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**ORIGINAL ARTICLE**



# **Ocular effects of exposure to low-humidity environment with contact lens wear: A pilot study**

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#### **Abstract**

**Purpose:** To compare the ocular effects of exposure to a low-humidity environment with and without contact lens (CL) wear using various non-invasive tests.

**Methods:** Fourteen habitual soft CL wearers were exposed to controlled low humidity (5% relative humidity [RH]) in an environmental chamber for 90min on two separate occasions. First, when wearing their habitual spectacles and then, on a separate visit, when wearing silicone hydrogel CLs that were fitted specifically for this purpose. All participants had adapted to the new CL prior to data collection. Three non-invasive objective measurements were taken at each visit: blinking rate, objective ocular scatter (measured using the objective scatter index) and ocular surface cooling rate (measured using a long-wave infrared thermal camera). At each visit, measurements were taken before the exposure in comfortable environmental conditions (RH: 45%), and after exposure to environmental stress (low humidity, RH: 5%).

**Results:** CL wearers showed increased blinking rate (*p*<0.005) and ocular scatter (*p*=0.03) but similar cooling rate of the ocular surface (*p*=0.08) when compared with spectacle wear in comfortable environmental conditions. The exposure to low humidity increased the blinking rate significantly with both types of corrections ( $p=0.01$ ). Interestingly, ocular scatter ( $p=0.96$ ) and cooling rate ( $p=0.73$ ) were not significantly different before and after exposure to low humidity. There were no significant two-way interactions between correction and exposure in any of the measurements.

**Conclusions:** CLs significantly increased the blinking rate, which prevented a quick degradation of the tear film integrity as it was refreshed more regularly. It is hypothesised that the increased blinking rate in CL wearers aids in maintaining ocular scatter quality and cooling rate when exposed to a low-humidity environment. These results highlight the importance of blinking in maintaining tear film stability.

#### **KEYWORDS**

adverse environment, blinking, contact lens, environmental chamber

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# **INTRODUCTION**

The tear film protects and moistens the cornea, providing a smooth refractive surface and enabling clear vision.<sup>1</sup> It consists of lipid and mucoaqueous layers, creating a double-layered barrier to the external environment.<sup>1</sup> The tear film is constantly replenished by blinking, a complex phenomenon influenced by many internal and exter-nal factors.<sup>[2](#page-7-1)</sup> Blinking is primarily an involuntary process that ensures tear coverage and expresses the meibomian glands, producing lipids.<sup>[2](#page-7-1)</sup> Lipid slows the tear evaporation rate and helps maintain the homeostasis of the tear film. An imbalance between lipids and mucoaqueous in the tear film leads to dry eye disease (DED), a multifactorial disease that may be influenced by different environmental conditions. In particular, the insertion of a contact lens (CL) on the eye may disrupt the delicate balance between these components, which could potentially lead to CL discom-fort.<sup>[3](#page-7-2)</sup> Soft CLs may also influence ocular comfort as they may generate an excess of tear evaporation, leading to tear insufficiency.<sup>4</sup>

Disruption of the tear film can also affect vision. Visual quality decreases when the tear film is altered,<sup>5,6</sup> for example in people wearing CLs.<sup>7</sup> If the smooth refractive surface of the tear film is disturbed, visual impairment has been reported in DED sufferers,<sup>[8](#page-7-6)</sup> and a higher objective scatter index (OSI) is correlated with DED severity.<sup>9</sup> Recent reports show that a significant correlation exists between the optical quality of vision and tear film break-up time, which is a measurement of tear film stability.<sup>10</sup>

Still, the effects of CL wear on vision in conditions where the environment imposes additional stress on the ocular surface are yet to be fully understood. Exposure to low humidity has been shown to affect vision and comfort after the insertion of a CL on the eye. $11-15$  Such an environment could also play a significant role in the CL dropout rate  $(12\% - 51\%)$ .<sup>16</sup> DED symptoms induced by environmental stress are frequent in office-style environments, and due to the COVID-19 pandemic, screen time has increased significantly.<sup>17</sup> This has been associated with a decrease in blinking rate when using digital screens,<sup>18,19</sup> which in turn has been shown to correlate with decreased tear stability, leading to DED symptoms and visual disturbances.<sup>[20](#page-8-0)</sup>

The aims of this study were to assess and compare the effect of low-humidity exposure with CL and spectacle wear using three non-invasive tests, as opposed to some of the routinely used clinical tests for tear assessment (e.g., tear break-up time). The tests used were: (i) blinking rate, which has been shown to have good specificity and sensitivity at detecting tear instability. It is one of the parameters recommended for DED diagnosis (Tear Film and Ocular Surface [TFOS] DEWS II)<sup>[21,22](#page-8-1)</sup>; (ii) ocular scatter, as an unstable tear film can influence vision quality and ocular scatter can assess objective visual quality<sup>23</sup> and (iii) infrared thermography, to measure the ocular surface temperature. This has been suggested as a viable way of measuring tear stability and is non-invasive. $24$  To our knowledge, neither

#### **Key points**

- Contact lens wear significantly increases the blinking rate, thereby contributing to tear film integrity.
- Ocular scatter is higher with contact lens wear compared with spectacles, suggesting a reduced quality of vision.
- Exposure to a low-humidity environment increases the blinking rate regardless of the type of refractive correction, suggesting a protective mechanism against tear film instability.

ocular scatter nor ocular surface temperature have been assessed in CL and spectacle wear before and after exposure to low humidity.

The hypothesis of this study is that after prolonged exposure to low humidity, (i) blinking will increase as a biomarker of tear instability, (ii) ocular scatter will increase as an unstable tear will influence vision quality and (iii) the dynamical changes of ocular surface temperature will be altered. All these potential changes to the tear film stability will be examined in people wearing CL and spectacles.

### **METHODS**

This prospective, crossover and comparative study was conducted in agreement with the tenets of the Declaration of Helsinki. The Ethics Committee of the Faculty of Health, Education, Medicine and Social Care reviewed and approved the study protocol. All the participants were informed about the study's characteristics and possible effects, and they signed a consent form before taking part in the study.

#### **Participants**

The study was conducted at the Vision and Eye Research Institute (VERI) at Anglia Ruskin University (ARU). Participants had to satisfy the following inclusion criteria:

- 1. Between 18 and 35years of age, to ensure they did not need multifocal prescriptions.
- 2. A spherical refraction between +6.00 and −8.00 D and astigmatism <1.00 D to ensure good vision could be achieved with a spherical CL design.
- 3. Up-to-date prescription and habitual soft CL wearer.

Exclusion criteria were:

1. Any sign of ocular inflammation or infection on the days of data collection.

- 2. Any chronic ocular or general disease, including eye allergy.
- 3. Use of any topical eye drops or taking any systemic medication that may produce DED during the 3months before the study.
- 4. History of corneal refractive surgery.

Habitual CL wearers were recruited from VERI staff and ARU students through advertisements placed on ARU campuses.

All participants were instructed not to wear their CLs for at least 8h before the data collection on the days of the study. All participants underwent an initial ocular examination during the first visit to ensure they met the study's inclusion criteria. New CLs were ordered based on the ocular measurements performed that day. A corneal topographer (Atlas 9000; ZEISS Medical Technology, [ZEISS.com\)](http://zeiss.com) was used to measure the corneal curvature. Ocular surface health was assessed with a slit lamp (Symphony, Keeler Optics Ltd., [Keeler.co.uk\)](http://keeler.co.uk), which was also used to assess the CL fit. The CL prescription was based on the habitual spectacle prescription of the participants. Visual acuity (VA) was measured using a retro-illuminated Early Treatment of Diabetic Retinopathy Study (ETDRS) chart with the room lights on. The Ocular Surface Disease Index (OSDI) questionnaire evaluated whether participants presented with any dry eye symptoms.<sup>[25](#page-8-4)</sup>

All eligible participants were successfully fitted with the same daily disposable silicone hydrogel CL (Clariti® 1Day, [coopervision.com\)](http://coopervision.com) using their spherical prescription. The characteristics of the CL used are shown in Table [1.](#page-2-0)

#### **Experimental protocol**

This was a crossover study; the same participants were evaluated with and without CLs. A baseline check was performed at the initial visit, which the participants attended wearing spectacles. Then, if the participants met the inclusion criteria, measurements for the first part of the study

<span id="page-2-0"></span>**TABLE 1** Characteristics of the contact lens used in this study.

<b>Commercial name</b>	Clariti <sup>®</sup> 1 day
Replacement	Daily
Material	Somofilcon A 5B
Water content (%)	56
Base curve (mm)	8.6
Diameter (mm)	14.1
Centre thickness (mm)	0.07
DK (Oxygen permeability; FATT/ISO)	60/45
Ultra-violet filter	Class <sub>2</sub>
Design	Aspherical (wavefront controlled)

were collected with the participants wearing their spectacles. To ensure measurements were always taken under the same conditions, participants were adapted for 5min in a controlled environmental chamber (CEC) (PSR-B; WEISS Technik UK, Weiss-[technik.co.uk\)](http://technik.co.uk) based in VERI, whose characteristics have been explained elsewhere (see García-Porta et al. $^{26}$ ). After this initial adaptation period, blinking rate, ocular scatter and ocular thermography were measured. The measurements were performed at 45% relative humidity (RH) and 23°C. Participants were then exposed to the low-humidity environment (RH: 5%, 23°C) for 90min, while they watched a movie on a computer screen or worked on a computer, placed at the same distance. After 1.5h of exposure, all tests were repeated (Figure [1\)](#page-3-0) under low-humidity conditions. The temperature  $(23^{\circ}C \pm 1^{\circ}C)$ and lighting (100 lux) were kept constant during the whole experiment.

The second visit (CL phase) was performed 2 or 3days after the initial visit. On this occasion, participants were asked to insert the Clariti® 1Day CLs and wait 15min to allow the lenses to settle. If required, more time was offered, and all subjects confirmed that the lenses were just as or more comfortable than their existing CL. After ensuring the CL fit was successful, the same protocol followed in Visit 1 was repeated (Figure [1\)](#page-3-0).

#### **Instrumentation**

The blinking rate was measured using a video camera connected to a computer while the participants watched a 5-min film on a TV screen placed at a distance of 50 cm.<sup>[27](#page-8-6)</sup> The same film was used for both pre- and post-exposure conditions to ensure that no blinking differences related to change in film scenes or the task's difficulty affected the measurements. $^{28}$  Two similar videos were used for this study, one for Visit 1 (spectacles visit) and another for Visit 2 (CL visit). The video used in each visit with each participant was randomised using online randomisation software [\(random.org\)](http://random.org).

During the 5-min video, participants wore their usual spectacle correction in the first visit and Clariti® 1Day CLs in the second visit. They were naïve to the measurement of the blinking rate. The head was placed on a chinrest with a headrest, and the camera was located on the right-hand side and did not interfere with the video that showed the film. MATLAB software ([mathworks.com](http://mathworks.com)) was used to detect and count the blinking rate. The blinking rate was calculated as the average number of blinks per minute during the last 4min of the video.

The objective quality of vision was assessed by measuring the ocular scatter with the Optical Quality Analysis System II (OQAS II; QQVision, [qqvision.com\)](http://qqvision.com), whose char-acteristics have been explained previously.<sup>[29](#page-8-8)</sup> Ocular scattering was quantified from the OQAS using the OSI, which is defined as the ratio between the integrated light in the periphery and the central peak of the double-pass (DP)



<span id="page-3-0"></span>**FIGURE 1** Scheme of the study protocol. CEC, controlled environmental chamber; CL, contact lens; OSDI, Ocular Surface Disease Index; RH, relative humidity; T, temperature; VA, visual acuity.

image. $^{29}$  $^{29}$  $^{29}$  To measure the OSI, participants were asked to look at the target on the OQAS device and blink normally.<sup>[30](#page-8-9)</sup> Twenty images (one reading per second) were collected, and an average OSI value was calculated automatically by the OQAS II. All images were acquired at best focus, using the Badal optometer within the instrument to correct for spherical defocus (from −8.00 to +6.00 D). OSI was measured before and after CL insertion in comfortable and low-humidity conditions. The larger the OSI value, the higher the ocular scatter.

Cooling rate: a long-wave infrared thermal camera (Therm-App Hz, Opgal Optronic Industries Ltd., [opgal.com\)](http://opgal.com), whose characteristics have been explained in Garcia-Porta et  $al.,<sup>26</sup>$  $al.,<sup>26</sup>$  $al.,<sup>26</sup>$  was used to collect the thermal images. Thermal images were analysed using MATLAB. Frames that corresponded to blinks were removed. Participants were asked to keep their eyes closed for 10s and then, after opening the eyes, to look straight ahead and blink normally. The cooling rate was evaluated from an elliptical area (major axis: 6mm, minor axis: 4mm) located in the centre of the cornea and evaluated from 0 to 2s, as our previous study found that the main changes occur during this period. $26$ The cooling rate was calculated as the slope of the linear function fitted to the obtained data. The cooling rate was measured before and after CL insertion in both comfortable and low-humidity conditions.

### **Statistics**

SPSS ([ibm.com](http://ibm.com)) was used to carry out the statistical analysis. The normal data distribution was evaluated using the Shapiro–Wilk test. To assess the impact of exposure to low humidity and the type of refractive correction on the dependent variables measured here (blinking rate, OSI and cooling rate), a repeated measurements ANOVA with two within factors: *type of correction* (spectacles vs. CLs) and *exposure to low humidity* (before vs. after) were performed. *p*-Values<0.05 were considered statistically significant. Data were collected only for the right eye of each participant.

# **RESULTS**

Fourteen habitual soft CL wearers (10 females and 4 males, with an average age of 25.79±4.00years [range: 20–35]) took part in the study. Of these, 64.29% (*n*=9) wore daily disposable and 35.71% (*n*=5) monthly replacement soft CLs. However, all of the participants were given new CLs for the study and given time to adapt. All the corneal topographic maps were normal; participants had the following average K-readings: K-flat =  $43.35 \pm 1.17$  D and K-steep =  $44.14 \pm 0.99$  D. The average spherical equivalent was −3.48 D (range: −1.00 to −6.00 D). All participants achieved a VA ≤0.00 LogMAR with their habitual spectacles and the new CLs. Regarding the baseline dry eye symptoms, the average OSDI value was 6.71 $\pm$ 6.71, with 13 patients not suffering from dry eye symptoms according to their OSDI score. One subject obtained a score compatible with DED symptoms (27).<sup>[25](#page-8-4)</sup>

### **Blinking rate**

ANOVA showed that the type of correction (spectacles or CLs) was a statistically significant factor that affected blinking rate before exposure. Blinking rate increased from a mean of  $13 \pm 1$  blinks/minute with spectacles to  $23 \pm 3$  blinks/ minute with CLs, *F*(1, 13)=24.70, *p*<0.005, before exposure.

Exposure to low humidity was also a significant factor affecting blinking. Blink rate increased from an average of

17.7±9.6 blinks/minute (before exposure) to an average of 21.2±10.7 blinks/minute (after exposure), *F*(1, 13)=8.84, *p*=0.01. However, there was no statistically significant interaction between the type of correction and the exposure to a low-humidity environment  $(F(1, 13)=1.53, p=0.24)$ . Figure [2](#page-4-0) shows all the data.

#### **Objective scatter index**

Two subjects were excluded from the OSI analysis due to failure to acquire results pre- or post-exposure to the low-humidity environment. ANOVA demonstrated that the type of correction (spectacle or CLs) was a statistically significant factor affecting OSI. OSI values were, on average,  $0.74 \pm 0.07$  and  $1.43 \pm 0.24$  when wearing spectacles and CLs, respectively  $(F(1, 11) = 6.09, p = 0.03)$ . Exposure to low humidity (before/after) did not show a significant difference (*F*(1, 11) = 0.00, *p* = 0.96). No statistically significant interaction between the type of correction and exposure existed,  $F(1, 11) = 4.12$ ,  $p = 0.07$ (Figure [3](#page-5-0) and Table [2](#page-5-1)).

# **Cooling rate**

ANOVA showed no statistically significant effects of the type of correction on the cooling rate. On average, the cooling rate was −0.21±0.05°C/s and−0.37±0.08°C/s when wearing spectacles and CLs, respectively (*F*(1, 13)=3.49, *p*=0.08). The effect of the exposure to low humidity did not have a significant effect (*F*(1, 13)=0.13, *p*=0.73), nor was there a significant interaction (*F*(1, 13) = 1.39, *p* = 0.26) (Figure [4;](#page-6-0) Table [2](#page-5-1)).

### **DISCUSSION**

This work examined the influence of two environmental variables (type of correction and exposure to low humidity) on three novel physiological parameters related to the ocular surface. In general, the results showed that a change in the type of refractive correction (spectacles vs. CLs) generated larger effects on the ocular surface than exposure for 90min to a low-humidity environment. The parameters measured, that is, blinking rate and light scattering, appear to be part of a cyclic physiological mechanism, as detailed in the following sections.

# **Effects of inserting a CL on the ocular surface**

The blinking rate measured under comfortable environmental conditions with participants wearing spectacles was  $13 \pm 1$  blinks/min. Blink rate can vary in CL wearers,  $31,32$ and the present values are in agreement with previous work.<sup>[33](#page-8-11)</sup> In line with Lopez-de la Rosa et al.,<sup>34</sup> placement of a CL on the eye disrupted the tear film, and this resulted in an increase in blinking rate to  $23 \pm 3$  blinks/min, even though the CL were given enough time to settle, and the subject responded positively to their comfort.

Ocular scattering also increased significantly with CLs compared with spectacles. This is likely due to a higher tear instability when wearing CLs, creating a less homogenous surface,<sup>35</sup> which increases ocular scatter. The addition of the CL would also contribute to the scatter.<sup>36</sup> Further studies assessing tear stability with commonly used clinical tests and comparing different lens materials, as well as lenses with and without surface coatings, are needed to test this hypothesis using the ocular scatter equipment incorporated in this



<span id="page-4-0"></span>**FIGURE 2** Blinking rate with spectacles and contact lenses before and after exposure to environmental stress (low humidity). The values for spectacle and CL wear are shown in blue and red, respectively. The green star shows the mean, and the red/blue line shows the median value. \*Significant difference (*p*<0.05) before and after exposure to low humidity with the same correction method. \*\*Significant difference (*p*<0.05) between wearing spectacles and CLs under comfortable conditions.



<span id="page-5-0"></span>**FIGURE 3** Ocular scatter with spectacles and contact lenses (CLs) before and after exposure to low-humidity environmental conditions. The values for spectacle and CL wear are shown in blue and red, respectively. The green star shows the mean, and the red/blue line shows the median value. \*\*Significant difference ( $p$ <0.05) between wearing spectacles and CLs under comfortable conditions.

<span id="page-5-1"></span>



Abbreviations: CL, contact lens; OSI, objective scatter index.

<span id="page-5-2"></span>\*A significant *p*-value.

<span id="page-5-3"></span>a *p*-Value for main effect of eye correction.

<span id="page-5-4"></span>b *p*-Value for exposure.

<span id="page-5-5"></span><sup>c</sup>p-Value for interaction between correction (spectacles vs. CLs) and exposure (before vs. after exposure to low humidity) for blinking rate, ocular scatter and cooling rate.

study. However, this effect is mitigated as the same type of CL for both baseline and after exposure was used.

The cooling rate increased after inserting a CL onto the eye, from −0.21±0.05°C/s to −0.37±0.08°C/s. Although the full ANOVA model did not reach a significant level (*p*=0.08), there was a tendency towards significance (Figure [4\)](#page-6-0). There are two possible explanations for this: first, the pre-lens tear film is thinner with the CL than without. $37$  The pre-lens tear film is also isolated from the corneal surface by the CL, which acts as a barrier against heat transfer from the human body to the pre-lens tear film. Therefore, a thinner tear film, which is separated from the cornea, will cool down faster than a larger amount of tears in contact with the cornea. The second possible reason may be because the tear film has a specific heat value very similar to water (4.18kilojoule

per kilogram\*Kelvin; kJ/KgK). Specific heat values for CLs are typically much lower. For instance, the specific heat values of two silicone hydrogel CLs used by Ooi et al.<sup>[38](#page-8-16)</sup> in a thermal simulation study were 2.26 and 2.54kJ/KgK. This is nearly half the specific heat of the tear film (water). Objects with lower specific heat values will cool down (and heat up) faster than those with higher values. Therefore, the ocular surface with a CL will tend to cool down faster than one without. The differences in specific heat values between CL and the tear film are likely to influence ocular surface cooling when wearing CLs. It should also be noted that in DED patients, the ocular surface immediately following opening of the eyes post-blink cools faster than in healthy subjects,<sup>[39](#page-8-17)</sup> producing a similar effect that as shown in our participants when wearing CL.



<span id="page-6-0"></span>**FIGURE 4** The cooling rate between 0–2s with spectacles and contact lenses (CLs) before and after exposure to low-humidity environmental conditions. The values for spectacles and CL wear are shown in blue and red, respectively. The green star shows the mean, and the red/blue line shows the median value.

### **Exposure to low humidity on the ocular surface**

A significant increase in the blinking rate was observed after exposure to low humidity, showing, on average, three more blinks per minute compared with before the exposure ( $p = 0.01$ ), in line with previous work.<sup>40</sup> However, in comparison, the magnitude of the blinking rate increase was relatively small compared to the nearly doubling of the blink ratio that occurred when comparing CL with spectacle wear (see previous subsection). This suggests that the tear film thinning, other tear disturbances and changes on the ocular surface generated by inserting a CL onto the eye have a much larger effect than those occurring after 1.5h of exposure to low humidity. It could be hypothesised that a longer exposure to low humidity may exacerbate the blink rate symptoms, and this needs further investigation.

The scatter parameter (OSI) and the cooling rate of the ocular surface after exposure to low humidity did not show any significant changes. Again, this is in line with the blinking data in that the observed changes on the ocular surface associated with a low-humidity environment were mild compared to those induced by inserting a CL on the eye.

### **Does wearing CLs exacerbate the effects of exposure to low humidity?**

The ANOVA results did not reveal any significant interaction between the independent variables (type of correction and exposure to low humidity) on the ocular surface parameters. A careful explanation for the lack of the interaction effect is given below for each of the parameters. Regarding blinking rate, exposure to a low-humidity environment affected the participants to the same effect when wearing CLs and spectacles, in line with Morgan and colleagues.<sup>41</sup>

The lack of a significant interaction effect for the OSI can be explained in different terms. The data presented in Figure [3](#page-5-0) do not show a similar change for each type of refractive correction after exposure to low humidity. Rather, there was a slight increase in OSI with spectacles and a slight decrease with CLs. This may have been due to participants blinking twice as frequently when wearing CLs, thereby increasing the protective barrier from the external conditions. Each blink stimulates the meibomian glands and spreads the tear film across the ocular and CL surface more frequently than when wearing spectacles, thus compensating for the low-humidity environment and preventing the dynamic degradation of the image quality at the retina.

This was also shown for the cooling rate of the ocular surface. With spectacle wear, there was a slight increase in the cooling rate after the exposure to low humidity, but with CLs, the opposite occurred with an average slight decrease in the cooling rate. Again, the small effect of the low-humidity environment on the cooling rate can be explained by the protective action of increasing the blinking rate.

The findings of this study must be interpreted in light of the limitations: the relatively small number of participants and the fact that one of the participants had an OSDI score that aligned with DED. This study evaluated only one type of CL, and so the lens material and lens design may have had an impact on the participant's comfort level. Additionally, the order of the visits was not randomised to minimise the number of visits needed, which may be a potential limitation.

In summary, this study has shown that CLs do not significantly exacerbate the effects of being exposed to a low-humidity environment, most likely due to the protective action of an increased blink rate. On average, both types of corrections induced similar physiological changes

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on the ocular surface. It is possible that the subjective comfort with CL is likely to be worse due to the increased blinking rate rather than the exposure to the low humidity. The increase in blinks might be associated with the faster cooling rate of the ocular surface on insertion of the CL, which in turn lowers and alters the heat capacity and balance of the ocular surface thermo-dynamical system. The results of this study demonstrated a cyclic process based on a compensation mechanism. Wearing a CL significantly increased the blinking rate, which prevented degradation of the tear film integrity when exposed to a low-humidity environment, furthering our understanding of the effect of CLs on the eye when the environment is altered.

# **AUTHOR CONTRIBUTIONS**

**Megan Vaughan:** Formal analysis (lead); funding acquisition (equal); investigation (equal); methodology (equal); writing – original draft (equal); writing – review and editing (equal). **Shahina Pardhan:** Conceptualization (lead); formal analysis (equal); funding acquisition (lead); methodology (equal); resources (equal); supervision (lead); writing – review and editing (equal). **Pablo Artal:** Resources (equal); writing – review and editing (equal). **Nery García-Porta:** Conceptualization (lead); formal analysis (equal); funding acquisition (equal); methodology (equal); writing – original draft (equal); writing – review and editing (equal). **Juan Tabernero:** Supervision (equal); writing – review and editing (equal). **Javier Gantes-Nuñez:** Software (equal); visualization (equal); writing – review and editing (equal).

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# **CONFLICT OF INTEREST STATEMENT**

The authors do not have any financial or proprietary interest in any material or method mentioned.

# **FUNDING INFORMATION**

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