Blunted sweating does not alter the rise in core temperature in people with multiple sclerosis exercising in the heat

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Running Head: Exercise and thermoregulation for people with MS

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Abstract

Purpose: To determine whether thermoregulatory capacity is altered by MS during exercise in the heat.

Methods: Sixteen MS (EDSS: 2.9±0.9; 47±8 y; 77.6±14.0 kg) and 14 healthy (CON) control participants (43±11 y; 78.6±17.0 kg) cycled at a heat production of 4 $W \cdot kg^{-1}$ for 60 minutes at 30˚C, 30%RH (WARM). A subset of 8 MS (EDSS: 2.6±0.5; 44±8 y; 82.3±18.2 kg) and 8 CON (44±12 y; 81.2±21.1 kg) also exercised at 35°C, 30%RH (HOT). Rectal (T_{re}), mean skin (T_{sk}) temperature, and local sweat rate on the upper-back (LSR_{back}) and forearm (LSR_{arm}), were measured.

Results: All CON, yet only 9 of 16, and 7 of 8 MS participants completed 60 min of exercise in WARM and HOT trials, respectively. All MS participants unable to complete exercise stopped with ΔT_{re} between 0.2-0.5˚C. The time to reach a ΔT_{re} of 0.2˚C was similar (MS:28±15 min, CON: 32±18 min; P=0.51). For MS participants completing 60-min of exercise in WARM, ΔT_{re} (P=0.13), ΔT_{sk} (P=0.45), LSR_{back} (P=0.69) and LSR_{arm} (P=0.54) were similar to CON, but ΔT_b (MS:0.16±0.13˚C, CON:0.07±0.06˚C; P=0.02) and onset time (MS:16±10 min, CON:8±5 min; P=0.02) for sweating were greater. Similarly, in HOT, ΔT_{re} (P=0.52), ΔT_{sk} (P=0.06), LSR_{back} (P=0.59) and LSR_{arm} (P=0.08) were similar, but ΔT_b (MS: 0.19±0.16˚C, CON: 0.06±0.04˚C; P=0.04) and onset time (MS:13±7 min, CON:6±3 min; P=0.02) for sweating were greater with MS.

Conclusion: Even at 35˚C, a delayed sweating onset didn't alter heat loss to sufficiently affect exercise-induced rises in core temperature. Heat intolerance with MS does not seem attributable to thermoregulatory impairments.

Keywords: Uhthoff's Phenomenon, autonomic dysfunction, heat sensitivity, thermoregulation

Introduction

Multiple sclerosis (MS) is an autoimmune, inflammatory demyelinating disease of the central nervous system (CNS). Up to 80% of people with MS have an intolerance to the heat (36), also known as Uhthoff's phenomenon (37), which describes a transient worsening of MS symptoms with exposure to a hot environment and/or during physical activity. An increase in core temperature from rest as small as 0.2 to 0.5°C has been reported to induce Uhthoff's phenomenon, likely due to altered conduction in temperature sensitive neurons (14, 32). In some patients, this heat intolerance subsequently reduces the capacity to work and perform household tasks (35), and increases postural sway, which potentially leads to an increased risk of falling (30). Indeed, ~30% of people with MS will leave their job, with an additional ~40% admitting their job is at risk due to heat intolerance and associated symptoms (35).

A contributing factor to the rapid onset of heat intolerance may be a disproportionate rise in core temperature for a given metabolic heat load, by virtue of an impaired thermoregulatory response. A sufficient sweating and skin blood flow response is critical for regulating core body temperature during exercise and/or heat exposure. The onset of these effector responses and the rate at which sweat output and skin blood flow increases for a given rise in body temperature dictates the rate at which heat is stored and distributed within the body (26).

It has recently been reported that people with relapsing-remitting MS demonstrate a blunted sudomotor, but not vasomotor response, during moderate exercise at a fixed heat production in a temperate (25°C) environment (1). While this blunted sudomotor response did not result in larger rises in core temperature compared to healthy controls (1), exercise in hotter conditions that approach skin temperature (i.e. 30 to 35˚C) may elicit a net thermal load that exceeds the thermoregulatory capacity of people with MS sufficiently to cause

greater rises in body temperature for a given activity level. During passive heating in an encapsulated environment with a 48°C water perfused suit to a similar rise in core temperature (0.8°C), Allen et al (2) reported an average local sweat rate that is 0.24 $mg \cdot cm^{-2} \cdot min^{-1}$ lower in people with MS relative to healthy control participants. If this difference in sweating is extended across the entire body surface, the parallel difference in evaporative potential in a non-encapsulated environment should be sufficient to elicit (assuming 50% evaporation) up to a ~0.8°C greater rise in core temperature in a 70-kg MS participant after 60-min of exercise. Whether these observations translate directly to a hot non-encapsulated environment though, remains unknown.

To assess any differences in time-dependent changes in core temperature and sweating between MS and healthy populations, any differences in body size must be accounted for in the experimental design. It has been recently demonstrated that prescribing exercise intensity to elicit a fixed metabolic heat production per unit total body mass (i.e. $W \cdot kg^{-1}$), irrespective of relative exercise intensity (i.e. percentage of maximum oxygen consumption; $\%VO_2max$) eliminates any systematic differences in the exercise-induced rise of core temperature due to biophysical factors (13, 21). Similarly, if participant groups are matched for body size, such an approach will also elicit a similar evaporative requirement for heat balance (E_{req}) per unit surface area, which has been shown to determine steady-state local sweat rates, again irrespective of $\%VO_2max$ (13).

The aims of this study were to assess whether, 1) people with MS demonstrate a disproportionate rise in core temperature relative to healthy controls during moderate exercise in a warm (30°C, 30% RH) and hot (35°C, 30% RH) environment due to impaired local sweating; and 2) any impaired thermoregulatory response with MS will be sufficient to reduce exercise tolerance in both warm and hot environments compared to age-matched health controls. We hypothesized that 1) people with MS will demonstrate a greater rise in

core temperature by virtue of a blunted sweat response in both the warm and hot environments, and 2) the greater rise in core temperature in MS participants will decrease exercise time to exhaustion at a fixed heat production in both the warm and hot environments compared to age-matched healthy controls.

Methods

Participants

Sixteen relapsing-remitting MS patients and 14 control participants, with a similar age and body size, were recruited to cycle in a 30°C, 30% RH (WARM) environment (Table 1). A subset of 8 relapsing-remitting MS participants and 8 control participants with a similar age and body size completed the same exercise bout in a 35°C, 30% RH (HOT) environment (Table 1). For the WARM trials, 9 participants were required based on a power calculation (Heinrich-Heine-Universität, Dusseldorf, Germany) using an α of 0.05 and a β of 0.7 and an effect size of 1.0 for the main outcome variable of differences in sweat rate in an encapsulated heat stress environment between MS and CON participants (2). For the HOT trials, a convenience sample was used with only 8 MS and 8 CON participants returning to complete this trial. Eligible participants were free of any cardiovascular or metabolic disorders and were not prescribed medication that contained a muscarinic antagonist agent. MS participants were excluded if they had experienced a relapse six months prior to commencing the study. Disease modifying treatments (DMT) used by MS participants in this study were as follows: Tysabri (natalizumab), n = 4; Copaxone (glatiramer acetate), n = 1; Avonex (interferon beta-1a), n = 1; Tecfidera (dimethyl fumarate), n = 2; Lemtrada (alemtuzumab), n = 1; Fampridine (fampyra), n = 1; Lioresal (Baclofen), n = 1; no DMT reported, n = 5. All participants were informed of any risks involved with the study and provided their written informed consent. This study was approved by the University of Sydney Human Research Ethics Committee (HREC: 2015/125).

Study design

All trials were performed in the Thermal Ergonomics Laboratory at the University of Sydney, Australia. All participants attended one preliminary trial, 8 MS and CON participants completed two experimental trials (WARM and HOT), while 8 MS and 6 CON participants completed one experimental trial (WARM ONLY). During the experimental trials, participants cycled on a semi-recumbent ergometer at a fixed metabolic heat production (H_{prod}) of 4 $W \cdot kg^{-1}$ for 60 minutes. Participants completed their trials in either a 30°C, 30% RH (16 MS, 14 CON) or 35°C, 30% RH (8 MS, 8 CON) environment. All participants were instructed to abstain from alcohol and avoided strenuous exercise up to 24 h before their trial.

Preliminary trial

During the preliminary session, height and weight were recorded followed by a submaximal aerobic test on a semi-recumbent cycle ergometer. A submaximal test was used to determine the relationship between external work rate and oxygen consumption (VO_2) and thus H_{prod} (12). The submaximal test protocol started with a 5-min warm-up period followed by 5-min of rest, after which the participant was fitted with a face mask attached to a metabolic cart. Participants began cycling at a resistance of 20 W below the predicted workload to elicit an individualized H_{prod} of 4 $W \cdot kg^{-1}$, at a cadence of 60 rpm. The external workload of the bike was then increased by 20 W every three minutes for 4 separate stages or until volitional exhaustion (25). A least square regression equation was employed using submaximal HR and oxygen consumption at the end of each stage and extrapolated to the maximal age-predicted HR (220 - age) (5) to determine VO_{2max} using the Young Men's Christian Association (YMCA) protocol (16).

Experimental trials

During each experimental trial, participants cycled on a semi-recumbent ergometer for 60 minutes in a climate chamber regulated at 30°C, 30% RH (WARM) or 35°C, 30% RH (HOT). Participants were instrumented, and baseline data was collected for 15 minutes, after which they began to cycle at a H_{prod} of 4 $W \cdot kg^{-1}$. At the cessation of exercise, ambient temperature was decreased to 20°C, 30% RH and participants sat quietly during a 30-minute recovery period.

Instrumentation

Partitional calorimetry: Breath-by-breath metabolic energy expenditure (*M*) was calculated using indirect calorimetry via a metabolic cart (Quark CPET, Cosmed, Asia Pacific PTY, NSW, Australia). Minute-averaged values were calculated using the following equation (28):

$$M = \dot{V}O_2 \cdot \frac{\left(\left(\frac{RER-0.7}{0.3}\right).Ec\right) + \left(\left(\frac{1-RER}{0.3}\right).Ef\right)}{60} \cdot 1000 \text{ [W]}$$

Where: $\dot{V}O_2$ is the rate of oxygen consumption ($L \cdot min^{-1}$); RER is the respiratory exchange ratio; Ec and Ef are the energetic equivalents of carbohydrate (21.13 $kJ \cdot L^{-1}$ of O_2) and fat (19.62 $kJ \cdot L^{-1}$ of O_2) respectively. External workload was regulated using a semi-recumbent cycle ergometer (Corival Recumbent, Lode B.V., Groningen, Netherlands). The rate of heat production (H_{prod}) was subsequently calculated as the difference between *M* and external workload (W) and then converted into $W \cdot kg^{-1}$ by dividing by total body mass.

The evaporative requirement (E_{req}) for heat loss was determined as described by Cramer and Jay (12) and expressed as $W \cdot m^{-2}$.

Core Temperature: Rectal (T_{re}) temperature was measured using general-purpose paediatric thermistor (TM400, Covidien, Massachusetts, USA) self-inserted to a depth of ~15 cm past the anal sphincter (23).

Skin Temperature: was measured at four sites across the left side of the body using T-type thermocouples (Concept Engineering, Connecticut, USA), secured to the skin using

surgical tape. Mean skin temperature (T_{sk}) was expressed as a weighted average in accordance with Ramanathan (31): chest 30%, shoulder 30%, thigh 20%, and calf 20%. All thermometric measurements were sampled every 5 seconds (NI cDAQ-91722 module, National Instruments, Texas, USA) and displayed in real-time using LabView (v7.0, National Instruments).

Local sweat rates (LSR): were measured using 4.1-cm^2 ventilated sweat capsules, secured to the skin using surgical tape (Transpore®, 3M, Ontario, Canada). Capsules were placed on the left upper back ~5 cm above the scapular spine over the trapezium and mid-forearm ~5 cm distal to the antecubital fossa. Anhydrous air was passed through each capsule at a constant flow rate of 750 $mL \cdot min^{-1}$ (Omega FMA-A2307, Omega Engineering, Connecticut, USA) and the temperature and humidity of outflowing air were measured every 5 s using factory-calibrated capacitance hygrometers (HMT333, Vaisala, Vantaa, Finland). LSR measures were calculated as the product of change in absolute humidity across the capsule and flow rate and expressed relative to the area under the capsule in $mg \cdot cm^{-2} \cdot min^{-1}$.

Electrocardiograph: A wireless 6-lead ECG system recorded measures of heart rate (Quark ECG stress system, Cosmed, NSW, Australia).

Thermoeffector responses: LSR onset thresholds and thermosensitivity of the forearm and upper back were determined as a function of meant body temperature (T_b). It is well established that core temperature has approximately a nine to ten times greater the influence on thermoeffector responses than skin temperature (18, 27). Therefore, T_b was calculated using a weighting of $0.9 \times T_{re}$ and $0.1 \times T_{sk}$ and ΔT_b was calculated as the 30-sec average change from baseline. Thermosensitivities for each participant were determined separately for LSR of the forearm and back, using a simple linear regression for the period of linear increase in LSR plotted against the ΔT_b.

Statistical Analysis

All data are expressed as a mean with standard deviation (±). For both the WARM and HOT experimental trials, an independent-samples two-tailed t-test was used to compare absolute baseline and changes from baseline of T_{re}, T_{sk} at the 30th and 60th minute of exercise and absolute measures of HR, LSR at the forearm and upper back at the 30th and 60th minute of exercise between the MS and CON groups. Furthermore, an independent-samples two-tailed t-test was used to compare the time taken (in minutes) to reach a rise in T_{re} of 0.2˚C between the MS and CON groups and the evaporative requirement of heat loss. Workload was determined by averaging work in watts (W), $W \cdot m^{-2}$ and $W \cdot kg^{-1}$ from the tenth minute of exercise until the end of the trial for each individual participant. An independent-samples two-tailed t-test was then used to assess the difference between MS and CON groups. An independent-samples two-tailed t-test was then used to assess ΔT_b onset thresholds, time at response of onset, and thermosensitivity of LSR on the forearm and upper back. Thermosensitivities for each participant were determined separately for LSR of the forearm and back, using a simple linear regression for the period of linear increase in LSR plotted against the ΔT_b. The level of significance for all analyses employed an α of 0.05. All multiple comparison p-values were adjusted using a Bonferroni correction. Statistical analyses were performed, and all data were graphed using GraphPad Prism (Version 7 La Jolla, CA, USA).

Results

Sample sizes for statistical analyses reflect the number of MS patients that completed 30 and 60 min of exercise, respectively, in the WARM and HOT trials. Absolute rectal temperature, heart rate and the absolute and relative workloads for both the WARM and HOT trials were not different between the MS and CON groups (Table 1). Furthermore, the evaporative requirement for heat loss was similar between the MS and CON groups for both the WARM and HOT trials (Table 1).

Exercise tolerance

WARM Trial: All control participants were able to complete 60 min of exercise. However, it was observed that 14 out of 16 and 9 out of 16 MS participants were able to complete 30 and 60 min of exercise, respectively. MS participants who were unable to sustain 60 min of cycling, exercised for 33 ± 11 min (range: 15 - 45 min) before volitional exhaustion.

HOT Trial: All control participants were able to complete 60 min of exercise. However, it was observed that 7 out of 8 MS participants were able to complete exercise for 60 min, the remaining 1 participant completed 20 min of exercise before volitional exhaustion.

Core and skin temperatures

WARM Trial: The change in T_{re} after 30 min (MS:-n = 14; CON: n = 14; P = 0.75) and 60 min of exercise (MS: n = 9; CON: n = 14; P = 0.13) were not different between groups (Figure 1A). The change in T_{sk} following 30 min (MS: n = 14; CON: n = 14; P = 0.13) and 60 min of exercise (MS: n = 9; CON: n = 14; P = 0.30) were not different between groups (Figure 1B). The time taken to reach a rise in T_{re} of 0.2°C, often considered as lower limit of Uhthoff's threshold, (Figure 1C) was not different between MS and CON groups (P = 0.51). The end of exercise change in T_{re} for the MS and CON groups are displayed in figure 1D-E. For all MS participants who were unable to complete 60 min of exercise, the end of exercise change in T_{re} was within the 0.2-0.5°C Uhthoff's phenomenon threshold except for one participant who stopped exercise after 15 minutes with a rise in T_{re} of 0.10°C.

HOT Trial: The change in T_{re} after 30 min (MS: n = 7; CON: n = 8; P = 0.48) and 60 min of exercise (MS: n = 7; CON: n = 8; P = 0.65) were again not different between groups (Figure 2A). The change in T_{sk} following 30 min (MS: n = 7; CON: n = 8; P = 0.14) and 60 min of exercise (MS: n = 7; CON: n = 8; P = 0.06) was not statistically different (Figure 2B). The time taken to reach a rise in T_{re} of 0.2°C (Figure 2C) was not different between the MS

and CON participants (P = 0.19). The end of exercise change in T_{re} for the MS and CON groups are displayed in figure 2D-E. For the MS participant who was unable to complete 60 min of cycling, the end change in T_{re} was within the 0.2-0.5°C threshold of Uhthoff's phenomenon.

Sweat rates and onset thresholds

WARM Trial: Data for upper back local sweat rate was not obtained for 1 MS participant. Local sweat rates of the upper back after 30 min (P = 0.19) and 60 min of exercise (P = 0.69) were not different between groups (Table 2). Similarly, local sweat rates of the forearm after 30 min (P = 0.19) and 60 min of exercise (P = 0.54) were not different between groups (Table 2). The change in mean body temperature onset threshold for the forearm and upper back LSR and the subsequent thermosensitivity are displayed in Figure 3. Onset and thermosensitivity calculations for local sweat rate were performed on 15 and 14 MS participants for the forearm and upper back local sweat rate respectively and 13 CON participants for the forearm and upper back because either no sweat rate data was collected (n = 1) or we were unable to define the period of linear increase in LSR plotted against the ΔT_b. The change in mean body temperature for the onset of forearm sweating was greater (P = 0.04) in the MS compared to the CON group but this difference was not observed for upper back sweating (P = 0.27). The time at onset was greater in the MS group for forearm (MS: 15 ± 10 min; CON: 8 ± 5 min; P = 0.03) but not the upper back (MS: 14 ± 12 min; CON: 10 ± 9 min; P = 0.26). The thermosensitivity was not different between groups for either the forearm (MS: 0.76 ± 0.72 $mg \cdot min^{-1} \cdot cm^{-2} \cdot °C$; CON: 1.18 ± 0.59 $mg \cdot min^{-1} \cdot cm^{-2} \cdot °C$; P = 0.34) or the upper back (MS: 0.78 ± 0.77 $mg \cdot min^{-1} \cdot cm^{-2} \cdot °C$; CON: 1.23 ± 0.85 $mg \cdot min^{-1} \cdot cm^{-2} \cdot °C$; P = 0.34).

HOT Trial: Local sweat rates for the upper back and forearm were not obtained for one participant, and another had an exercise time under 30 min, therefore, data were analysed

for 6 out of 8 MS participants. Local sweat rates of the upper back after 30 min (P = 0.78) and 60 min of exercise (P = 0.59) were not different between groups (Table 2). Similarly, local sweat rates of the forearm after 30 min (P = 0.06) and 60 min of exercise (P = 0.08) were not different between groups (Table 2). The change in mean body temperature onset threshold for the forearm and upper back LSR and the subsequent thermosensitivity are displayed in Figure 3. Onset and thermosensitivity calculations for local sweat rate were performed on 7 out of 8 MS participants for both the forearm and upper back local sweat rate because local sweat rate data was not collected on 1 participant. The change in mean body temperature for the onset of forearm sweating was greater (P = 0.04) in the MS compared to the CON group but this difference was not observed for upper back sweating (P = 0.12). The time at onset was greater in the MS group for forearm (MS: 13 ± 7 min; CON: 6 ± 3 min; P = 0.02) but not the upper back (MS: 10 ± 7 min; CON: 7 ± 4 min; P = 0.29). The thermosensitivity were not different between groups for either the forearm (MS: 1.01 ± 0.43 $mg \cdot min^{-1} \cdot cm^{-2} \cdot °C$; CON: 1.59 ± 1.24 $mg \cdot min^{-1} \cdot cm^{-2} \cdot °C$; P = 0.26) or the upper back (MS: 1.37 ± 1.66 $mg \cdot min^{-1} \cdot cm^{-2} \cdot °C$; CON: 1.06 ± 0.69 $mg \cdot min^{-1} \cdot cm^{-2} \cdot °C$; P = 0.63).

Heart rate

30°C trial: Heart rate was not different between groups after 30 min (MS: 99 ± 14 bpm, *n* = 14; CON: 106 ± 26 bpm, *n* = 14; P = 037) and 60 min of exercise (MS: 101 ± 18 bpm, *n* = 9; CON (102 ± 35 bpm, *n* = 14; P = 0.91).

35°C trial: Heart rate was not different between groups after 30 min (MS:101 ± 6 bpm, *n* = 7; CON: 103 ± 15 bpm, *n* = 8; P = 0.62) or 60 minutes of exercise (MS: 102 ± 8 bpm, *n* = 7; CON: 101 ± 23 bpm, *n* = 8; P = 0.89).

Discussion

Our collaborative group has recently shown that compared to healthy controls, people with MS demonstrate a blunted sudomotor, but not vasomotor response during moderate

intensity exercise at a fixed metabolic H_{prod} (4.5 $W \cdot kg^{-1}$) in a temperate climate (25°C, 30% RH) (1). However, the blunted sweat response with MS was not large enough to alter the rise in rectal and esophageal temperature in that study, possibly due to the relatively cool conditions tested (1). The findings of the present study extend our previous investigations to much hotter conditions (up to T_a=35°C). The ability of people with MS to complete exercise at a fixed heat production in warm (30°C, 30% RH) or hot (35°C, 30% RH) environments in this study was compromised compared to healthy controls. Furthermore, onset of sweating in people with MS was delayed in both a warm (30°C) and hot (35°C) environment, however decrements were only observed on the forearm, but not the upper back. Nevertheless, similar rises in rectal temperature were observed between the MS and CON group throughout 60 minutes of exercise in both the WARM and HOT trials, showing that at high air temperatures, thermoregulatory impairments in people with relapsing-remitting MS are not sufficient to accelerate body heating during exercise. Even for those participants who could not complete 60 minutes of exercise, the time required to reach a rise in rectal temperature of 0.2˚C, which is the theoretical lower limit at which Uhthoff's phenomenon is observed, was the same compared to the CON participants in both the WARM and HOT trials. Taken together, these findings suggest that temperature-induced MS symptoms (i.e., Uhthoff's phenomenon) during exercise in warm and hot environments may occur prior to potential impairments in thermoregulatory function in MS can be observed.

Previously our lab has demonstrated rectal temperature is not different between MS and CON groups following 60 min of exercise in a thermoneutral (25˚C) environment (1). However, despite participants exercising in a cooler environment than in the current study, the rise in rectal temperature for the MS participants was greater (~0.8˚C) in the thermoneutral environment compared to the 30˚C (~0.45˚C rise in rectal temperature) and 35˚C (0.59˚C rise in rectal temperature) environment. It is likely that the lower change in

rectal temperature observed in the current study is due to the lower workload. It is possible that a greater change in core temperature between the MS and CON groups may have been observed if participants were working at a greater external workload. However, the fact that even when working at 4 $W \cdot kg^{-1}$ over 40% of MS participants could not complete exercise in the 30˚C trial despite no difference in core temperature between groups, further confirms for some people with MS, heat-related fatigue reflects an inherent sensitivity to smaller rises in core temperature prior to any initiation of thermoregulatory response that may be impaired. Sweat rates are predominantly determined by the amount of evaporation required to maintain heat balance (6), which by design was fixed between the MS and CON groups in the present study (Table 1). A rise in deep and peripheral tissue temperature during exercise in the heat activates local temperature-sensitive neurons that relay afferent information to the preoptic area of the anterior hypothalamus (33). Neuronal firing rates are subsequently altered to elicit an efferent response such as an increase in sudomotor output. The present observation of a delayed onset of sweating in the MS group indicates that pathophysiological events within the CNS with MS may in some way impair this process. Indeed, it is known that injured neurons cause a reduction in conduction velocity and depress the efficiency of a postsynaptic response relative to a presynaptic stimulus (4, 11, 15). Noronha (29) and Andersen (3) reported qualitative evidence of sudomotor impairments in MS patients during a bout of passive heating using the quinizarin powder test method. According to both studies (3, 29) intravenous pilocarpine (a sympathetic cholinergic agonist) adequately increased whole body sweating rate in patients who previously demonstrated a blunted sweating response to passive heating. They postulated that a likely cause of sudomotor dysfunction for people with MS is the damage to neurons within the descending sudomotor pathway. Despite a delayed onset of sweating on the forearm, MS participants were still able to achieve the required steady state sweat rate after 30 and 60 minutes of exercise which is consistent with previous work by our

362 laboratory (1). As such, demyelination of neurons potentially only transiently weakens the
363 temporal sudomotor response to mild exercise in 30°C and 35°C environments.

364 It is widely acknowledged that local sweat rate can vary considerably across different
365 regions of the body in healthy individuals (19, 22, 34), however, it is unclear why a delayed
366 onset of sweating was observed on the forearm only and not the upper back in people with
367 MS. Demyelination and scarring within the CNS is highly variable in terms of location and
368 severity (29). While we can only speculate, it is possible that a blunted sudomotor response
369 on the forearm is due to a) demyelination specific regions within the CNS and/or b) local
370 sweat gland atrophy. Although a delayed onset of sweating was observed on the forearm in
371 the MS compared to CON group, there were no differences in the onset of sweating between
372 the forearm and upper back within the MS group for both the WARM and HOT trial.
373 Therefore, these data may not necessarily indicate regional specificity in LSR differences in
374 people with MS. Notably, findings from our previous work regarding the LSR onset and
375 thermosensitivities are not consistent with the current study. For example, our previous work
376 demonstrated that LSR thermosensitivity was blunted in people with MS, whereas findings
377 from the current study demonstrate a delayed change in mean body temperature and onset
378 time for LSR, with no differences in thermosensitivities between the MS and CON
379 participants. This is possibly because in the current study, we investigated the onset and
380 thermosensitivities of individual sites (i.e. forearm and upper back) separately, whereas in our
381 previous work, LSR of the forearm and upper back were combined, potentially diluting any
382 regional-specific differences in sweating onset and thermosensitivities (1). Collectively, these
383 findings suggest that people with MS do demonstrate some sudomotor impairments,
384 however, due to the heterogeneity of MS, these impairments may present differently.
385 Nevertheless, irrespective of the underlying cause, MS participants were still able to achieve
386 similar steady state sweat rates compared to the CON group in both the current study and

from our previous investigations (1). Given the rise in core temperature was similar between MS and CON participants, any differences in evaporative heat loss due to a delayed onset of sweating at the forearm seems to be minimal and/or possibly compensated for greater sweating/evaporation at other body regions that were not measured.

In both the WARM and HOT trials, it was observed that only 9 out of 16 and 7 out of 8 MS participants were able to complete 60 minutes of cycling, respectively. It has previously been reported that people with MS have been unable to complete 60 min of exercise in a 25°C (1) and 30°C (9) environment, possibly due to heat-related fatigue. All MS participants stopped exercise due to volitional exhaustion. Although the reason for this exhaustion is unclear, given the similar aerobic capacity between the MS (2.4 $L \cdot min^{-1}$) and CON (2.8 $L \cdot min^{-1}$) groups it is possible that the high dropout rate for the MS participants is the result of a reduced exercise capacity due to heat sensitivity, independently of increases in core temperature. For those who could not complete 60 minutes of cycling in both the WARM and HOT trials, the final change in core temperature was within the threshold of Uhthoff's phenomenon (0.2-0.5°C), irrespective of exercise time (Figure 1 and 2). However the time it took to reach a rise in core temperature of 0.2°C was not different between the MS and CON groups, nor was the final change in core temperature following 30 and 60 minutes of cycling in both the WARM and HOT trials. Early research investigating Uhthoff's phenomenon ex vivo and in animal models, suggested that increases in temperature of ~0.5˚C of a demyelinated nerve reduces its conduction velocity by a greater amount compared to a myelinated nerve (14) potentially contributing to heat-related symptoms. More recently, White et al (38) reported an increase in core temperature of 0.6˚C in people with MS reduced conduction velocity, increased fatigue perception and impairments in force production to a greater extent compared to healthy controls for the same rise in core temperature. On the other hand, White et al (39) also demonstrated for the same rise in core temperature (~0.5˚C)

work output in people with MS was greater following a bout of whole-body cooling (baseline core temperature = 36.4˚C) compared to no cooling (baseline temperature = 37.0˚C). Furthermore, Chaseling et al (9) also demonstrated a 30% increase in exercise time in people with MS with ingestion of cold water (1.5˚C), despite no difference in the rise of core temperature compared to ingestion of thermoneutral water (37˚C). Collectively these studies suggest that a definitive rise in core temperature of 0.2-0.5˚C may not exclusively influence heat-related symptoms for people with MS, and perhaps anticipatory or psychological factors may also play a role (24). For example, it is possible that some participants stopped exercise prematurely in their first trial in anticipation of the onset of any heat-related symptoms, which may explain why some MS participants were able to complete exercise in the HOT compared to WARM trial. It is also possible given the heterogeneity of the disease (lesion location and severity), some participants may be less sensitive to the heat which could explain why some MS participants were able to complete 60 minutes of exercise while others could not. Lastly, it is possible in the current study, people with MS stopped exercising at a core temperature of 0.2-0.5˚C due to a decreased conduction velocity, thereby increasing perceptions of fatigue and reductions in force output. However, further research is warranted to completely understand this.

Limitations

It is unclear if whole body sweat losses were different between the MS and CON group as this was not measured in the present study. However, the primary concern for people with MS during heat exposure is heat-related fatigue, which is presently believed to be tied to the rise in core temperature (7). It follows that irrespective of whether whole-body sweating was different in the MS group or not, any MS-related reductions in sudomotor output due to a delayed onset of sweating were apparently insufficient to alter core temperature. Measures of skin blood flow were not reported in this study, and therefore, it is

unclear whether similarities in core temperature were due to differences in baseline skin blood flow as indicated by higher baseline skin temperature in the MS group. However it has previously been documented (2, 8) that people with MS do not demonstrate an impairment in vasomotor function. For example, Allen et al (2) reported differences in sweat output, but not cutaneous vascular conductance in MS compared to CON groups following a bout of whole body heating in a 48°C water perfused suit. It therefore seems that pathways within the sympathetic nervous system that are impacted by MS are restricted to the sudomotor apparatus (20).

The sample size of this study is small because of the high rate of dropouts during exercise within the MS group, which is an inherit limitation within the MS population. Nevertheless, according to Cohen's *d* (10) the magnitude of differences for the change in T_{re} in the 30°C (d = 0.25) and 35°C (d = 0.24) further demonstrate a small difference between the MS and CON group means. Another possible limitation is the use of rectal instead of esophageal temperature to assess thermoeffector control. Obtaining esophageal temperature within this specific population proved difficult. Esophageal temperature measures were only obtained in 8 MS and 6 CON participants in the 30°C trials and in no MS or CON participants in the 35°C trials. As such, an insufficient number of esophageal temperature values were attained to conduct an appropriately powered thermoeffector analysis. Furthermore, while all 16 MS participants who participated in the WARM trial were invited to return for the HOT trial, only 8 of these participants accepted. Only 5 of the 9 MS participants who completed 60 minutes of exercise in the WARM trial returned to participate in the HOT trials. While 1 participant was unable to complete 60 minutes of exercise in both the WARM and HOT trials, 2 participants were able to complete 60 minutes of exercise in the HOT but not the WARM trial. While it is possible that there was some self-selection bias among the participants who participated in both the WARM and HOT trials, it is also

possible that there was a learning effect given that all WARM trials were conducted before the HOT trials.

Lastly, the results from this study are only limited to people with relapsing remitting MS (RRMS). While people with RRMS make up for 80% of people diagnosed with MS, it is unclear whether the results of the current study would translate to people with secondary and/or primary progressive MS.

Conclusion

The ability of people with MS to complete exercise at a fixed heat production in a warm (30°C, 30% RH) or hot (35°C, 30% RH) environment in this study was compromised compared to healthy controls despite similar increases in core temperature. Furthermore, despite a delayed onset of sweating on the forearm in the MS group, local sweat rates and the change in core temperature were similar between the MS and CON group. These findings suggest that temperature-induced MS symptoms (i.e. Uhthoff's phenomenon) that occur during exercise in warm and hot environments are not likely the result of a disproportionately greater rise in core temperature due to thermoregulatory impairments. Given these findings, future research should focus on practical and economical cooling strategies to overcome heat-related fatigue and MS symptom onset during physical activity and/or heat exposure in warm and hot environments. Future research is also needed to identify whether these findings translate to people with a greater MS disease severity.

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Conflicts of Interest

The authors have no conflicts of interest to disclose.

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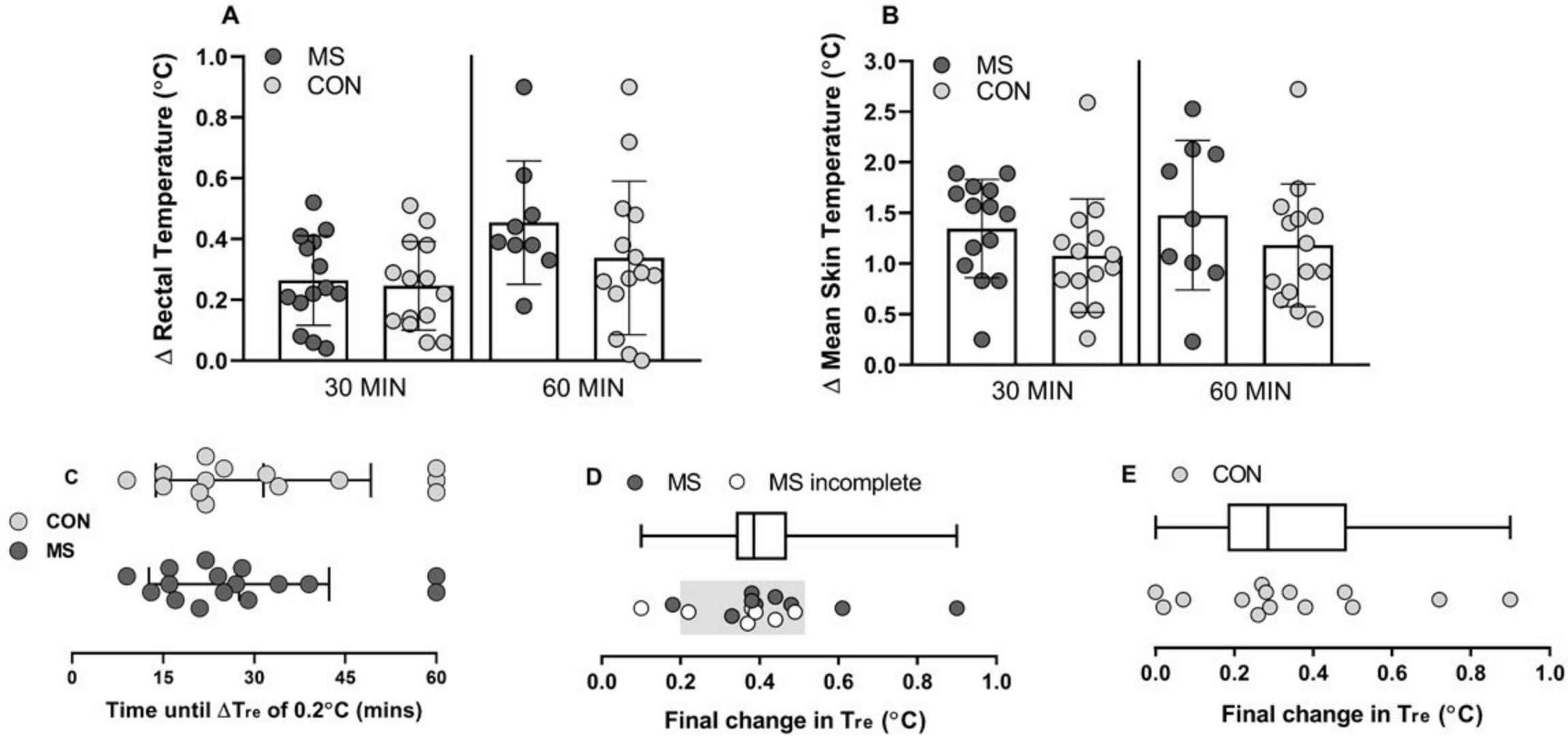
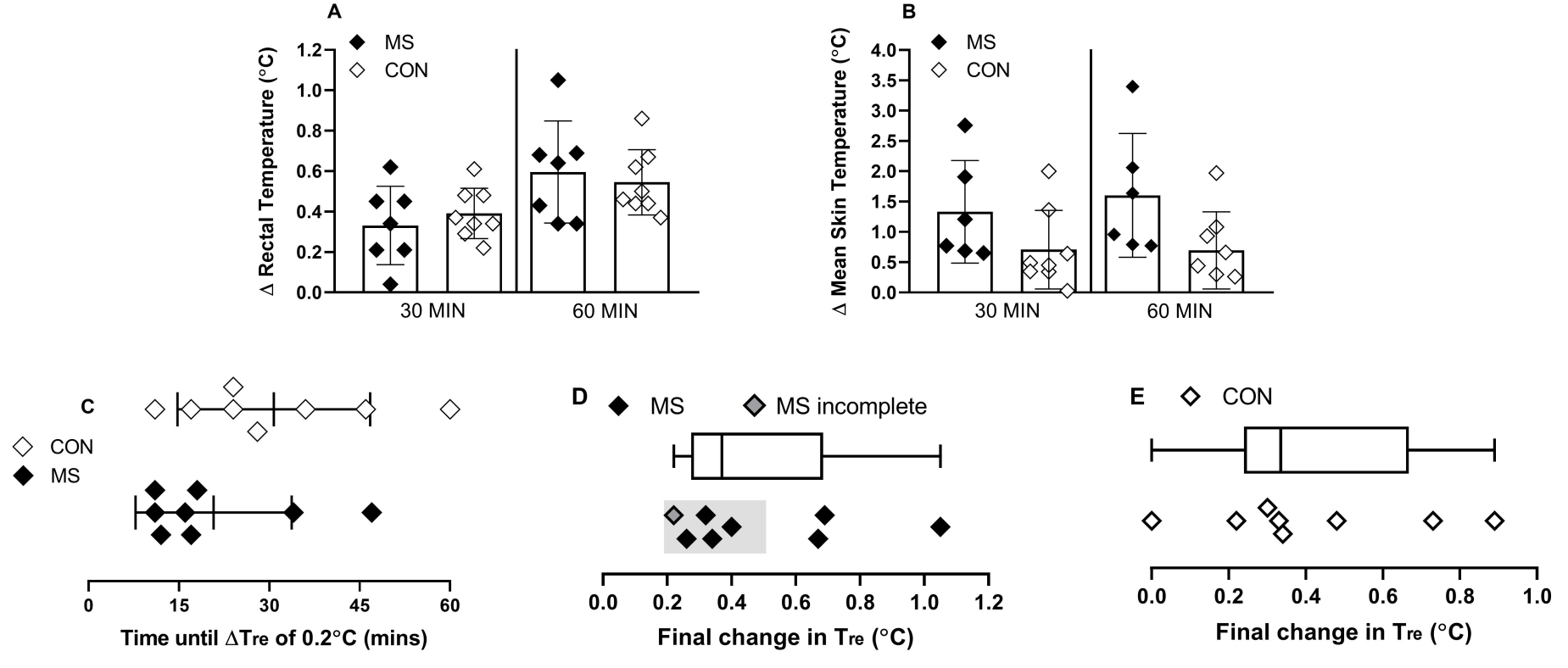
Figure Legends

Figure 1A-E. The upper panel shows individual values for the change in rectal (**A**) and skin (**B**) temperature for the MS (dark grey circles) and CON (light grey circles) group following 30 (MS: n = 14; CON: n = 14) and 60 (MS: n = 9; CON: n = 14) minutes of exercise in the WARM trial. The lower panel shows the time taken to reach a rise in rectal temperature of 0.2°C (**C**) in the WARM trial for the MS (dark grey circles) and CON (light grey circles). The change in rectal temperature at the end of exercise in the WARM trial for MS group who completed exercise (**D**; dark grey circles), who could not complete 60 minutes of exercise (white circles) and for the CON group (**E**; light grey circles), all of which completed 60 minutes of exercise. The grey shading on panel D demonstrates the change in rectal temperature at which Uhthoffs phenomenon is reportedly induced (17).

Figure 2 A-E. The upper panel shows individual values for the change in rectal (**A**) and skin (**B**) temperature for the MS (white diamonds) and CON (black diamonds) group following 30 (MS: n = 7; CON: n = 8) and 60 (MS: n = 7; CON: n = 8) minutes of exercise in the HOT trial. The lower panel shows the time taken to reach a rise in rectal temperature of 0.2°C (**C**) in the HOT trial for the MS (black diamonds) and CON (white diamonds). The change in rectal temperature at the end of exercise in the HOT trial for MS group who completed exercise (**D**; black diamonds), who could not complete 60 minutes of exercise (**D**; light grey diamond) and for the CON group (**E**; white diamonds), all of who completed 60 minutes of exercise. The grey shading on panel D demonstrates the change in rectal temperature at which Uhthoffs phenomenon is reportedly induced (17).

Figure 3A-D. Mean and 95% confidence intervals for the change in mean body temperature in the WARM trial (circles) plotted against the rise in upper back (**A**) and forearm (**B**) local sweat rate (LSR) during the and HOT trial (diamonds) fir the upper back (**C**) and forearm (**D**). Asterisk denotes $P < 0.05$.


A
Δ Rectal Temperature (°C)
1.0
0.8
0.6
0.4
0.2
0.0
MS
CON
30 MIN
60 MIN
B
Δ Mean Skin Temperature (°C)
3.0
2.5
2.0
1.5
1.0
0.5
0.0
MS
CON
30 MIN
60 MIN
C
CON
MS
0
15
30
45
60
Time until ΔTre of 0.2°C (mins)
D
MS
MS incomplete
0.0
0.2
0.4
0.6
0.8
1.0
Final change in Tre (°C)
E
CON
0.0
0.2
0.4
0.6
0.8
1.0
Final change in Tre (°C)


A
MS
CON
Δ Rectal Temperature (°C)
1.2
1.0
0.8
0.6
0.4
0.2
0.0
30 MIN
60 MIN
B
MS
CON
Δ Mean Skin Temperature (°C)
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
30 MIN
60 MIN
C
CON
MS
0
15
30
45
60
Time until ΔTre of 0.2°C (mins)
D
MS
MS incomplete
0.0
0.2
0.4
0.6
0.8
1.0
1.2
Final change in Tre (°C)
E
CON
0.0
0.2
0.4
0.6
0.8
1.0
Final change in Tre (°C)

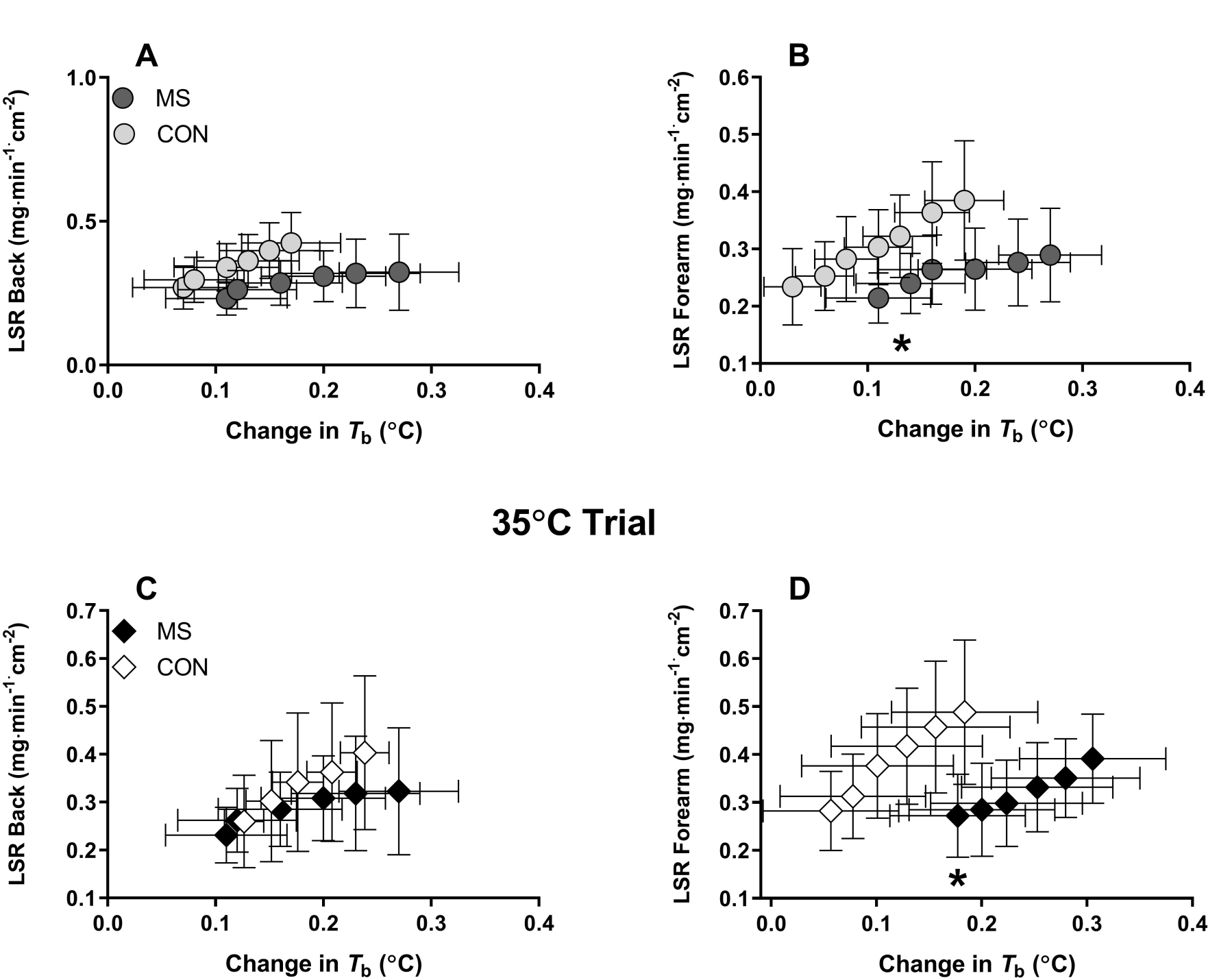

30°C Trial
A
MS
CON
LSR Back (mg·min-1·cm-2)
Change in Tb (°C)
B
LSR Forearm (mg·min-1·cm-2)
Change in Tb (°C)
*
35°C Trial
C
MS
CON
LSR Back (mg·min-1·cm-2)
Change in Tb (°C)
D
LSR Forearm (mg·min-1·cm-2)
Change in Tb (°C)
*

Table 1. Participant characteristics and workloads

	WARM			HOT		
	MS (n=16)	***CON (n=14)***	***P value***	***MS (n=8)***	***CON (n=8)***	***P value***
Sex	8F / 8M	8F / 6M		3F / 5M	4F / 4M	
Age (y)	47 ± 8	43 ± 11	0.31	44 ± 7	44 ± 12	0.92
Weight (kg)	77.6 ± 14.0	78.6 ± 17.0	0.86	82.3 ± 17	81.2 ± 21.1	0.91
Height (m)	1.7 ± 0.1	1.7 ± 0.1	0.91	1.7 ± 0.1	1.7 ± 0.1	0.98
VO_{2max} ($ml \cdot min^{-1} \cdot kg^{-1}$)	30.1 ± 11.1	35.6 ± 8.4	0.19	37.0 ± 9.8	33.8 ± 7.1	0.97
EDSS	2.7 ± 0.8	-	-	2.7 ± 0.4	-	-
Disease duration (y)	11 ± 10 y	-	-	8 ± 8 y	-	-
Baseline T_{re} (˚C)	36.89 ± 0.35	37.03 ± 0.39	0.39	36.80 ± 0.44	36.85 ± 0.28	0.83
Baseline HR (bpm)	73 ± 11	77 ± 21	0.64	73 ± 11	76 ± 10	0.71
E_{req} ($W \cdot m^{-2}$)	115 ± 21	128 ± 23	0.12	169 ± 48	169 ± 44	0.99
	External Workloads					
	MS (n=16)	***CON (n=14)***	***P value***	***MS (n=8)***	***CON (n=8)***	***P value***
W	49 ± 15	55 ± 21	0.32	52 ± 19	58 ± 21	0.60
$W \cdot m^{-2}$	151 ± 29	166 ± 23	0.14	184 ± 58	171 ± 35	0.61
$W \cdot kg^{-1}$	3.7 ± 0.7	4.1 ± 0.6	0.11	4.4 ± 1.4	4.2 ± 0.7	0.69

MS: multiple sclerosis; CON: control; *n*: number of participants; y: year; kg: kilograms; m: meters; ml: millilitres; m^{-2}: per meter squared; T_{re}: rectal temperature; HR: heart rate; E_{req}: evaporative requirement

Table 2. Sweat rates for the MS and CON groups in both the WARM and HOT trials.

	WARM			HOT		
Forearm	***MS***	***CON***	***P value***	***MS***	***CON***	***P value***
30-min LSR (mg·min^{-1}·cm^{-2})	0.35 ± 0.18 *(n=14)*	0.44 ± 0.19 *(n=14)*	0.19	0.50 ± 0.15 *(n=6)*	0.68 ± 0.16 *(n=8)*	0.06
60-min LSR (mg·min^{-1}·cm^{-2})	0.45 ± 0.17 *(n=9)*	0.48 ± 0.18 *(n=14)*	0.69	0.55 ± 0.11 *(n=6)*	0.68 ± 0.13 *(n=8)*	0.08
Upper back						
30-min LSR (mg·min^{-1}·cm^{-2})	0.38 ± 0.29 *(n=13)*	0.48 ± 0.27 *(n=14)*	0.32	0.63 ± 0.33 *(n=6)*	0.58 ± 0.25 *(n=8)*	0.78
60-min LSR (mg·min^{-1}·cm^{-2})	0.47 ± 0.32 *(n=8)*	0.55 ± 0.25 *(n=14)*	0.54	0.72 ± 0.35 *(n=6)*	0.64 ± 0.24 *(n=8)*	0.59

MS: multiple sclerosis; CON: control; *n*: number of participants; LSR: local sweat rate; mg: milligrams; m^{-2}: per meter squared.