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Short Communication

Comparing two anti-inflammatory reflexes: Splanchnic and hypothalamic–pituitary–adrenal

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ABSTRACT

Both the autonomic nervous system and the hypothalamic–pituitary–adrenal axis respond to systemic immune challenge by initiating anti-inflammatory reflexes. Here we compare those two homeostatic responses *in vivo*. We first confirmed in male urethane-anaesthetized rats that disabling the autonomic reflex by bilateral section of the splanchnic sympathetic nerves increased plasma tumor necrosis factor α (TNF) responses to systemic lipopolysaccharide (LPS, 60 μg/kg i.v.) while reducing levels of the key anti-inflammatory cytokine, interleukin 10 (IL-10). Bilateral adrenalectomy, removing both adrenal catecholamines and glucocorticoids, increased TNF responses to LPS by a factor similar to splanchnic nerve section, but unlike splanchnic nerve section, did not reduce IL-10 responses. Both the splanchnic anti-inflammatory reflex and the adrenal glucocorticoid response independently suppress TNF production. When either pathway was disabled individually, TNF responses to LPS increased. When both were disabled simultaneously, by combining adrenalectomy with splanchnic nerve section, TNF levels rose further, in an approximately additive manner. In contrast, IL-10 responses reflected the balance between catecholamine-driven enhancement and glucocorticoid-mediated suppression. When compared to adrenal nerve section, which prevents adrenal catecholamine release, bilateral adrenalectomy (removing both adrenaline and glucocorticoids) actually increased IL-10 responses to LPS. This indicates that circulating glucocorticoids actively suppress IL-10 as well as TNF. That inference was confirmed by restoring plasma corticosterone levels in adrenalectomized rats. We conclude that systemic immune challenge initiates two early, powerful anti-inflammatory reflexes that suppress TNF with similar potency. These reflexes act through independent mechanisms and exert opposing control over IL-10, highlighting their broader regulatory role in cytokine balance.

1. Introduction

It has been known for over forty years that the autonomic nervous system, as well as the hypothalamic–pituitary–adrenal (HPA) axis can modulate immune responses (Benedek, 2011; Besedovsky, 1986; Besedovsky, 1979; Streng and Nathan, 1973). Furthermore, it was recognized that signals related to immune status reach the brain causing the generation of inhibitory immunomodulatory influences mediated by both the HPA axis and sympathetic nerves (Besedovsky and Del Rey, 2024; Besedovsky and del Rey, 2006). More recently, the splanchnic sympathetic nerves have been identified as the major efferent arm of the sympathetic, inhibitory influence on systemic inflammation (Martelli, 2014; McKinley, 2022; Occhinegro, 2023; Occhinegro, 2021). Regarding the HPA axis, adrenal secretion of glucocorticoid hormones provides a neuroendocrine inhibitory influence on systemic inflammation (Streng and Nathan, 1973; Besedovsky and Del Rey, 2024). The relationship and possible interaction between these two major endogenous anti-inflammatory mechanisms are not established.

The aims of this investigation were (i) to ascertain the relative potency of the HPA axis versus the splanchnic sympathetic nerves in acutely suppressing the production of the pro-inflammatory cytokine tumor necrosis factor α (TNF) and promoting the release of the anti-inflammatory cytokine interleukin 10 (IL-10), (ii) to determine whether there is a synergistic, additive or redundant aspect of any interaction between these two anti-inflammatory responses.

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2. Methods

2.1. Animals and ethical approval

Adult male Sprague Dawley rats (body weight 298–556 g) were obtained from Ozgene, Perth, Western Australia. These animals were housed individually in cages that were provided with food and water *ad libitum* in a room maintained at 22 °C with 12:12 h day-night cycle. All experimental procedures and protocols were approved prior to experimentation by the Animal Ethics Committee of the Florey Institute of Neuroscience and Mental Health (Approval 19–033 FINMH) which adheres to the Australian Code for the Care and use of Animals for Scientific Purposes endorsed by the National Health and Medical Research Council of Australia.

2.2. Surgical Preparation

Anaesthesia was induced by intraperitoneal injection of pentobarbital sodium (60 mg/kg). After shaving the trunk and cannulating the trachea, anesthesia was continued with 2 % isoflurane/oxygen gas administered by artificial ventilation using a rodent ventilator (Ugo Basile, Italy). A warming blanket was used to maintain a core body temperature at 37 ± 0.3 °C, measured by thermocouple inserted 5 cm into the rectum. The right femoral artery and vein were then cannulated with polyethylene tubing filled with isotonic saline that in the case of the artery contained heparin (50 U/ml). The arterial cannula was used for measuring arterial pressure and sampling blood for cytokine and corticosterone assays, the venous cannula was used for administration of drugs. Airway pressure, arterial pressure and rectal temperature were monitored using a computer-based acquisition system (Power 1401 interface and Spike 2 software, Cambridge Electronic Design, Cambridge, U.K.).

Following cannulations, one of the following surgical procedures was performed (1) bilateral adrenalectomy, (2) bilateral section of the splanchnic nerves, (3) bilateral adrenalectomy plus bilateral section of the splanchnic nerves, (4) bilateral adrenal denervation, or (5) sham surgery, in which these structures were exposed by the same retroperitoneal approach on each side, but adrenal gland, splanchnic nerves and adrenal nerves were left undamaged. On completion of the surgery, anaesthesia was changed over by intravenous administration of 20 % (w/v) urethane to a dose of 1.2 g/kg over a period of 10–15 min while gradually withdrawing isoflurane from the oxygen supply. Adequate anaesthesia was ensured by the absence of withdrawal reflexes.

2.3. Standard experimental protocol

Four to seven rats were included in each experimental group. Following the completion of surgery and the switch to urethane anaesthesia, rats were left untouched for 30 min to stabilise. A blood sample (1 ml) was then drawn for baseline cytokine measurements. These were used to exclude animals with ongoing infection or inflammation, as described previously (McKinley, 2022). Ten minutes after the baseline blood sample, lipopolysaccharide (LPS, 60 μg/kg i.v., derived from *Escherichia coli* 0111:B4; Sigma-Aldrich, St. Louis, MO, USA) was injected via the femoral vein. A final blood sample (1.5 ml) was taken either 75 min (experiments 1 and 3) or 90 min (experiment 2) later for the measurement of plasma TNF and IL-10 responses to systemic LPS. Those times was chosen to capture near-peak plasma levels (Martelli, 2014). After the final blood sample the experiment was terminated and the animal killed by bolus intravenous injection of 1.5 ml of 20 % urethane.

2.4. Assay procedures

Blood samples (~1.5 ml) were drawn from the femoral artery into chilled Eppendorf tubes containing EDTA. These tubes were centrifuged at 4 °C for 12 min, then the plasma was collected into three Eppendorf tubes which were stored at −80 °C. Subsequently, after thawing and appropriate dilution, ELISA (R & D Systems, Minneapolis, MN) was performed on these samples for determination of TNF and IL-10 concentration. The limits of detectability for TNF and IL-10 were 2 and 3 pg/ml respectively, while the inter-assay co-efficients of variation were 9.7 and 9.9 % respectively. Corticosterone concentration was also measured by ELISA (Abnova, Catalogue number KA0468) in plasma samples from rats which had been adrenalectomized then infused with either corticosterone or vehicle. The minimum detectable level was 0.3 ng/ml with inter-assay co-efficient of variation of 10.7 %.

2.5. Statistical procedures

Statistical tests were performed using GraphPad Prism 10.4.1 software. Results are expressed as mean and standard deviation. For comparison of cytokine levels with either three or four experimental groups (experiments 1 and 2), a single factor analysis of variance (ANOVA) was performed. In cases of non-homogeneity of variance, data were transformed to $\log_{10}$ values. Where a significant F value ($p < 0.05$) was obtained, Tukey's multiple comparison test followed. Where two experimental groups were compared, Student's t-test or, where appropriate, paired t-test was used. Three animals were excluded from analysis: one because a high baseline TNF level indicated ongoing infection/inflammation (McKinley, 2022), a second because a surgical mishap resulted in a TNF value 17 standard deviations above the remaining population, a third because the corticosterone infusion pump failed.

2.6. Experimental groups

Three experiments were conducted using the standard protocol to compare the separate and combined influences of adrenal nerves, splanchnic nerves and adrenal corticosteroids on systemic TNF and IL-10 responses to intravenous LPS.

2.6.1. Separate and combined effects of splanchnic nerve section and bilateral adrenalectomy

Four experimental groups were studied; (1) sham surgery, (2) bilateral adrenalectomy, (3) bilateral section of the splanchnic nerves, (4) combined bilateral adrenalectomy and bilateral splanchnic nerve section. Four rats were used in each experimental group. Following the completion of surgery and the switch to urethane anaesthesia, rats were left untouched for a period to ensure that 2 h had elapsed following the completion of the bilateral adrenalectomy or sham surgery. A blood sample (1 ml) was then drawn for baseline cytokine measurements. Ten minutes after the baseline blood sample, LPS was injected via the femoral vein. A second blood sample (1.5 ml) was taken 75 min later for the measurement of plasma TNF and IL-10 responses to systemic LPS. The experiment was then terminated.

2.6.2. Comparing adrenal nerve section with bilateral adrenalectomy

After bilateral adrenal denervation (n = 6), adrenalectomy (n = 6) or sham surgery (same for both; n = 5), a blood sample was obtained 30 min after completion of the anaesthetic switch to urethane. After a further 10 mins, LPS (60 μg/kg) was injected into the femoral vein. After a further 90 min, a second blood sample was obtained and the experiment concluded.

2.6.3. Effect of restoring corticosterone in adrenalectomized rats

Rats were bilaterally adrenalectomized after taking a blood sample to measure pre-adrenalectomy corticosterone levels. In one group (n = 5), after removal of adrenals and establishing urethane anaesthesia, an intravenous infusion of corticosterone (166 μg/h, ascertained as appropriate from preliminary experiments) was started and continued for the duration of the experiment. A jugular vein was cannulated to allow injection of LPS without disrupting the infusion. In a second group of rats (n = 6), the same protocol was followed, except that 1.66 %

ethanol/saline vehicle was infused rather than corticosterone. Two hours later a blood sample was taken for baseline cytokine measurements. After a further 10 min, LPS (60 μg/ kg) was injected into the jugular vein. A final blood sample was taken 75 min later, and the experiment concluded.

3. Results

3.1. Experiment 1. Comparing the effects of bilateral adrenalectomy with bilateral splanchnic nerve section on cytokine responses to systemic LPS.

These experiments were to elucidate the separate and combined actions of reflexes from the splanchnic nerves and the HPA axis. Individually, either bilateral adrenalectomy or bilateral section of the splanchnic nerves resulted in approximately four-fold increases in LPS-induced plasma TNF levels compared with those seen in sham operated rats (Fig. 1A). The effect of splanchnic nerve section replicates our previous findings (Martelli, 2014; McKinley, 2022; Martelli, 2014; Martelli, 2019). There was no significant difference between the TNF responses of splanchnic denervated and adrenalectomized groups. When adrenalectomy was combined with splanchnic nerve section, the resultant plasma TNF levels in response to LPS increased further, to levels more than double those observed with either adrenalectomy or splanchnic nerve section alone (Fig. 1A).

In regard to LPS-induced plasma IL-10 concentration, no significant change was observed with bilateral adrenalectomy compared with sham operated rats, whereas bilateral splanchnic nerve section caused a large and significant reduction in plasma IL-10 levels, confirming previous findings (McKinley, 2022; Martelli, 2014; Martelli, 2019; Komegae, 2018) (Fig. 1B). Combined adrenalectomy and splanchnic nerve section caused plasma IL-10 levels in response to LPS to fall significantly below those of sham operated animals, but significantly above those subjected to splanchnic nerve section alone (Fig. 1B).

3.2. Experiment 2. Comparing the effects of bilateral adrenal nerve denervation with bilateral adrenalectomy on cytokine responses to systemic LPS

These experiments were to discriminate the reflex actions of the HPA axis. Rats subjected to bilateral adrenalectomy (removing both adrenocorticoids and adrenal catecholamines) or adrenal denervation (removing adrenal catecholamines but not adrenocorticoids) both showed significantly greater increases in TNF following LPS compared with sham-operated animals. However, the effect of adrenalectomy on plasma TNF was significantly greater than that of adrenal denervation (Fig. 1C).

In this series, neither adrenalectomy nor adrenal nerve section caused the plasma IL-10 response to systemic LPS to change significantly. However, there was a tendency for IL-10 levels to fall after adrenal denervation (in line with previous findings (McKinley, 2022) but to rise after adrenalectomy, such that mean plasma IL-10 levels in adrenalectomized rats were significantly greater than those of adrenal-denervated rats (Fig. 1D).

3.3. Experiment 3. Effect of corticosterone replacement on cytokine responses to systemic LPS in adrenalectomized rats

These experiments were to directly test the actions of corticosterone given in place of the HPA axis reflex. Corticosterone was infused intravenously into adrenalectomized rats at a rate to produce plasma levels comparable to those measured in non-adrenalectomized rats under the same conditions. Prior to adrenalectomy, plasma concentrations of corticosterone were 166 ± 47 ng/ml (n = 9 rats). After adrenalectomy and 3.25 h continuous infusion of either corticosterone or vehicle, the

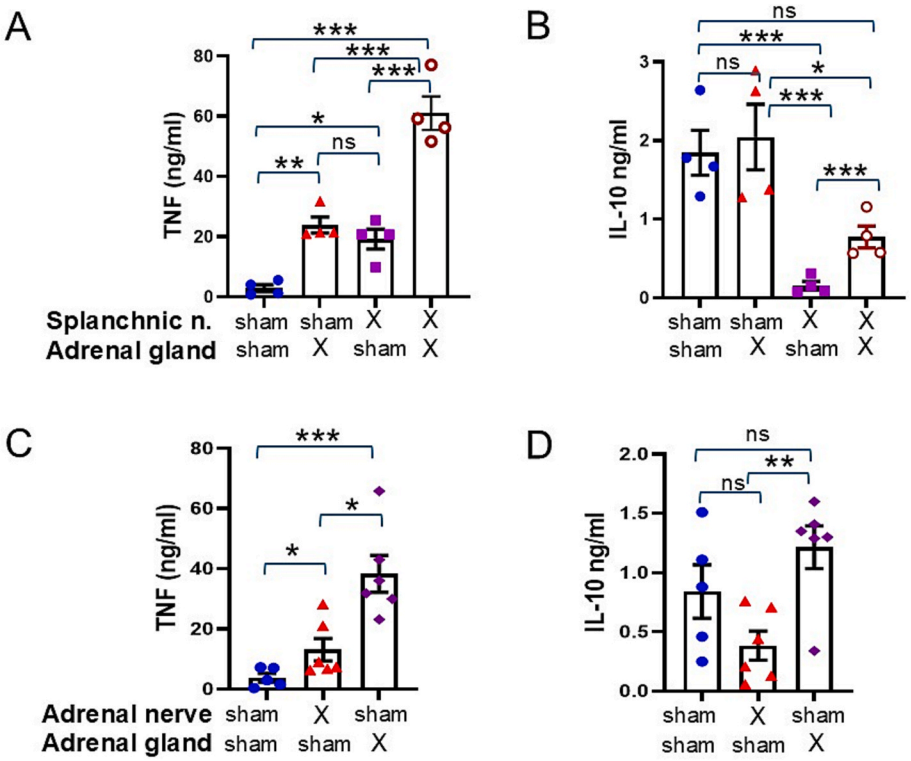

Fig. 1. (A and B: Experiment 1). (A) Plasma tumor necrosis factor-α (TNF) and (B) interleukin-10 (IL-10) levels 75 mins after lipopolysaccharide (LPS, 60 μg/kg i.v.) in male rats that had undergone sham adrenal surgery (n = 4), bilateral adrenalectomy (n = 4), bilateral splanchnic nerve section (n = 4) or combined bilateral adrenalectomy and splanchnic nerve section (n = 4). (C and D: Experiment 2). (C) Plasma TNF and (D) IL-10 levels 90 mins after LPS (60 μg/kg i.v.) in male rats that had undergone sham adrenal surgery (n = 5), bilateral adrenal denervation (n = 6), or bilateral adrenalectomy (n = 5). X indicates denervation or extirpation of relevant organs. ANOVA followed by Tukey's test statistic, *= $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$, ns = not significant.

values were 126 ± 32 (n = 5) and 16 ± 9 ng/ml (n = 6), respectively (difference $p < 0.001$). As expected, i.v. infusion of corticosterone suppressed LPS-induced plasma TNF levels to below those seen in vehicle infused rats (Fig. 2A). Interestingly, corticosterone replacement also reduced LPS-induced plasma IL-10 levels to below those observed in vehicle-infused, adrenalectomized rats (Fig. 2B).

4. Discussion

As expected, the reflex actions of both the splanchnic nerves and the HPA axis were found to be anti-inflammatory, as measured by their ongoing suppression of the TNF response to LPS. Comparing the two, we have found that the reflex action of the splanchnic nerves was as strong as that of the HPA axis in moderating acute inflammation, and that the two actions were additive. The physiological response to acute inflammation appears to be the sum of two independent reflexes.

This study follows a series of investigations on the splanchnic anti-inflammatory reflex using this protocol. The reflex works similarly in all species so far tested – rats, mice and sheep (McKinley, 2022; Occhinegro, 2021; Lankadeva, 2020). However, some limitations should be noted. The findings are based specifically on acute systemic inflammation (responses happening within hours up to ~ 1 day after the inflammatory challenge (Martelli, 2014; Lankadeva, 2020). They may well not apply to chronic inflammation. Different rules may also apply where the inflammation is localized (e.g. intraperitoneal) rather than systemic. A further limitation is the use of animals under anaesthesia, which is itself known to reduce inflammation (Fuentes, 2006; Kotanidou, (1985), 1996) and to raise background corticosterone levels (Jacobsen, 2012). Nevertheless, the splanchnic nerve reflex action has been shown to work effectively and similarly with or without general anaesthesia (Martelli, 2014), and one would expect raised baseline corticosterone levels, if anything, to amplify the consequences of removing them by adrenalectomy. The acute anti-inflammatory action of the HPA axis, via glucocorticoid release, was clearly demonstrable in the present experiments. Finally, a single mid-range dose of LPS (60 μg/kg i.v.) was used here to test the reflexes. While less than 1 % of the lethal dose, dose–response studies have shown that it is sufficient to cause near maximal plateau levels of plasma TNF and corticosterone (Meltzer, 2003).

Perhaps surprisingly, no previous study has succeeded in directly comparing the acute reflex anti-inflammatory actions of the sympathetic nervous system and the HPA axis. An earlier study by Melzer et al (Meltzer, 2003) attempted this by focusing on the role of the splenic nerves, comparing the effects of adrenalectomy and splenic nerve section on cytokine responses to LPS. To their surprise they found (Meltzer, 2003), and we later confirmed (McKinley, 2022; Martelli, 2019), that splenic nerve section on its own was ineffective in changing acute cytokine responses to LPS. To effectively disable the sympathetic inflammatory reflex requires bilateral section of the splanchnic nerves, denervating multiple abdominal viscera (Martelli, 2019). The present study once again confirms this action. An earlier study by Besedovsky and colleagues investigated the effects of adrenalectomy and sympathetic nerves on *adaptive* immunity (Besedovsky, 1979). In this case, adrenalectomy alone was ineffective, but enhanced the readout of splenic plaque-forming cells when it was combined with neonatal 6-hydroxydopamine treatment to globally destroy sympathetic nerves (Besedovsky, 1979).

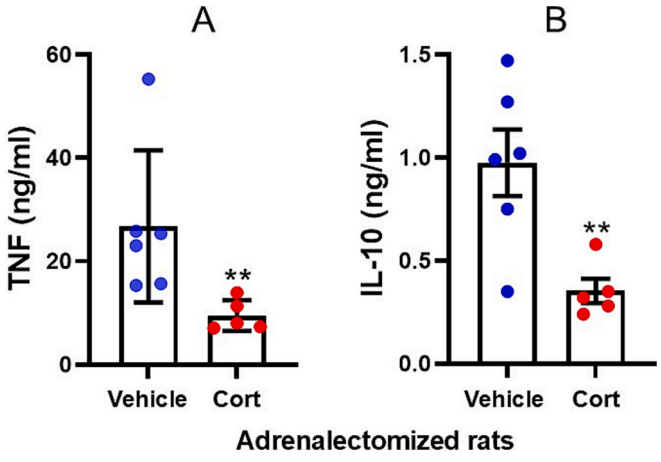

Fig. 2. Experiment 3. (A) Plasma tumor necrosis factor-α (TNF) and (B) interleukin-10 (IL-10) levels 75 min after lipopolysaccharide (LPS, 60 μg/kg i.v.) in male rats that had been bilaterally adrenalectomized, then infused intravenously with either corticosterone (Cort; 166 μg/h, n = 5) or vehicle (n = 6). *t*-test statistic, ** = $p < 0.01$.

Besides removing corticosterone, adrenalectomy prevents adrenaline secretion from the adrenal medulla. The adrenal nerves are branches of the splanchnic nerves, so section of either interrupts the neural drive to secrete adrenal medullary catecholamines. We have previously shown that adrenaline thus released, acting via β_2 adrenoreceptors, contributes to the inflammatory reflex mediated by the splanchnic nerves (McKinley, 2022). However, simply preventing adrenaline secretion by cutting the adrenal nerves was less effective than bilateral adrenalectomy in disinhibiting the TNF response to LPS (Fig. 1C). The difference between these two interventions indicates the strength of endogenous corticosteroids in inhibiting TNF release. This inference is supported by the reversal of the excess TNF response in adrenalectomized rats by corticosterone replacement (Fig. 2A).

In the case of IL-10, the opposite reflex actions on this anti-inflammatory cytokine's responses to LPS between the splanchnic nerves and the HPA axis were unexpected. Several previous studies indicated that glucocorticoids may promote synthesis and release of IL-10 (Tabardel, 1996; van der Poll, 1996; Visser, 1998). We therefore expected to find that the reflex action of HPA axis, like that of the splanchnic anti-inflammatory reflex (McKinley, 2022; Occhinegro, 2021) would be to drive a co-ordinated anti-inflammatory state by enhancing IL-10 responses to LPS while suppressing TNF. In the event, we found the opposite. Adrenalectomy (removing adrenocorticoids as well as adrenal catecholamines) resulted in substantially greater IL-10 responses to LPS than simply removing adrenal catecholamine secretion by cutting the adrenal or splanchnic nerves (Fig. 1B). The inference that glucocorticoids were suppressing both IL-10 and TNF response to LPS was confirmed by corticosterone replacement after adrenalectomy (Fig. 2B).

An inhibitory effect of glucocorticoids on IL-10 production in response to LPS was previously described by Gayo et al. (Gayo, 1998). Their study demonstrated that while methylprednisolone increased plasma IL-10 levels in patients with multiple sclerosis, it reduced the IL-10 synthesis provoked by LPS treatment in peripheral blood mononuclear cells (PBMCs) isolated from the same patients. A similar finding was reported by Borish et al. (Borish, 1996), who observed glucocorticoid-mediated inhibition of LPS-induced IL-10 production in PBMCs from asthmatic patients. These findings suggest that the anti-inflammatory effects of endogenous glucocorticoids released by the adrenal cortex, particularly during infections caused by Gram-negative bacteria, are not uniform across immune cell populations. Instead, glucocorticoids likely exert distinct effects on different leukocyte subpopulations, as previously reported (Fauci and Dale, 1974; Mozo et al., 2004), perhaps accounting for the seemingly paradoxical effects of endogenous glucocorticoids on IL-10.

In summary, this study has again confirmed that the splanchnic anti-inflammatory pathway, mediating the neural inflammatory reflex, both suppresses the TNF response to LPS and enhances IL-10. The hormonal anti-inflammatory response mediated by the HPA axis, however, suppresses the TNF response to LPS with a potency similar to that of the splanchnic nerves. Those two actions are additive, and thus presumably independently mediated. Interestingly, we found that the two reflexes

had opposite actions on IL-10 responses: the splanchnic nerves enhanced them, while glucocorticoids from the HPA axis suppressed them. The immune cells responsible for each action and the consequences of these findings for host responses to infection still need to be worked out.

CRediT authorship contribution statement

Michael McKinley: Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation, Conceptualization. **Song T Yao:** Writing – review & editing, Investigation, Formal analysis, Conceptualization. **Davide Martelli:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Robin McAllen:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

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

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Data availability

Data will be made available on request.

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