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ORIGINAL RESEARCH

Assessment of potential maladaptive pain in dogs with elbow osteoarthritis using a von Frey aesthesiometer

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Abstract

Background: This study aimed to investigate the possible presence of maladaptive pain in the thoracic limbs of dogs with elbow osteoarthritis (OA) using an electronic von Frey aesthesiometer (eVFA).

Methods: Twenty-eight client- and staff-owned dogs (OA, $n = 14$; controls, $n = 14$) were enrolled in the study. Every dog underwent a full orthopaedic examination, and then five von Frey measurements were obtained from each carpal pad of each dog. A maximum test threshold of 400 g was set and approved by an ethics committee.

Results: eVFA thresholds were significantly lower ($p < 0.001$) in dogs with OA (median 248 g, range 128–369 g) than in control dogs (median 390 g, range 371–400 g). In the OA group, the sensory threshold was significantly lower ($p = 0.048$) in the more severely affected limb than the less severely affected limb.

Limitation: The low maximum threshold required for ethical approval may influence the variability in the control group.

Conclusions: Dogs with elbow OA had significantly lower sensory thresholds than control dogs, which is compatible with the presence of maladaptive pain, potentially due to central sensitisation. Further research is required to evaluate the potential use of the eVFA for monitoring clinical progression and treatment response in dogs with elbow OA.

KEYWORDS
dogs, elbow osteoarthritis, maladaptive pain, mechanical sensory threshold, pain assessment, von Frey aesthesiometer

INTRODUCTION

Elbow osteoarthritis (OA) is an important cause of lameness in dogs regardless of their age, often developing secondary to elbow dysplasia.[1] OA is a chronic degenerative condition of synovial joints that leads to progressive damage of the subchondral bone and cartilage, with formation of osteophytes, thickening of the joint capsule and synovitis.[2] Elbow OA is estimated to affect 20% of adult dogs,[3] resulting in chronic pain and lameness, which is challenging to manage and becomes increasingly disabling for the dogs.[4] Objective assessment of pain and response to treatment is difficult,[5] so subjective visual analysis and owner questionnaire assessments, such as the Canine Brief Pain Inventory (CBPI),[6] the Helsinki Chronic Pain Index (HCPI)[7] and the Liverpool Osteoarthritis Assessment in Dogs (LOAD) clinical metrology instrument, are often used in the clinical setting. The LOAD instrument is widely used, having been tested for construct validity against CBPI and HCPI instruments, and shows a significant although weak correlation with force-plate data.[8] These questionnaires include semi-objective rating of disease severity, such as lameness, gait and limb use and willingness to exercise, that allow a standardisation of the pain assessment; however, no completely objective method is available to evaluate chronic pain.[9]

The chronic pain seen in OA is considered to be 'maladaptive' when its persistence provides no protective or other benefits to the patient.[10] Such pain is challenging to manage, as in addition to the localised

joint pain, the continuous peripheral input into the nociceptive pathway in patients with OA is thought to lead to the development of central sensitisation.[11] Central sensitisation is defined as a state in which neurons activated by nociceptive stimuli become sensitised by the stimuli such that they become hyperresponsive to subsequent stimulation of the neuron's receptor.[12]

Peripheral sensitisation, defined as reduced threshold and augmented response of the peripheral ends of nociceptors, is considered to play a significant role in the development and maintenance of central sensitisation.[13,14] The abnormal excitability in the peripheral and central pain pathways is thought to contribute to the intensity of the pain reported by human patients with OA,[10] which does not necessarily correlate with the severity of the changes seen on radiographs of the joints.[13]

Maladaptive pain has previously been assessed in dogs and humans by quantitative sensory testing (QST) using non-invasive techniques to evaluate possible somatosensory alterations.[15–17] The electronic von Frey aesthesiometer (eVFA) is a device used for QST that measures sensory thresholds to a punctate mechanical stimulus (a plastic probe applied to the skin) and records absolute values (in grams), enabling subsequent statistical analysis. The punctate stimulus is detected by Meissner's capsules, with the resultant stimulus then transmitted by either Aβ or AÕ afferent fibres: an increase or decrease in sensitivity of these receptors and pathways can be detected using QST.[18] While other techniques can be used, the eVFA enables a more rapid assessment and has better reproducibility compared to other methods.[16] The eVFA has been used to identify maladaptive pain by measuring sensory mechanical thresholds in dogs with cranial cruciate rupture,[19] hip OA,[20] spinal cord injury[21] and general chronic pelvic limb pain.[22] To the best of the authors' knowledge, no studies have been conducted to evaluate the presence of maladaptive pain or central sensitisation arising from joint disease in the thoracic limbs. If such sensitisation occurs, then the eVFA could be a useful technique to contribute to the assessment of pain in dogs being managed for elbow disease.

The aim of the present study was to investigate the possible presence of maladaptive pain potentially resulting from central sensitisation in the thoracic limbs of dogs with elbow OA, compared to normal dogs, by testing sensory thresholds using an eVFA, along with the LOAD metrology instrument. We hypothesised that dogs with elbow OA would have higher LOAD scores and lower thresholds to stimulation with the eVFA in comparison to healthy dogs, and that lower thresholds would be obtained when comparing their clinically more severely affected thoracic limb with their less affected thoracic limb.

MATERIALS AND METHODS

Animals

Twenty-eight dogs were enrolled in the study: 14 dogs clinically affected by elbow OA (OA group) and 14 dogs without orthopaedic disease (control group). All dogs underwent a full clinical and orthopaedic examination at the time of the study. The control dogs were considered to be unaffected by clinical OA if, on clinical examination, they were not lame and showed a normal range of pain-free motion on palpation and manipulation of all joints, including both elbows.

All the dogs enrolled in the OA group had a previous radiographic (radiographs or CT) diagnosis of elbow OA and at the time of enrolment into the study, showed clinical signs of lameness and exhibited pain on manipulation of one or both elbows, without clinically significant orthopaedic disease being identified elsewhere.

To be included in the study, dogs had to be aged over 1 year and weigh over 15 kg with a body condition score (BCS) between 4 and 7 out of 9. Dogs in the control group were not on any medication, but standardisation of medication was not possible for dogs enrolled in the OA group. Subjects were enrolled from both staff- and client-owned dogs and written informed consent was obtained from all owners.

Electronic von Frey aesthesiometer

The eVFA (IITC, II-2391, World Precision Instruments) consists of a handpiece with a rigid 0.8 mm diameter plastic tip, connected to an internal load cell (measurement range 0.1–800 g) and recording device (Figure 1a). Mechanical force was applied to the carpal pad of each thoracic limb via the plastic tip (Figure 1b), and the load (in grams) at which the dog reacted/withdrew the limb was noted—the maximum mechanical threshold was set at 400 g.[22]

eVFA measurement

The eVFA measurements were carried out in a quiet room, and dogs were allowed to acclimatise to the testing area for at least 10 minutes prior to the start of the examination. Attention was given by the investigators (petting, treats or other positive interactions) if the dog initiated the interaction. Following acclimatisation, all dogs underwent a complete physical examination, including a specific orthopaedic examination to identify any lameness or discomfort and to determine whether one thoracic limb was more painful than the other.

The eVFA testing was then performed with the dog in a standing position, gently restrained by an

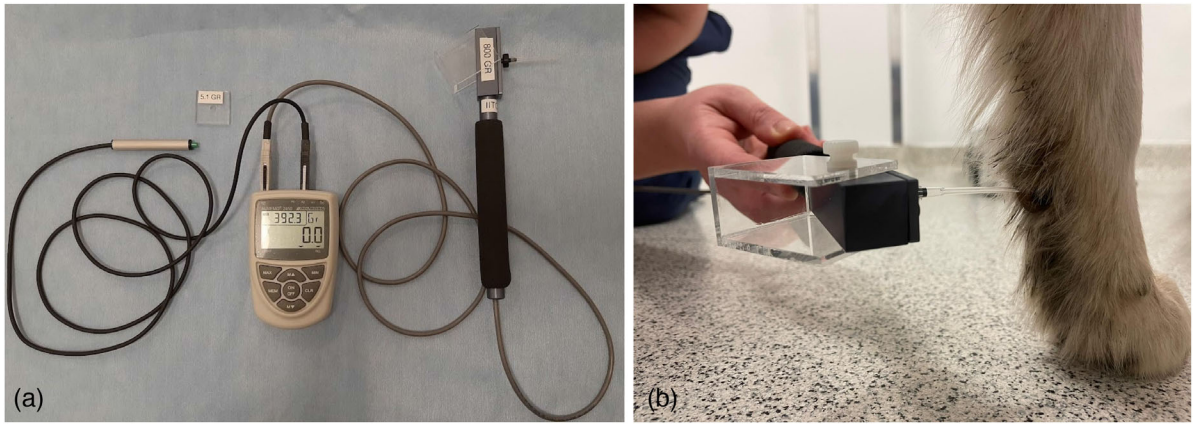

FIGURE 1 (a) Electronic von Frey aesthesiometer (b) Testing carpal pad

assistant. Both thoracic limbs were evaluated by applying the eVFA tip to each carpal pad in a randomised order to obtain five measurements from each foreleg, with a delay of 30 seconds between each measurement. Gentle steadily increasing load was applied with the device until a reaction was observed (withdrawal of the paw, vocalisation) or a maximum load of 400 g was applied (in accordance with the ethical approval guidance). A flinch or immediate withdrawal of the limb at first contact of the device to the carpal pad was not considered a valid trial. The test was easily escapable and could be interrupted at any moment if the dog showed any signs of distress.

The person applying the eVFA did not see the values being recorded (i.e., was blinded to the results), but was advised by the assistant if the 400 g threshold was reached, at which point the test was stopped.

LOAD scores

All owners were asked to complete a LOAD questionnaire to assess their dog's mobility. The questionnaire consists of a series of questions with answers being scored from 0 to 4. The aggregate score gives an indication of the extent to which the dog's mobility is affected: score 0–10, mild; 11–20, moderate; 21–30, severe; and 31–52, extreme.

Statistical analysis

Categorical variables were presented as counts (n) and percentages and were compared between groups using the maximum likelihood G-test or Fisher's exact test if the count in any cell of the contingency table was less than 5.

Continuous variables were assessed for normality using normal probability Q–Q plots and the Shapiro–Wilk W-test. As the normality assumption was generally violated, continuous variables were presented as the median and range or the median, interquartile range and individual dog measurements. The same applied to BCS (ordinal variable).

Mechanical sensory thresholds (expressed in grams) were compared between elbows (averaged five measurements from each thoracic limb) using the Wilcoxon signed-rank test and between groups (averaged five measurements from each thoracic limb, and averaged 10 measurements from each dog) using the Mann–Whitney U-test. Correlations between numerical variables were evaluated using the Spearman's rank correlation coefficient (R_S). Variability of repeated measurements (five from each thoracic limb as well as 10 from each dog) was expressed as the coefficient of variability (CV% = standard deviation/arithmetic mean). All tests were two tailed. A significance level (α) was set at 0.05. The statistical analysis was performed in TIBCO Statistica 13.3 (TIBCO Software).

The number of dogs required in each group was calculated to ensure at least 80% power for comparison of groups using the Mann–Whitney U-test or Wilcoxon signed-rank test, assuming a minimum difference of median eVFA measurement between groups (absolute effect size) of 75 g and $\alpha = 0.05$. The minimum absolute effect size (corresponding to the lowest clinically significant difference) was based on differences between healthy and diseased dogs observed in previous studies[14,16] and on expert opinion. Due to lack of knowledge of the expected distribution of eVFA measurements, the calculation of required group size was performed assuming eVFA measurements would follow the beta-PERT distribution (a theoretical probability distribution based on three parameters: the minimum, maximum and most likely value of the variable[17]); with a minimum value of 100 g, a maximum value of 400 g and the most likely value (mode) differing by 100 g between groups, which corresponded to a difference in group medians of 75 g. The actual power of the comparisons of groups containing 14 dogs ranged from 81% to 85% for the absolute effect size of 75 g, and was greater than 95% for the absolute effect size of 100 g.

TABLE 1 Demographic characteristics of dogs from the two groups

Demographic characteristic	Osteoarthritis group ($n = 14$)	Control group ($n = 14$)	p-Value
Sex			0.999[a]
Males	8 (57%)	8 (57%)	
Females	6 (43%)	6 (43%)	
Neuter status	11 (79%)	9 (64%)	0.678[b]
Neutered males	5	7	
Spayed females	6	2	
Age (years)[c]	8 (1–12)	5 (1–10)	0.142[d]
Bodyweight (kg)[c]	32 (17–40)	23 (17–43)	0.092[d]
Body condition score[c]	6/9 (5/9–6/9)	5/9 (4/9–7/9)	0.170[d]
Breed	Labrador Retriever (7 dogs) Springer Spaniel and Rottweiler (2 dogs each) Golden Retriever, Siberian Husky and crossbreed (1 dog each)	Labrador Retriever (5 dogs) Border Collie (4 dogs) Springer Spaniel (2 dogs) Lurcher, German Shepherd dog and Siberian Husky (1 dog each)	

[a]Maximum likelihood G-test.
[b]Fisher's exact test.
[c]Presented as median (range).
[d]Mann–Whitney U-test.

RESULTS

All 28 dogs tolerated the testing well and were retained in the study (Table S1). Demographic characteristics did not differ significantly between groups (Table 1).

Measurement variability

Measurement variability was significantly greater ($p < 0.001$) in the OA group (median CV% 21.8%; range 15.6%–49.5%) than the control group (median CV% 4.4%; range 0%–9.3%). However, no significant difference was found in measurement variability between the more severely affected thoracic limbs (median CV% 24.3%; range 0.9%–53.9%) and less severely affected thoracic limbs (median CV% 20.5%; range 0%–46.2%) in the OA group ($p = 0.331$) or between the left (median CV% 2.6%; range 0%–12.4%) and right (median CV% 4.5%; range: 0%–12.0%) thoracic limbs in the control group ($p = 0.311$).

eVFA measurements

The eVFA threshold at which the dogs responded was significantly lower ($p < 0.001$) in OA dogs (median 248 g; range 128–369 g) than healthy dogs (median 390 g; range 371–400 g). The difference was significant irrespective of whether the more or less severely affected limb was compared to the normal limbs of healthy dogs (Figure 2). Moreover, eVFA measurements were significantly lower in the more severely affected thoracic limb (median 229 g; range 130–397 g) than in the less severely affected thoracic limb (median 275 g; range 126–400 g) of OA dogs ($p = 0.048$) (Figure 2).

No significant difference was identified in eVFA measurements for the left (median 391 g; range 358–400 g) and right (median 386 g; range 364–400 g) thoracic limbs of healthy dogs ($p = 0.553$). Complete eVFA measurement data are presented in Table S2.

LOAD scores

Owner-reported LOAD scores were significantly higher for the OA dogs (median 26; range 10–32) than the healthy dogs (median 1; range 0–7) ($p < 0.001$), indicating greater disability and supporting the clinical significance of OA in those dogs. In the OA group, seven dogs (50%) had a 'severe' score, four (29%) had a 'moderate' score, two (14%) had an 'extreme' score and one (7%) had a 'mild' score. In the control group, all 14 dogs had a 'mild' score.

Correlations between eVFA measurements and demographic characteristics

Correlation between eVFA measurements and bodyweight/BCS

There was no significant correlation between mechanical sensory thresholds and bodyweight in either the control group ($R_S = -0.22$, $p = 0.443$) or the OA group ($R_S = 0.33$, $p = 0.255$). There was also no significant correlation between mechanical sensory thresholds and BCS (control group: $R_S = -0.24$, $p = 0.409$; OA group: $R_S = -0.11$, $p = 0.715$).

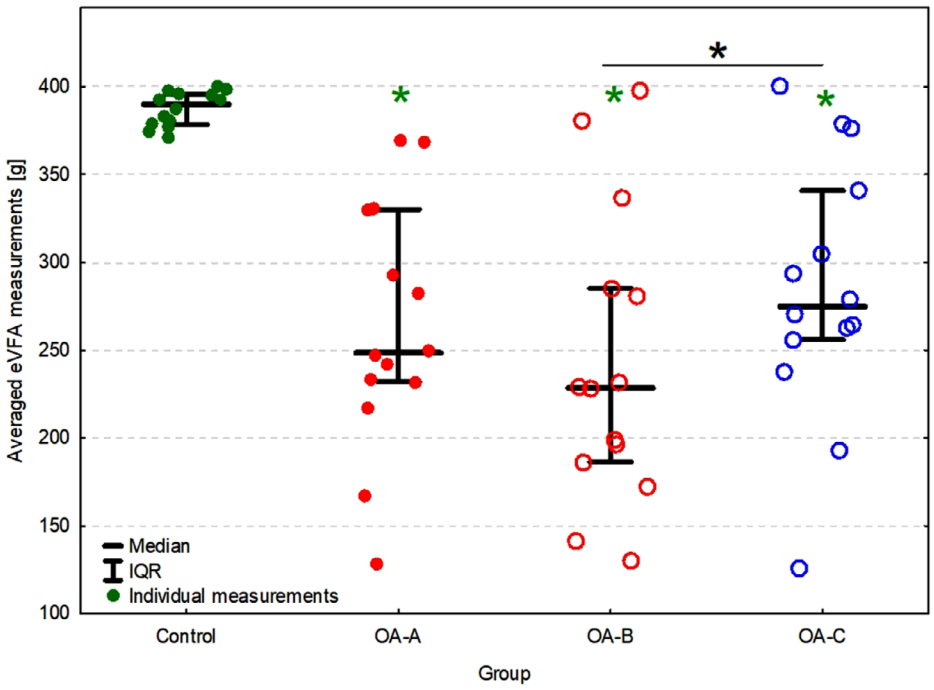

FIGURE 2 The electronic von Frey aesthesiometer (eVFA) measurements in the control group (averaged 10 measurements—five from left and five from right thoracic limb) and in the osteoarthritis (OA) group (averaged 10 measurements from both limbs [OA-A], averaged five measurements from more severely affected thoracic limb [OA-B] and averaged five measurements from less severely affected thoracic limb [OA-C]). Green asterisks denote significant differences compared to the control group ($p < 0.001$) and a black asterisk denotes a significant difference between the more and less severely affected thoracic limbs ($p = 0.048$). IQR, interquartile range

Correlation between eVFA measurements and age

There was no significant correlation between mechanical sensory threshold and age in either the control group ($R_S = -0.41$, $p = 0.143$) or the OA group ($R_S = 0.19$, $p = 0.520$).

Correlation between eVFA measurements and LOAD score

There was no significant correlation between mechanical sensory threshold and LOAD score in either the control group ($R_S = 0.15$, $p = 0.616$) or the OA group ($R_S = 0.13$, $p = 0.652$).

DISCUSSION

To the best of the authors' knowledge, this is the first study in which maladaptive pain and potential central sensitisation have been assessed using the eVFA in dogs with thoracic limb orthopaedic disease, specifically, elbow OA. We found that dogs with elbow OA had significantly lower thresholds to the eVFA stimulus compared to normal dogs, and that in the dogs with OA, the thresholds were significantly lower in the more severely affected of the two thoracic limbs.

Our results are in agreement with previous reports of maladaptive pain in dogs with other joint pathology, including hip OA[21] and cruciate ligament disease.[19] Dogs in the study on cruciate ligament disease[19] were tested using interdigital von Frey filaments rather than an electronic device to assess mechanical sensory thresholds, and significant differences were identified between affected and contralateral hindlimbs, with lower mechanical sensory thresholds reported for the affected limbs. In the study of dogs with hip OA,[21] the mechanical sensory threshold was found to be significantly increased 12 months after successful total hip replacement, demonstrating the use of mechanical sensory threshold testing for assessment of treatment responses. The authors suggested that the changes were due to a reduction in central sensitisation postoperatively.[20]

We did not find a significant correlation between age or bodyweight and mechanical sensory thresholds in either affected or normal dogs. Other authors comparing mechanical sensory thresholds between healthy dogs and dogs with 'presumptive' hindlimb OA found a negative correlation between stimulus threshold and age, reporting that older dogs tended to react at lower stimuli.[23] In another study of normal dogs by the same group, a significant positive correlation was identified between bodyweight/BCS and mechanical sensory threshold, with heavier dogs reacting at a higher threshold.[25] The authors discuss the difficulty in isolating the effect of OA on mechanical thresholds from the effect of age, noting that the dogs with presumptive OA were significantly older than the control dogs,[23] in contrast to those in our study. However, when both bodyweight and age were controlled, the dogs with OA still had lower thresholds than normal dogs,[23] in agreement with our findings.

In a pilot trial, we assessed the use of the eVFA on different anatomical landmarks, and with the dogs both in standing position and lateral recumbency. First, we considered whether the stimulus response (withdrawing the paw) might be affected by the extent of discomfort in the contralateral limb in dogs with bilateral OA, as such dogs may show a slower response and/or higher thresholds due to reluctance to transfer weight to the contralateral limb. We therefore assessed the feasibility of testing the dogs in lateral recumbency. In general, however, most dogs were less compliant and/or more anxious when placed in lateral recumbency. In humans, stress-induced analgesia has been well documented,[20] and a similar physiological response has been hypothesised in dogs with OA.[21] Based on these studies, we assumed that a higher level of anxiety could significantly influence the response to the eVFA; therefore, we elected to test the dogs in a standing position.

We also assessed the response of the dogs to testing with the eVFA at a variety of anatomical landmarks, including the medial epicondyle, lateral epicondyle and olecranon. However, due to the variable extent of the OA, joint remodelling resulted in anatomical variability that made accurate and repeatable placement of the eVFA probe less reliable.

Testing using the carpal pad was previously reported,[28,29] and is considered more straightforward and reproducible. In addition, testing a region distal to the area affected by the pathology has been used in other studies, where a lower mechanical threshold was detected in regions distal to the joint (hip or stifle) of dogs affected by OA.[6] As widespread hyperaesthesia is considered to be a consequence of altered pain modulation at the spinal or supraspinal level, testing an area distal to a lesion (e.g., osteoarthritic joint) is reported to be a more robust way of identifying maladaptive pain, suggesting the presence of central sensitisation.[30] Further research into the presence of secondary hyperalgesia and maladaptive pain in dogs with elbow OA, and the underlying aetiopathogenesis of such pain, may help identify potential in more centrally acting and/or novel analgesics for the long-term pain management of affected dogs. This has been reported in other studies of central pain sensitisation, for example, in dogs with syringomyelia-associated pain.[31]

Limitations

It was challenging to blind the examiner to whether the dog was in the OA group or in the control group, as the dogs with elbow OA were obviously clinically affected, presenting with moderate to severe lameness and thickened elbow joints. Similar difficulties have been reported in other studies.[21,25] However, this was mitigated by the fact that the assessor was blinded to the eVFA values being recorded during the test. We are aware that another potential limitation is the fact that the dogs within the OA group were on different medication regimens; however, it would not have been ethically appropriate to modify or withdraw treatment from the OA dogs for the sole purpose of our study. Furthermore, the severity of OA and degree of cartilage damage was not directly assessed in the affected dogs at the time of testing, and would have varied between individuals, and not necessarily reflected by the clinical examination findings. Similarly, radiographic screening of the control dogs' elbows or other joints was not performed, as sedation would have been required and this could not be justified on an ethical basis.

Another potential limitation of the study is the fact that eVFA testing was not repeated days or week later. While good repeatability of the measurements has been reported,[32] other studies have suggested a lack of consistency in the response obtained with the described stimuli when patients have been re-examined 2 or 4 weeks apart.[33,34] Predictably, there was greater variability in the results of dogs with elbow OA than in the control group, as the former group had differing degrees of OA and associated pain and impairment. In addition, several of our healthy patients did not react despite having reached the predetermined maximum 400 g threshold, and it could be the case that greater variability might have become apparent had these levels been exceeded. Finally, testing was also quite time consuming, with data collection taking 40–45 minutes per patient (including acclimatisation); however, this time could be expected to be much shorter when testing a single limb in a clinical case.

CONCLUSION

The dogs with elbow OA in this study had lower sensory thresholds in response to mechanical stimulation with the eVFA compared to healthy dogs, and when comparing their more affected leg with their less affected leg. Such maladaptive pain may be indicative of the presence of central sensitisation, contributing to the difficulty in effectively managing pain in elbow OA in many animals. Further studies are merited to assess the potential of the eVFA as a simple and non-invasive method of objectively monitoring clinical progression and response to treatment in dogs with elbow OA.

AUTHOR CONTRIBUTIONS

Maria Dalla Fontana contributed to conception of study, study design, acquisition and analysis of data and interpretation. Simone Anesi contributed to conception of study, study design and acquisition of data. Sandra A. Corr contributed to conception of study, study design and analysis of data and interpretation. Michal Czopowicz contributed to study design and data analysis and interpretation. All authors drafted, revised and approved the submitted manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare they have no conflicts of interest.

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DATA AVAILABILITY STATEMENT

The data used in this study are available in the Supporting Information of this article.

ETHICS STATEMENT

The study was approved by the Ethics Committee of the University of Glasgow.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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