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Ocular Motility Abnormalities in Ehlers-Danlos Syndrome: An Observational Study

Anna Maria Comberiati [1], Ludovico Iannetti [1,*], Raffaele Migliorini [1], Marta Armentano [1], Marika Graziani [1], Luca Celli [2], Anna Zambrano [3], Mauro Celli [3], Magda Gharbiya [1] and Alessandro Lambiase [1]

[1] Department of Sense Organs, University Sapienza, 00161 Rome, Italy
[2] Section Endocrinology, Department of Internal Medicine, Amsterdam Bone Center, Amsterdam University Medical Centre, 1105 AZ Amsterdam, The Netherlands
[3] Rare Bone Metabolism Center, AOU Policlinico Umberto I—Sapienza Università di Roma, 00161 Rome, Italy
* Correspondence: ludovicoiannetti@gmail.com

Abstract: Purpose: To evaluate ocular motility (OM) abnormalities associated with Ehlers-Danlos Syndrome (EDS). Materials and methods: In this cross-sectional observational study, patients with EDS underwent a complete orthoptic examination. The following orthoptic tests were performed: corneal light reflex test, stereoscopic test, cover test, OM assessment, evaluation of eye pain in different gaze positions and red filter test for diplopia. Results: The corneal light reflex test at 33 cm showed an intermittent divergent deviation in 31.7% of patients and an intermittent horizontal deviation associated with a vertical deviation in 4.9% of patients. A manifest strabismus was observed in 2.4% of patients, whereas 2.4% of patients showed a microstrabismus. The corneal light reflex test at 5 m revealed microstrabismus in 9.8% and manifest strabismus in 2.4% of our patients. Moreover, intermittent exotropia was observed in 2.4% of cases. No significant alterations involving the inferior rectus and the superior oblique muscles were observed. Significant associations were observed between medial rectus muscle deficit of both eyes with pain (p = 0.020) and diplopia (p = 0.014). Furthermore, a significant association between lateral rectus muscle alteration of both eyes and pain was observed (p = 0.004). Conclusions: Our results show various OM alterations in patients with EDS, specifically superior and medial rectus muscle hypofunction. A full orthoptic evaluation in these patients is recommendable to detect OM involvement and possible ligamentous laxity changes over time through an accurate OM assessment.

Keywords: Ehlers-Danlos Syndrome; collagen alteration; ocular motility; strabismus

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1. Introduction

Ehlers-Danlos Syndrome (EDS) is a rare disease that includes a clinically and genetically heterogeneous variety of connective tissue diseases. This hereditary pathology affects predominantly the skin, joints, and the musculoskeletal apparatus. Nowadays, 13 forms of EDS are recognized, and pathogenetic mutations have been identified in 20 different genes. The global incidence and prevalence of the disease is unclear. The incidence of one of the most frequent variants, the classic type (cEDS), has been estimated at around 1:20.00. The vascular one (vEDS) is one of the rarest forms and its incidence is approximated to be between 1:50.00 and 1:200.000. The most frequent mutations concern genes encoding for fibrillary collagen types I, III and IV, enzymes linked to the biosynthetic process of these proteins or other components of the extracellular matrix [1]. Many classifications have been proposed over time, the most famous being the Villefranche classification, introduced in 1997 [2]. The most recent revision of the EDS classification was introduced in 2017 and includes 13 types with well-characterized genetic features. Moreover, this new classification provides a detailed list of major and minor criteria to help the clinician during the diagnostic process [3]. Thanks to DNA sequencing analysis, for the majority

of EDS variants, a genetic cause has been identified. cEDS is determined by heterozygous pathogenetic variants in COL5A1 or COL5A2, leading to haploinsufficiency in type V procollagen. vEDS is caused by defects in type III procollagen resulting from COL3A1 mutations. Different types of alterations involving type I procollagen are responsible for Arthrochalasia EDS, Dermatosparaxis EDS and Cardiac Valvular EDS. Defects of collagen crosslinking or folding are detectable in Kyphoscoliotic EDS forms. Classical-like EDS and Myopathic EDS are attributable to dysfunction in extracellular matrix (ECM) components. Musculocontractural EDS and Spondylodysplastic EDS are attributable to defects in glycosaminoglycans' biosynthetic process. In Periodontal EDS, an abnormal interaction between the complement and ECM has been recognized. The brittle cornea syndrome is attributable to the mutation of a zinc finger protein (ZNF469) with unknown function and a transcriptional regulator (PRDM5) leading to dysregulation in many genes, such as COL4A, COL11A1 and genes involved in ECM deposition. Regarding the hypermobile variant, a genetic cause has not been identified [1]. All EDS forms share some pathognomonic clinical characteristics, particularly joint hypermobility, cutaneous hyperlaxity, atrophic scarring, skin fragility and the tendency to develop spontaneous ecchymosis [3]. The classic and hypermobile variants are the most frequently diagnosed, representing around 90% of all forms. The vEDS is one of the rarest, being identified in less than 5% of cases. As a result of the clinical overlapping of EDS with other inheritable connective tissue disorders, a purely clinical diagnosis is often difficult to perform. For this reason, the possibility to confirm the diagnosis with genetic analysis is fundamental [4]. At the same time, for many patients with a clear EDS clinical presentation, a genetic anomaly is not detectable [5].

EDS ophthalmological manifestations involve corneal, conjunctival, orbital and vascular structures. Corneal abnormalities described in the literature are microcornea, megalocornea, corneal thickness and curvature alterations, surface irregularity and decreased corneal sensitivity. The progressive corneal thinning and steepening can lead to spontaneous ruptures with subsequent scarring and to elevated astigmatism and keratoconus [6,7]. These alterations are linked to an important reduction in type 5 collagen in the corneal stroma and reduced density of collagen fibrils. The finding of larger-diameter fibrils and irregular organization can also affect corneal transparency [8]. The corneal involvement is frequently encountered in cEDS patients, in the presence of type V collagen mutations. Conjunctival abnormalities observed in EDS are severe conjunctivochalasis, recurrent subconjunctival hemorrhages and conjunctival irritation with chemosis and foreign body sensation [7]. Orbital and ocular adnexa alterations such as blepharochalasis, palpebral ptosis, floppy eyelid, ectropion, hypertelorism, epicanthal folds, orbital pain and periorbital hemorrhages or swelling have been described [8–10]. Moreover, in EDS, tear film instability and deficiency, blue sclera, myopia and degenerative myopia have been reported, oftentimes associated with vitreo-retinal degenerations and abnormalities due to scleral thinning and bulging in consequence of abnormal collagen deposition. High myopia can lead to the development of myopic staphyloma, choroidal thinning, retinal atrophy and lacquer cracks [11,12]. Strabismus was reported in this clinical condition, mostly due to craniofacial bone asymmetry with orbital misalignment, and to abnormal collagen deposition in the extraocular muscles. Ocular imbalance due to orbital discrepancy can also cause diplopia, amblyopia and stereopsis reduction [7,13,14]. A higher incidence of open angle glaucoma associated with altered development of the aqueous outflow tract has been reported. This complication is mostly detected in vEDS, because collagen type III is a fundamental component of the juxtacanalicular meshwork and Schlemms canal [15]. Regarding retinal involvement, this condition is characterized by vessel fragility and malformation that may lead to vitreous hemorrhages. In particular, vEDS is linked to a higher incidence of rhegmatogenous retinal detachment and angioid streak formation [16]. Moreover, EDS patients suffering from cardiovascular and valvular diseases are more likely to develop retinal ischemic perivascular lesions, recognizable with ocular coherence tomography [17]. Lens involvement occurs less frequently compared to other heritable connective tissue disorders, particularly Marfan Syndrome. Ectopia lentis and dislocation have rarely been

described [18,19]. Interestingly, a higher incidence of small lens opacities has been found among young EDS patients [12]. Furthermore, in patients with important scleral thinning, cases of spontaneous globe rupture have been described. A secondary cause of vision loss can be linked to systemic and cerebrovascular complications, such as cervical artery dissection or aneurysms, which can determine ischemic/hemorrhagic brain injury. These events can manifest with visual symptoms such as nystagmus, visual field loss, visual acuity reduction, diplopia and ocular motility disorders. Carotid cavernous fistula has also been described in EDS patients, potentially responsible for relative afferent pupillary defects, episcleral vein congestion, pulsating exophthalmos and retinal thromboembolism [7]. The most recent EDS classification includes the brittle cornea syndrome. This pathology has an autosomal recessive inheritance and patients present mostly ocular signs. Pathognomonic characteristics of this syndrome are a thin cornea associated with an elevated risk of developing keratoglobus or keratoconus in early life. This condition can cause corneal rupture, perforation and infections as consequences of mild injuries in young patients. Progressive corneal thinning may result in corneal opacities and scarring, potentially vision-threatening. Central corneal thickness is often <400 µm. These patients are prone to high myopia due to an elevated ocular axial length, associated with blue sclera. In these cases, patients can also be subjected to retinal complications such as retinal detachment or secondary glaucoma. Additionally, this pathology presents a systemic involvement with deafness, hypercompliant tympanic membrane, hip dysplasia, scoliosis, arachnodactyly, joint hypermobility, finger contractures and hyper-extensible and fragile skin [3,7,20]. Moreover, in BCS patients, altered ECM protein expression in Bruch's membrane has been demonstrated. Bruch's membrane weakness can be responsible for the development of choroidal neovascularization at a young age [21].

In this cross-sectional observational study, we evaluated the orthoptic features and the ocular motility (OM) abnormalities associated with Ehlers-Danlos Syndrome.

2. Materials and Methods

From January 2021 to December 2022, 132 patients with EDS were consecutively observed from the Centre of Rare Diseases at the Policlinico Umberto I University Hospital. Among these 132 patients, 41 patients were recruited for the study, which was approved by Sapienza University of Rome's Ethics Board and was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants. The 41 enrolled patients were 36 females and 5 males, with a mean age of 28 + 12.6 (range 6–55). Moreover, 90.2% of patients (N = 37) had hypermobile EDS, 2.4% (N = 1) a vascular type and 7.3% (N = 3) of patients were not classified. All patients were already diagnosed with EDS and genetically classified. A full orthoptic evaluation, including the corneal light reflex test (CLR) and the cover test (CT) examination, was performed. We checked for the presence of OM disorders and associated diplopia or tenderness during ocular movements in all gaze positions. The stereoscopic sense was evaluated with the Lang test I and II. The BCVA evaluation at 5 m with the Snellen chart and a full ophthalmological examination were performed only during the recruitment stage, with the sole purpose of screening the patients for the exclusion criteria. The exclusion criteria were all ophthalmological diseases apart from OM abnormalities, and a Best Corrected Visual Acuity (BCVA) below a 0.1 decimal, to guarantee correct fixation during the orthoptic examination. Moreover, patients with vascular, neurodegenerative and systemic diseases (e.g., multiple sclerosis, Parkinson's disease or diabetes) that could influence the orthoptic evaluation were excluded.

Statistical Analysis

Descriptive statistical analysis was performed considering all data collected. For each categorical variable, percentages and frequencies were calculated. The chi square test was employed to evaluate possible associations between the orthoptic parameters. The analysis was conducted using R (version 4.2.2, R Foundation for Statistical Computing, Vienna, Austria). A p value < 0.05 was considered significant.

3. Results

Orthoptic Evaluation

The CLR at 33 cm appeared symmetrical in 58.5% of patients (N = 24). Moreover, this test showed an intermittent divergent deviation in 31.7% (N = 13), an intermittent horizontal deviation associated with a vertical deviation in 4.9% (N = 2), a manifest strabismus in 2.4% (N = 1) and a microstrabismus in 2.4% (N = 1) of patients.

The CLR at 5 m appeared symmetrical in 85.4% (N = 35) of patients. This examination showed an intermittent exotropia in 2.4% (N = 1), a manifest strabismus in 2.4% (N = 1) and a microstrabismus in 9.8% (N = 4) of patients.

The CT at 33 cm revealed orthophoria in 19.5% (N = 8), exophoria in 22% (N = 9), intermittent exotropia in 43.9% (N = 18), exotropia in 2.4% (N = 1), esophoria in 2.4% (N = 1), intermittent esotropia in 4.9% (N = 2) and esotropia in 4.9% (N = 2) of patients.

The CT at 5 m revealed orthophoria in 75.6% (N = 31), exophoria in 9.8% (N = 4), intermittent exotropia in 7.3 % (N = 3), esophoria in 2.4% (N = 1) and esotropia in 4.9% (N = 2) of patients.

The CT at 33 cm showed a vertical deviation in 65.9% (N = 27) of patients; in particular, 41.5% (N = 17) presented a right/left (R/L) and 24.4% (N = 10) a left/right (L/R) deviation. The CT at 5 m showed a vertical deviation in 24.4% (N=10); in particular, R/L was observed in 14.6% (N = 6) and L/R in 9.8% (N = 4) of patients.

The Lang test showed an absence of stereopsis in 4.9% (N = 2) of patients. One of the patients revealed a microstrabismus and the other one presented a partially accommodative esotropia with an angle of 20 prismatic diopters (PD) measured at 33 cm and 40 PD measured at 5 m.

All data regarding OM of the right eye (RE) and the left eye (LE) are summarized in Tables 1 and 2.

Table 1. Ocular motility of the right eye.

Muscle	Severe Muscle Hyperfunction	Moderate–Mild Hyperfunction	Severe Muscle Hypofunction	Moderate–Mild Hypofunction	Normal Muscle Functioning
MR	2.4% (N = 1)	12.2% (N = 5)	14.6% (N = 6)	29% (N = 12)	41.4% (N = 17)
LR	17.1% (N = 7)	26.8% (N = 11)	4.9% (N = 2)	2.4% (N = 1)	48.7% (N = 20)
SR	N = 0	N = 0	17.1% (N = 7)	24.4% (N = 10)	58.5% (N = 24)
IR	N = 0	N = 0	N = 0	N = 0	100% (N = 41)
SO	N = 0	2.4% (N = 1)	N = 0	N = 0	97.6% (N = 40)
IO	24.4% (N = 10)	34.2% (N = 14)	N = 0	N = 0	41.5% (N = 17)

MR: Medial Rectus, LR: Lateral rectus, SR: Superior Rectus, IR: Inferior Rectus, SO: Superior Oblique, IO: Inferior Oblique.

Table 2. Ocular motility of the left eye.

Muscle	Severe Muscle Hyperfunction	Moderate–Mild Hypofunction	Severe Muscle Hypofunction	Moderate–Mild Hypofunction	Normal Muscle Functioning
MR	4.9% (N = 2)	7.3% (N = 3)	19.5% (N = 8)	29.2% (N = 12)	39% (N = 16)
LR	9.8% (N = 4)	28.4% (N = 12)	2.4% (N = 1)	2.4% (N = 1)	56% (N = 23)
SR	N = 0	2.4% (N = 1)	17.1% (N = 7)	36.8% (N = 11)	53.7% (N = 22)
IR	N = 0	N = 0	N = 0	N = 0	100% (N = 41)
SO	N = 0	N = 0	N = 0	N = 0	100% (N = 41)
IO	9.8 % (N = 4)	19.5 % (N = 8)	N = 0	N = 0	70.7% (N = 29)

MR: Medial Rectus, LR: Lateral rectus, SR: Superior Rectus, IR: Inferior Rectus, SO: Superior Oblique, IO: Inferior Oblique.

Among our patients, 41.5% (N = 17) complained of diplopia, while 58.5% (N = 24) showed single binocular vision. Furthermore, 75.6% (N = 31) of patients reported tenderness during OM examination. Half of the diplopic patients presented pain in the upward gaze and in the right or left lateroversion. The inferential analysis, reported in Tables 3 and 4, allowed us to evaluate the associations between the orthoptic parameters

and the presence of diplopia and pain. Significant associations were observed between a Medial Rectus muscle (MR) deficit of the RE with pain ($p = 0.020$) and diplopia ($p = 0.014$). Furthermore, there was also a significant association between alteration of the Lateral Rectus muscle (LR) of the RE and the presence of eye pain ($p = 0.004$). As regards the LE, a significant association was observed between the MR deficit and pain ($p < 0.001$) and diplopia ($p = 0.030$) and between the LR deficit and pain ($p = 0.011$).

Table 3. Univariate analysis of the RE orthoptic parameters with pain/diplopia.

Variable		Pain		*p*	Diplopia		*p*
		Absent	Present		Absent	Present	
MR	Normal	9	10	0.020 °	15	4	0.014 *
	Alteration	1	21		9	13	
LR	Normal	9	11	0.004 °	14	6	0.146 *
	Alteration	1	20		10	11	
SR	Normal	8	16	0.152 °	16	8	0.209 *
	Alteration	2	15		8	9	
IR	Normal	10	31	NC	24	17	NC
	Alteration	—-	—-		—-	—-	
SO	Normal	10	30	1.000 °	24	16	0.415 °
	Alteration	0	1		0	1	
IO	Normal	7	10	0.063 °	12	5	0.187 *
	Alteration	3	21		12	12	

MR: Medial Rectus, LR: Lateral rectus, SR: Superior Rectus, IR: Inferior Rectus, SO: Superior Oblique, IO: Inferior Oblique. * *p*-value Chi-Square Test; ° *p*-value Fisher Test; NC: not calculable.

Table 4. Univariate analysis of the LE orthoptic parameters with pain/diplopia.

Variable		Pain		*p*	Diplopia		*p*
		Absent	Present		Absent	Present	
MR	Normal	9	7	<0.001 °	14	2	0.030 *
	Alteration	1	24		10	15	
LR	Normal	9	13	0.011 °	14	8	0.476 *
	Alteration	1	18		10	9	
SR	Normal	7	15	0.292 °	15	7	0.177 *
	Alteration	3	16		9	10	
IR	Normal	10	31	NC	24	17	NC
	Alteration	—-	—-		—-	—-	
SO	Normal	10	31	NC	24	17	NC
	Alteration	—-	—-		—-	—-	
IO	Normal	8	21	0.694 °	19	10	0.184 °
	Alteration	2	10		5	7	

MR: Medial Rectus, LR: Lateral rectus, SR: Superior Rectus, IR: Inferior Rectus, SO: Superior Oblique, IO: Inferior Oblique. * *p*-value Chi-Square Test; ° *p*-value Fisher Test; NC: not calculable.

4. Discussion

In our study, a complete and detailed OM evaluation describes the characteristics of the extraocular muscle disorders in patients with diagnosed EDS. A manifest strabismus was observed in a small group of the included patients. However, several extraocular muscles,

such as MR, LR, SR and IO, were affected, with different frequencies, by hypofunction or hyperfunction, while the IR and SO showed no alteration. In detail, considering the diagnostic gaze position in the right lateroversion, the left MR had severe hypofunction in 19.5% and the right LR had moderate–mild hyperfunction in 26.8% of cases. On the other hand, in the left lateroversion, moderate–mild hypofunction was observed in the right MR in 29% and hyperfunction of the same degree in the left LR in 28.4% of cases. Considering the diagnostic gaze position up and to the right, we found moderate–mild hypofunction in the right SR in 24.4%, with contralateral synergistic muscle hyperfunction (left IO) in 19.5% of cases. The last gaze position in which the OM examination revealed deficits was up and to the left, where the left SR showed moderate–mild hypofunction in 36.8% and the right IO showed moderate–mild hyperfunction in 34.2% of cases. The two horizontal gaze positions to the right and left were associated with the presence of eye pain and diplopia. The presence of diplopia shows how oculomotor alteration appeared after the plastic period (0–6 years) as a consequence of the EDS progression. These orthoptic alterations suggest that the ligamentous laxity observed in EDS tends to involve the extraocular muscles. Our findings suggest that ligamentous laxity and muscular fiber alterations can in fact affect the ocular district, determining functional changes over the years. Ophthalmological and orthoptic evaluation should be considered as part of the regular diagnostic assessment in this pathology. In our cohort, only a minority of patients presenting ocular motility disorders reported diplopia. These data suggest that an important part of ocular muscular dysfunction remains subclinical and underdiagnosed. An early diagnosis of this muscular involvement might be crucial in these patients to monitor the evolution of the disease over time. Moreover, the ocular muscular district offers the possibility of an easy clinical evaluation and can mirror the condition of the systemic muscular apparatus. Furthermore, EDS children during the plastic period should be closely checked, because the development of subclinical strabismus can represent an important cause of amblyopia. In children, the occurrence of subtle forms of strabismus is not associated with the onset of double vision, but can lead to silent sight suppression.

Meyer et al. studied the structures of the fibrils of the dermal collagen and the fibrils of the extraocular muscles and the conjunctivae of both eyes of a child affected by EDS. They observed that in the reticular dermis, 48% of fibrils presented a normal diameter, 23% were enlarged and 29% were thinner than normal. In the extraocular muscle, they found that 77% of fibrils were of normal size, 14.5% of larger size and 8.5% of smaller size. In the conjunctivae, 73% of the fibrils were of normal size, 22% were enlarged and 5% were smaller. In healthy controls, no small fibrils were found in the extraocular muscles [14]. To the best of our knowledge, this is the first study that analyzes specifically the extraocular muscle abnormalities in EDS through a complete and accurate orthoptic assessment. Furthermore, the previous studies that described OM alterations in EDS had by far a smaller sample compared to ours. Perez-Roustit et al. reported OM disorders in 15 (71.4%) of 21 patients affected by EDS, with convergence insufficiency in 13 of them [22]. Louie et al. reported, among 467 patients with confirmed EDS, 17 cases that underwent strabismus correction surgeries, out of which 14 (82.4%) underwent surgery before receiving their EDS diagnosis [13]. Other authors reported strabismus in EDS patients in combination with particular craniofacial features such as down-slanting palpebral fissures, palatine alterations, microretrognathia or protruding jaw and crowded teeth, contributing to congenital contractures and malocclusion [23,24]. It can be hypothesized that bone craniofacial alterations, malocclusion and frequent orthopedic spine issues, leading to incorrect posture, might represent an additional risk factor for the development of strabismus [25,26]. Moreover, we can suppose that these OM disorders are additionally attributable to muscular dysfunction due to the altered deposition and organization of collagen fibrils in the muscles, leading to reduced muscle mass and weakness. Muscular atrophy, hypotonia and contractures are described in the literature in this pathology relatively to other muscular districts, defining a myopathic subtype of EDS [27]. In our sample, these alterations in OM cannot be correlated with compromised binocular vision, because motor fusion was within

the normal limits and stereopsis, although in some cases coarse, was present. Promising results in the assessment of stereopsis could be obtained by measuring the ocular following responses (OFR). OFR are configured as short-latency, slow eye movements that constitute a visual tracking system. These responses aim to adjust the fixation as the visual stimulus varies. OFR allows physiological shifts in fixation, between near and far objects appearing in the visual field during everyday activities. Binocular gaze shift is usually permitted thanks to a combination of saccades and vergence movements. It helps to stabilize the eyes on the visual scene [28,29]. Different studies highlighted a possible role of OFR in the evaluation of binocular vision and inter-eye collaboration, through the analysis of eye movements. Neurons localized in the primary visual cortex elicit stronger responses if activated by binocular stimuli, determining enhanced OFR. These findings suggest that OFR might reveal the presence of binocular collaboration and summation in patients [30]. Moreover, OFR can be detected also in young children or in patients in whom it may be difficult to assess stereopsis using common tests for binocular vision [31]. The present study has some limitations, such as its retrospective nature, the small sample size and the poor homogeneity of the sample relative to gender and age, which could affect the generalizability of the findings. On the other hand, as EDS is an extremely rare disease, we chose to recruit, in our study, the largest number of affected patients that we had at our disposal, despite the fact that this has disadvantaged data homogeneity. Another important limit of our study is that our main focus has been on ocular motility disorders, without taking into consideration the possibility to correlate these data with other eventual intraocular manifestations. Further studies are warranted to evaluate the potential correlation between alterations in eye movement and muscular alterations in other corporeal districts. Another field in which to improve research on EDS could be represented by the histological analysis of extraocular muscle features. At present, only one article on this topic is available in the literature [14].

5. Conclusions

The present study describes the characteristics of OM abnormalities in patients with EDS and suggests how accurate orthoptic screening together with the ophthalmological evaluation could provide a significant contribution to the management of the patients affected by this rare syndrome. An orthoptic protocol of rehabilitation should be planned in cases of OM alterations that interfere with the patient's quality of life. Further studies are warranted to confirm the findings of the present research on the OM abnormalities associated with EDS, and it would be desirable to perform a genetic investigation to understand the link between the gene and the extraocular muscle involved.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data that support the findings of this study are not publicly available to protect the privacy of research participants but are available from the corresponding author, L.I.

Conflicts of Interest: The authors declare no conflict of interest.

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