*	35; 8.4%	81; 20.5%	< 0.001*[2]
Refractive surgery *(N of subjects; percentage of subjects)*	11; 2.6%	6; 1.5%	0.26[2]
Acne *(N of subjects; percentage of subjects)*	63; 15.1%	80; 20.2%	0.06[2]
Allergies *(N of subjects; percentage of subjects)*	69; 16.6%	105; 26.5%	0.001*[2]
Anxiety *(N of subjects; percentage of subjects)*	54; 13.0%	109; 27.5%	< 0.001*[2]
Migraine headaches *(N of subjects; percentage of subjects)*	31; 7.5%	81; 20.5%	< 0.001*[2]
Eczema *(N of subjects; percentage of subjects)*	14; 3.4%	37; 9.3%	< 0.001*[2]
Asthma *(N of subjects; percentage of subjects)*	16; 3.8%	37; 9.3%	0.002*[2]
Psoriasis *(N of subjects; percentage of subjects)*	4; 1.0%	8; 2.0%	0.21[2]
Depression *(N of subjects; percentage of subjects)*	11; 2.6%	26; 6.6%	0.007*[2]
Vitamin deficiency *(N of subjects; percentage of subjects)*	7; 1.7%	25; 6.3%	0.001*[2]
Rosacea *(N of subjects; percentage of subjects)*	1; 0.2%	10; 2.5%	0.005*[2]
Pelvic pain in females *(N of subjects; percentage of subjects)*	7; 1.7%	26; 6.6%	< 0.001*[2]
Diabetes *(N of subjects; percentage of subjects)*	4; 1.0%	3; 0.8%	0.75[2]
Fertility problems *(N of subjects; percentage of subjects)*	2; 0.5%	5; 1.3%	0.23[2]
Thyroid disease *(N of subjects; percentage of subjects)*	7; 1.7%	13; 3.3%	0.14[2]
Irritable bowel syndrome *(N of subjects; percentage of subjects)*	5; 1.2%	13; 3.3%	0.04*[2]
Sclerosis *(N of subjects; percentage of subjects)*	2; 0.5%	5; 1.3%	0.23[2]
Liver disease *(N of subjects; percentage of subjects)*	1; 0.2%	2; 0.5%	0.53[2]
Medication			
Oral contraceptive therapy *(N of subjects; percentage of subjects)*	36; 8.7%	82; 20.7%	< 0.001*[2]
Antihistamines *(N of subjects; percentage of subjects)*	32; 7.7%	60; 15.2%	0.001*[2]
Anxiolytics *(N of subjects; percentage of subjects)*	4; 1.0%	24; 6.1%	< 0.001*[2]
Antidepressants *(N of subjects; percentage of subjects)*	3; 0.7%	9; 2.3%	0.07[2]
Hormone replacement therapy *(N of subjects; percentage of subjects)*	5; 1.2%	11; 2.8%	0.11[2]
Anti-inflammatories *(N of subjects; percentage of subjects)*	6; 1.4%	7; 1.8%	0.71[2]
Analgesics *(N of subjects; percentage of subjects*	1; 0.2%	2; 0.5%	0.53[2]

Dry eye questionnaires			
OSDI *(median; IQR)*	6.3; 2.3-10.4	22.5; 16.7-31.8	< 0.001*[1]
DEQ-5 *(median; IQR)*	5; 3-8	11; 8-14	< 0.001*[1]
CLDEQ-8 *(mean ± SD)*	11 ± 5	17 ± 6	< 0.001*[3]

CLDEQ-8 = 8-item Contact Lens Dry Eye Questionnaire; DEQ-5 = 5-item Dry Eye Questionnaire; IQR = Interquartile range; OSDI = Ocular Surface Disease Index; N = Number. * Indicates statistically significant values ($p < 0.05$). [1] Mann-Whitney U test. [2] chi-square test. [3] Unpaired T-test.

Table 15.4. Univariate and multivariate logistic regression analysis and odds ratios of the group with positive OSDI score (OSDI ≥ 13).

Characteristic	**Unadjusted univariate logistic regression**		**Multivariate-adjusted logistic regression**	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
Demographics				
Female sex	3.134 (2.308–4.256)	< 0.001*	2.056 (1.352–3.107)	0.001*
Hours of online lectures per week	1.113 (1.012–1.230)	0.10	1.032 (1.023 –1.040)	0.02*
Digital displays				
Hours of computer use per day	1.057 (1.007–1.109)	0.02*	1.002 (0.929-1.081)	0.96
Hours of tablet use per day	1.115 (1.016–1.224)	0.02*	1.129 (0.971-1.313)	0.11
N of devices used simultaneously	1.186 (0.985–1.428)	0.07	1.360 (1.090–1.852)	0.008*
Dry eye risk factors				
Smoking	1.370 (0.894–2.098)	0.15	1.199 (0.643-2.234)	0.57
Not drinking caffeine	0.763 (0.569–1.023)	0.07	0.992 (0.561-1.755)	0.98
Units of caffeinated drinks per day	1.139 (1.014–1.280)	0.03*	1.024 (0.807-1.300)	0.84
Hours of exercise per week	0.955 (0.911–1.001)	0.06	1.031 (0.964-1.104)	0.38
Hours of face mask use per day	1.037 (0.989–1.088)	0.14	1.039 (0.963-1.120)	0.32
Contact lens wear	2.201 (1.607–3.014)	< 0.001*	1.414 (0.662-3.024)	0.37
Soft contact lens wear	3.209 (1.311–7.856)	0.01*	0.919 (0.765-1.106)	0.37
Days of contact lens wear per week	1.144 (1.077–1.216)	< 0.001*	1.056 (1.052-1.115)	0.55
Hours of contact lens wear per week	1.020 (1.010–1.029)	< 0.001*	1.018 (1.006–1.030)	0.003*
Poor health quality	2.432 (1.664–3.555)	< 0.001*	1.386 (0.788-2.437)	0.26
Stress	2.799 (1.833–4.276)	< 0.001*	2.606 (1.477–4.596)	0.001*
Eczema	2.959 (1.574–5.564)	0.001*	2.651 (1.034-6.794)	0.04*
Acne	1.419 (0.986–2.040)	0.06	0.881 (0.522-1.488)	0.64
Allergies	1.815 (1.290–2.553)	0.001*	0.968 (0.516-1.816)	0.92
Depression	2.587 (1.261–5.310)	0.01*	2.976 (1.213–7.303)	0.02*
Vitamin deficiency	3.937 (1.683–9.210)	0.002*	1.794 (0.586-5.495)	0.31
Rosacea	10.751 (1.370–84.379)	0.02*	2.526 (0.229-27.912)	0.45
Migraine headaches	3.194 (2.057–4.958)	< 0.001*	1.923 (1.062–3.483)	0.03*
Anxiety	2.546 (1.774–3.653)	< 0.001*	1.183 (0.680-2.058)	0.55
Pelvic pain in females	4.106 (1.761–9.571)	0.001*	4.419 (1.428–13.672)	0.01*
Asthma	2.577 (1.409–4.711)	0.002*	3.185 (1.498–6.771)	0.003*
Thyroid disease	1.983 (0.783–5.023)	0.15	1.535 (0.319-7.383)	0.59
Irritable bowel syndrome	2.790 (0.985–7.900)	0.05	1.120 (0.292-4.293)	0.87
Oral contraceptive therapy	2.757 (1.812–4.193)	< 0.001*	1.455 (0.795-2.665)	0.22
Antihistamines	2.143 (1.362–3.372)	0.001*	1.184 (0.526-2.666)	0.68

Antidepressants	3.202 (0.860–11.913)	0.08	0.702 (0.122-4.034)	0.69
Anxiolytics	6.645 (2.284–19.329)	0.001*	2.003 (0.504-7.960)	0.32
Hormone replacement therapy	2.349 (0.809–6.821)	0.12	1.563 (0.249-9.825)	0.63
Dry eye questionnaires				
DEQ-5	1.387 (1.325–1.452)	< 0.001*	1.369 (1.301–1.441)	< 0.001*
CLDEQ-8	1.208 (1.140–1.280)	< 0.001*	1.116 (1.025–1.214)	0.01*

CI = Confidence interval; CLDEQ-8 = 8-item Contact Lens Dry Eye Questionnaire; DEQ-5 = 5-item Dry Eye Questionnaire; OR = Odds ratio; OSDI = Ocular Surface Disease Index; N = Number. *Indicates statistically significant values ($p < 0.05$).

15.4 Discussion

Before the COVID-19 pandemic, there was already a growing trend in education technology across centres. Nevertheless, the restrictive measures adopted by governments to control the spread of the disease led to the overnight switch to online learning at all levels, with its impact on ocular health being hitherto unknown. Online education not only increased digital display use but also led to meaningful modifications of habits and lifestyle. This is particularly relevant considering that lifestyles are key to several ocular diseases, particularly DED.

15.4.1 Dry eye disease risk factors

The results of this study indicate that students who attended online lectures used the computer for more hours a day and a week, and more days a week, than students who attended in-person lectures. Not only this but using the computer for more hours a day was independently associated with attending online lectures; therefore, as expected, higher computer use was intrinsic to online education modalities.

As addressed on several occasions throughout this work, hazardous effects of computer use on the ocular surface are widely acknowledged. Increased dry eye symptoms and tear film osmolarity, along with reduced tear film stability and alterations in tear volume have been reported in previous chapters, even after as little as 15 or 20 minutes of computer use (Chapters 4-10). Additionally, tear film abnormalities have been shown to increase with screen time (Choi et al., 2018; Yazici et al., 2015).

In the present study, the number of hours of tablet use per day and the number of hours of computer use per day and week were identified as potential risk factors for dry eye symptoms. Nevertheless, despite this and the aforementioned relationship between digital displays and DED, no independent association was found between a positive OSDI score and the number of hours of digital display use. These results are likely to have

occurred as a consequence of the interaction of other variables included in the multivariate model, resulting in a non-significant p-value.

Nowadays, students generally own more than one device. Using two or more devices simultaneously is therefore common, especially among younger adults. In the present survey, participants used an average of three devices simultaneously. Most importantly, the present survey revealed that the number of devices used simultaneously was independently associated with obtaining a positive OSDI score, although no association was found with the online group. In line with this, a higher prevalence of DES has been reported in individuals who use two or more devices simultaneously compared to those who use one device at a time (75% vs 53%, respectively) (Sheppard & Wolffsohn, 2018). This is particularly relevant considering that dry eye symptoms make one of the main groups of DES symptomatology (Portello et al., 2012).

Although a significant independent association between the number of devices used simultaneously and a higher OSDI score was found, no significant difference was observed between symptomatic (OSDI $\geq$ 13) and asymptomatic (OSDI < 13) participants. To date, there are no studies in the literature addressing the effect of display multitasking on DES or dry eye. Future research should corroborate these findings and consider this factor when assessing the effects of digital display use on dry eye.

Among the most popular measures aimed at controlling the spread of the COVID-19 disease, there is the use of face masks. Although the use of face masks is globally considered essential for the prevention of COVID-19, clinicians point out that it may cause ocular dryness and irritation. It is suspected that wearing a face mask causes exhaled air to blow upwards (Raevis et al., 2021), leading to an increase in airflow to the ocular surface which likely contributes to the evaporation of the tear film and consequently to eye discomfort and dry eye symptoms.

According to the results of this chapter, students who attended online lectures used a face mask less than those who attended in-person lectures. Likewise, the number of hours of face mask use per day was independently associated with attending online lectures, with an OR lower than 1. Therefore, online students were exposed to a lower impact of the face mask. However, students with a positive OSDI score did not wear a face mask more than asymptomatic students, nor was there an association between face mask use and dry eye symptoms.

Furthermore, students who attended online lectures spent fewer hours a day outdoors and were, consequently, less exposed to harmful environmental factors such as air pollution, wind, or low humidity, which have been shown to impact DED (Galor et al., 2014). In parallel, online students significantly practised more hours of exercise per week. Previous research reported that lower levels of physical activity and sedentary behaviour are associated with DED (Kawashima et al., 2014), albeit longitudinal studies and studies with large groups of participants are still required.

Students who attended online lectures also suffered fewer allergy and psoriasis episodes than students in the in-person group, both conditions being potential risk factors for DED (Aragona et al., 2018; Villani et al., 2018). Logistic regression multivariate analysis revealed that suffering from allergies was associated with lower odds of being in the online group. The lower prevalence of allergies and psoriasis in the online group could be intrinsic to the sample in this study or a consequence of their lower environmental exposure. Despite these differences between groups, none of these factors revealed a significant independent association with dry eye symptoms, though suffering from allergies was significantly associated with a positive OSDI score when analysed in isolation (univariate analysis) and was more prevalent in students with dry eye symptoms. Therefore, it may be a risk factor for dry eye symptoms in students who attend in-person lectures.

15.4.2 Dry eye symptoms

Despite a lower prevalence of DED risk factors in students who attended online lectures, they obtained on average a significantly higher OSDI score than students who attended in-person lectures. Students with a positive OSDI score attended more hours of online lessons per week. Also, this factor was independently associated with having dry eye symptoms. Despite the close link between online lecture attendance and higher OSDI scores, no relationship was found between this factor and DEQ-5 or CLDEQ-8 scores, which could be attributed to differences in the questionnaires.

Finally, many factors other than attendance to online lectures or simultaneous use of digital displays were independently associated with positive OSDI scores. For instance, female sex, hours of CL wear, and various health conditions such as high stress levels, depression, eczema, migraine headaches, pelvic pain, and asthma were all independently associated with OSDI, with ORs greater than 1. Likewise, many others were also

identified as potential risk factors for dry eye symptoms in the univariate analysis. Because all the DED risk factors surveyed in the present study were chosen based on scientific evidence (Stapleton et al., 2017), these results are not unexpected.

The present study had some limitations to consider. First, risk factors were self-reported by volunteers, which might have induced recall bias. Moreover, the study was carried out in the same university, which may have introduced selection bias. Finally, recruitment by means of advertisement could have induced a higher prevalence of subjects with dry eye symptoms than expected in the general population.

In conclusion, online students had a significantly lower prevalence of various DED risk factors than in-person class attendees. Nevertheless, attending online lectures was associated with greater dry eye symptoms, likely due to the increased use of the computer by online students, which was characteristic of participants with a positive OSDI score. Given the rise in education technology worldwide and the likelihood of online learning becoming an integral part of student life, clinicians should be aware of the potential impact of online education on DED and its risk factors.

16.

General conclusions and future investigations

16.1 General conclusions

The use of digital displays is ubiquitous and has become a common and essential practice in our everyday life, with people using these devices in every aspect of their professional and private lives. This tremendous change in work and lifestyle experienced in the recent decades has been accompanied by an increase in health-related complaints, particularly eye-related ones. With the emergence of new technologies DES has become increasingly prevalent. This may explain the relatively high prevalence of DED observed in younger individuals in recent years. The growing reports of eye discomfort in younger individuals and the increase in technological resources worldwide have given rise to a renewed interest in the effects of digital screens on the eyes.

This doctoral thesis presents a total of 12 independent studies, each of which has been described in detail in each of the chapters of this work and which was designed to fill a particular gap in the existing literature. The following conclusions can be extracted from this work.

- Several dry eye-related risk factors and health conditions are associated with suffering from DES. A higher prevalence of dry eye-related risk factors and health conditions was found in individuals with DES, including poorer health quality, more stress, allergies, vitamin deficiency and anxiety. In parallel, individuals with DES took more medication, such as antihistamines, anxiolytics antidepressants, and oral contraceptives, proven to promote dryness. Most importantly, using the computer for longer periods, CL wear, and suffering from stress and migraine were independently associated with having DES. At the same time, having greater dry eye symptoms increased the odds of suffering from DES. Considering the close association between DES and dry eye, special attention should be paid to screen users with dry eyes. Likewise, clinicians should acknowledge the relevance of triaging questions, systemic comorbidities, and DED risk factors when dealing with individuals who use digital displays for extended periods.
- The blinking pattern and kinematics vary considerably with the form of presentation, with these differences being attributable to the way the displays are set up and used and the cognitive demand of the task. The blink rate was significantly reduced when reading on digital displays compared to a non-device, low-demanding control task, probably as a consequence of the higher cognitive demand of reading, while no

differences between the digital displays (computer, tablet, e-reader and smartphone) were apparent. Incomplete blinking increased as displays were placed further and at higher gaze angles, and were greater when reading on the computer, possibly due to an additive effect between larger palpebral fissures and a higher cognitive demand. Blink amplitude was directly related to gaze angle, and it was lower for devices with lower visualization angles. Furthermore, closing and opening blink durations did not vary with the devices used, while opening and closing speeds decreased progressively with gaze angle and distance and were found to be lowest when using a smartphone.

- The impact of digital display use on the ocular surface and tear film varies depending on the form of presentation and depends on how the digital display is set up and used, which determines its effects on blinking and ocular surface exposure. Greater dry eye symptoms and DES, lower tear volume and tear stability, along with higher osmolarity and conjunctival redness, were observed after reading on a computer compared to reading on handheld devices (tablet, e-reader and smartphone) or a non-device control condition. The smartphone and the e-reader caused the least impact, probably due to a lower gaze angle associated with smartphone use and to the enhanced optical properties of the e-reader.
- Baseline ocular surface and tear film parameters can be used to predict the impact of computer use on dry eye signs and symptoms. Having greater symptoms of dry eye was predictive of a greater increase in symptoms, while a longer NIKBUT predisposed the study participants to a greater reduction in tear stability, potentially leading to a reduced NIKBUT following computer use. Furthermore, having a greater increase in conjunctival redness was a significant predictor of a greater reduction in tear stability. Conversely, the spontaneous blinking pattern exhibitted before the task and meibomian gland dropout percentage were not predictors of alterations following computer use.
- The instillation of high-viscosity artificial tears and blink control are the best management strategies for preventing the short-term effects of digital display use on dry eye signs and symptoms. Techniques based on blink control may be helpful, although they may hinder task performance. Taking regular, brief breaks may partially reduce ocular desiccation, and should not be advised in isolation. Finally, using a blue light filter was not found to be effective in preventing dry eye signs and symptoms during computer use.

- Disposable CL wear has no additive effects on signs and symptoms of dry eye when using digital devices for short periods. The use of CLs during short periods of digital display use significantly increased signs and symptoms of dry eye, although this increase was not greater than when reading on the displays (computer and smartphone) without CLs. The instillation of artificial tears was an effective strategy for counteracting the effects of digital display use on dry eye signs and symptoms in both CL wearers and non-wearers.
- Ocular symptoms following computer use are comparable between post-LASIK and non-operated individuals, although a worsening of dry eye signs was only observed in operated participants. Using a computer for 30 minutes significantly increased the frequency and severity of dry eye symptoms in normal and post-LASIK individuals. The increase in symptoms of dry eye and the symptoms of DES reported during the computer task were comparable between both study groups. Symptoms were accompanied by a significant worsening of dry eye signs in the LASIK group, while no significant changes were found in the control group. The instillation of artificial tears was effective in preventing the worsening of dry eye signs in post-LASIK individuals.
- Symptoms of DES, particularly those related to dry eye, are associated with increased sensitivity of the cornea to cold stimuli. Symptomatic computer users exhibited lower cold sensation thresholds compared to asymptomatic users, which suggests alterations in the corneal sensory function among computer users with DES. Likewise, greater symptoms of DES, particularly dry eye-related symptoms, were associated with lowered excitation thresholds of the corneal neurons to corneal cooling. Based on previous findings on discomfort and dry eye, the enhanced cooling sensitivity of symptomatic computer users and their increased symptoms of dryness during computer use could be partially attributable to changes in the excitability of high threshold/low activity cold thermoreceptors.
- Changes in corneal nerve function after short-term computer work were not observed. Short-term computer use had no effect on the sensitivity of the central cornea to mechanical and cold stimuli. Additionally, no relationships were found between the changes in corneal sensitivity following computer use and demographic variables, everyday symptoms of dryness and discomfort or the symptoms experienced during the computer task.

- While visual acuity remained unchanged, several aspects of visual function and quality of vision declined over a day of computer use. These changes were accompanied by greater dry eye symptoms and tear film alterations, which are likely to have played a fundamental role. Computer workers exhibited greater dry eye symptoms, along with a decline in perceived quality of vision, tear film quality and contrast sensitivity throughout the working day, while no worsening was observed in any variable in workers who only occasionally used the computer. Similarly, computer workers exhibited an increase in light disturbance throughout the working day as opposed to no change in non-computer workers. In contrast, optical aberrations remained unchanged in both groups of participants.
- The 20-20-20 rule is an effective strategy for reducing DES and dry eye symptoms, although 2 weeks was not enough to considerably improve binocular vision or dry eye signs. Following the 20-20-20 rule significantly changed the way the participants used their computers by increasing the total number of breaks taken per day, and by reducing the duration of breaks as well as the time spent looking at the computer screen without rest. However, the blinking pattern exhibited during device use was not different and the blink rate remained low. The 20-20-20 rule improved binocular accommodative facility, although it had no effects on any other accommodative or vergence parameters. In contrast, the 20-20-20 rule was effective in reducing DES and dry eye symptoms, although it was not sufficient to prevent DES or a positive OSDI score. The improvement in symptoms was barely sustained one week after discontinuation; the frequency of dry eye symptoms was no longer different from baseline, although the severity remained slightly better. Conversely, no improvement in dry eye signs was observed during the study period.
- Attending online lectures is independently associated with having dry eye symptoms. Despite a lower overall prevalence of DED risk factors, increased computer use is likely the reason behind the greater ocular surface dryness reported by online students. Online students had a significantly lower prevalence of various DED risk factors than in-person class attendees. Nevertheless, taking online lessons was associated with increased dry eye symptoms, likely due to increased computer use by online students, which was characteristic of participants with a positive OSDI score. Given the rise in education technology worldwide and the likelihood of online learning becoming an integral part of student life, clinicians should be aware of the potential impact of online education on DED and its risk factors.

16.2 Future investigations

Although this thesis has addressed several aspects of the relationship between the use of digital displays and the ocular surface and tear film, several other aspects are yet to be studied. Likewise, further investigation in specifically designed studies is needed to confirm the findings described in the present work and address its limitations. Below are some points to address in future investigations:

- Developing case-control studies to explore the identified commonalities in DES and DED individuals.
- Further research on the impact of longer periods of computer use on the ocular surface and tear film.
- Research to evaluate the effects of different CL materials and wearing modalities on dry eye during device use.
- Assessing the impact of longer durations of computer use on the ocular surface of individuals after kerato-refractive procedures, especially during the early postoperative period.
- More research on corneal hypersensitivity to cold stimuli as a marker of ocular discomfort during computer use and on the potential mechanisms leading to corneal nerve damage in DES and DED.
- Assessing and comparing the effectiveness of the 20-20-20 rule in different population groups, especially in individuals with different durations of computer usage.
- Large-scale follow-up studies to understand the long-term implications of digital display use on the eye surface.

Appendix

Appendix A. Ocular Surface Disease Index (OSDI)

Please answer the following questions by checking the box that best represents your answer.

Have you experienced any of the following during **the last week:**

	All of the time	**Most of the time**	**Half of the time**	**Some of the time**	**None of the time**	
1. Eyes that are sensitive to light?	4	3	2	1	0	
2. Eyes that feel gritty?	4	3	2	1	0	
3. Painful or sore eyes?	4	3	2	1	0	
4. Blurred vision?	4	3	2	1	0	
5. Poor vision?	4	3	2	1	0	

Have problems with your eyes limited you in performing any of the following during **the last week:**

6. Reading?	4	3	2	1	0	N/A
7. Driving at night?	4	3	2	1	0	N/A
8. Working with a computer or bank machine (ATM)?	4	3	2	1	0	N/A
9. Watching TV?	4	3	2	1	0	N/A

Have your eyes felt uncomfortable in any of the following situations during **the last week:**

10. Windy conditions?	4	3	2	1	0	N/A
11. Places or areas with low humidity (very dry)?	4	3	2	1	0	N/A
12. Areas that are air conditioned?	4	3	2	1	0	N/A

Appendix B. 5-item Dry Eye Questionnaire (DEQ-5)

1. Questions about **EYE DISCOMFORT:**					
a. During a typical day in the past month, **how often** did your eyes feel discomfort?	**0** Never	**1** Rarely	**2** Sometimes	**3** Frequently	**4** Constantly
b. When your eyes feel discomfort, **how intense was this feeling of discomfort** at the end of the day, within two hours of going to bed?	Never have it **0**	**1**	**2**	**3**	Not at all Intense **4** Very intense **5**
2. Questions about **EYE DRYNESS:**					
a. During a typical day in the past month, **how often** did your eyes feel dry?	**0** Never	**1** Rarely	**2** Sometimes	**3** Frequently	**4** Constantly
b. When your felt dry, **how intense was this feeling of dryness** at the end of the day, within two hours of going to bed?	Never have it **0**	**1**	**2**	**3**	Not at all Intense **4** Very intense **5**
3. Questions about **WATERY EYES:**					
a. During a typical day in the past month, **how often** did your eyes look or feel excessively watery?	**0** Never	**1** Rarely	**2** Sometimes	**3** Frequently	**4** Constantly

Appendix C. Symptom Assessment in Dry Eye (SANDE)

SANDE I

1. Frequency of symptoms:

Please place an "X" on the line to indicate how often, on average, your eyes feel dry or irritated:

Rarely ——————————— All the time

2. Severity of symptoms:

Please place an "X" on the line to indicate how severe, on average, you feel your symptoms of dryness and/or irritation are:

Very mild ——————————— Very severe

SANDE II

1. Frequency of symptoms:

Please place an "X" on the line to indicate how often, on average, your eyes feel dry or irritated now *compared to at your last visit/before the task*:

Much less frequent ——————▲—————— Much more frequent

Last visit

2. Severity of symptoms:

Please place an "X" on the line to indicate how severe, on average, you feel your symptoms of dryness and irritation are now *compared to at your last visit/before the task:*

Much less severe ——————▲—————— Much more severe

Last visit

Appendix D. Ocular Comfort Index (OCI)

This questionnaire was designed to grade the comfort of your eyes. For each question please circle your answer.

Example: In the last week, how often were your eyes *red?*

Never						**Always**
0	1	2	(3)	4	5	6

There are no right or wrong answers. Do not spend too long on any one question.

1. In the last week, how often did your eyes feel *dry*?

Never						**Always**
0	1	2	3	4	5	6

When your eyes felt dry, typically, how intense was the *dryness*?

Never had it						**Severe**
0	1	2	3	4	5	6

2. In the last week, how often did your eyes feel *gritty*?

Never						**Always**
0	1	2	3	4	5	6

When your eyes felt gritty, typically, how intense was the *grittiness*?

Never had it						**Severe**
0	1	2	3	4	5	6

3. In the last week, how often did your eyes feel *stingy*?

Never						**Always**
0	1	2	3	4	5	6

When your eyes stung, typically, how intense was the *stinging*?

Never had it						**Severe**
0	1	2	3	4	5	6

4. In the last week, how often did your eyes feel *tired*?

Never						**Always**
0	1	2	3	4	5	6

When your eyes felt tired, typically, how intense was the *tiredness?*

Never had it						**Severe**
0	1	2	3	4	5	6

5. In the last week, how often did your eyes feel *painful*?

Never						**Always**
0	1	2	3	4	5	6

When your eyes felt painful, typically, how intense was the *pain*?

Never had it						**Severe**
0	1	2	3	4	5	6

6. In the last week, how often did your eyes *itch*?

Never						**Always**
0	1	2	3	4	5	6

When your eyes itched, typically, how intense was the *itching*?

Never had it						**Severe**
0	1	2	3	4	5	6

Appendix E. Instant Ocular Symptoms Survey (IOSS)

Please complete the following questions about your current dry eye symptoms.

If your eyes are feeling discomfort, how intense is this feeling of discomfort right now?

Never have it	Not at all intense				Very intense
0	1	2	3	4	5

If your eyes are feeling dry, how intense is this feeling of dryness right now?

Never have it	Not at all intense				Very intense
0	1	2	3	4	5

Appendix F. 8-item Contact Lens Dry Eye Questionnaire (CLDEQ-8)

1. Questions about **EYE DISCOMFORT:**					
a. During a typical day in the past 2 weeks, **how often** did your eyes feel discomfort while wearing your contact lenses?	**0** Never	**1** Rarely	**2** Sometimes	**3** Frequently	**4** Constantly
b. When your eyes feel discomfort, **how intense was this feeling of discomfort** at the end of your wearing time?	Never have it **0**	Not at all Intense **1**	**2**	**3**	**4** Very Intense **5**
2. Questions about **EYE DRYNESS:**					
a. During a typical day in the past 2 weeks, **how often** did your eyes feel dry?	**0** Never	**1** Rarely	**2** Sometimes	**3** Frequently	**4** Constantly
b. When your felt dry, **how intense was this feeling of dryness** at the end of your wearing time?	Never have it **0**	Not at all Intense **1**	**2**	**3**	**4** Very Intense **5**
3. Questions about **CHANGEABLE, BLURRY VISION:**					
a. During a typical day in the past 2 weeks, **how often** did your vision change between clear and blurry or foggy while wearing your contact lenses?	**0** Never	**1** Rarely	**2** Sometimes	**3** Frequently	**4** Constantly
b. When your vision was blurry **how noticeable was the changeable, blurry, or foggy vision** at the end of your wearing time?	Never have it **0**	Not at all Intense **1**	**2**	**3**	**4** Very Intense **5**
4. Question about **CLOSING YOUR EYES:**					
During a typical day in the past 2 weeks, **how often** did your **eyes bother you so much that you wanted to close them**?	**0** Never	**1** Rarely	**2** Sometimes	**3** Frequently	**4** Constantly
5. Question about **REMOVING YOUR LENSES:**					
During a typical day in the past 2 weeks, did your eyes *bother you so much* while wearing your contact lenses that you felt as if you needed to stop whatever you were doing and **take out your contact lenses?**	**1** Never	**2** Less than once a week	**3** Weekly	**4** Several times a week	**5** Daily **6** Several times a day

Appendix G. Computer Vision Syndrome Questionnaire (CVS-Q)

Indicate whether you experience any of the following symptoms during the time you use the computer at work. For each symptom, mark with an **X**:

a. First, the frequency, that is, how often the symptom occurs, considering that:
NEVER = the symptom does not occur at all
OCCASIONALLY = sporadic episodes or once a week
OFTEN OR ALWAYS = 2 or 3 times a week or almost every day

b. Second, the intensity of the symptom: Remember: if you indicated NEVER for frequency, you should not mark anything for intensity.

	a. Frequency			b. Intensity	
	NEVER	OCCASIONALLY	OFTEN OR ALWAYS	MODERATE	INTENSE
1 Burning					
2 Itching					
3 Feeling of a foreign body					
4 Tearing					
5 Excessive blinking					
6 Eye redness					
7 Eye pain					
8 Heavy eyelids					
9 Dryness					
10 Blurred vision					
11 Double vision					
12 Difficulty focusing for near vision					
13. Increased sensitivity to light					
14. Coloured halos around objects					
15. Feeling that sight is worsening					
16 Headache					

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9. Talens-Estarelles, C., Mechó-García, M., McAlinden, C., Cerviño, A., García-Lázaro, S., & González-Méijome, J. M. (2023). Changes in visual function and optical and tear film quality in computer users. Ophthalmic and Physiological Optics, 00, 1–13. https://doi.org/ 10.1111/opo.13147. Publication associated with the work carried out at the University of Minho in Braga, Portugal.
10. Talens-Estarelles, C., Cerviño, A., García-Lázaro, S., Fogelton, A., Sheppard, A., & Wolffsohn, J. S. (2023). The effects of breaks on digital eye strain, dry eye and binocular vision: Testing the 20-20-20 rule. Contact Lens and Anterior Eye, 46(2), 101744. https://doi.org/10.1016/j.clae.2022.101744. Publication associated with the work carried out at Aston University in Birmingham, UK.
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Conference contributions

1. Talens-Estarelles, C., Sanchis-Jurado, V., Esteve-Taboada, J. J., Pons, Á. M., Díez-Ajenjo, M. A., López-Alemany, A., & García-Lázaro, S. (2021, April 16–18). *Uso de dispositivos electrónicos y alteraciones de la superficie ocular.* 26º Congreso Internacional de Optometría, Contactología y Óptica Oftálmica (OPTOM), Madrid, Spain.
2. Talens-Estarelles, C., García-Marqués, J. V., Martínez-Albert, N., Cerviño, A., & García-Lázaro, S. (2021, April 16–18). *Uso de dispositivos electrónicos y alteraciones de la superficie ocular (revisión bibliográfica).* 26º Congreso Internacional de Optometría, Contactología y Óptica Oftálmica (OPTOM), Madrid, Spain.
3. Talens-Estarelles, C., García-Marqués, J. V., Martínez-Albert, N., Cerviño, A., Esteve-Taboada, J. J., Sanchis-Jurado, V., Pons, Á. M., & García-Lázaro, S. (2020, November 23–30). *Efecto del uso de dispositivos electrónicos sobre la superficie ocular.* 5º Congreso Internacional Online de Jóvenes Optometristas (SIYO), Valencia, Spain.

4. Talens-Estarelles, C., García-Marqués, J. V., Cerviño, A., & García-Lázaro, S. (2022, October 14–28). *Effects of contact lens wear and computer use on the ocular surface.* VI International Online Symposium of Young Optometrists (SIYO), Valencia, Spain.
5. Talens-Estarelles, C., Sanchis-Jurado, V., Esteve-Taboada, J. J., Pons, Á. M., & García-Lázaro, S. (2022, October 14–28). *Effects of computer use on blinking kinematics.* VI International Online Symposium of Young Optometrists (SIYO), Valencia, Spain.
6. Talens-Estarelles, C., Golebiowski, B., Ehrmann, K., García-Lázaro, S., Cerviño, A., & Stapleton, F. (2023, April 23–27). *Ocular symptoms in computer users are associated with higher corneal cold sensitivity.* ARVO annual meeting, New Orleans, LA, USA.
7. Talens-Estarelles, C., Cerviño, A., García-Lázaro, S., Fogelton, A., Sheppard, A., & Wolffsohn, J. S. (2023, May 7–8). *Digital eye strain.* The ABC of Optometry: Ametropia, Binocularity and Correction, Rimini, Italy.
8. Talens-Estarelles, C., Golebiowski, B., Ehrmann, K., García-Lázaro, S., Cerviño, A., Stapleton, F. (2023, June 9–11). *Changes in mechanical and cold corneal sensitivity with computer use.* BCLA clinical conference & exhibition, Manchester, UK.

Book chapters

1. Talens-Estarelles, C., García-Marqués, J. V., Martínez-Albert, N., Cerviño, A., Esteve-Taboada, J. J., Sanchis-Jurado, V., Pons, Á. M., & García-Lázaro, S. (2021). Efecto del uso de dispositivos electrónicos sobre la superficie ocular. In A. Gené Sampedro, I. Bueno Gimeno, M. J. Luque Cobija, M. A. Díez Ajenjo, M. C. García Domene, J. J. Esteve Taboada, & R. M. Hernández Andrés (Eds.), Temas Actuales en Optometría. SIYO 2021 (pp. 295–306). Obrapropia.