Cold Water Ingestion Improves Exercise Tolerance of Heat-Sensitive People with MS

GEORGIA K. CHASELING[1], DAVIDE FILINGERI[1,2], MICHAEL BARNETT[3], PHU HOANG[4], SCOTT L. DAVIS[5,6], and OLLIE JAY[1,7]

[1]Thermal Ergonomics Laboratory, Faculty of Health Sciences, University of Sydney, Lidcombe, NSW, AUSTRALIA; [2]Environmental Ergonomics Research Centre, Loughborough University, Leicestershire, UNITED KINGDOM; [3]Brain and Mind Research Centre, Sydney Medical School, University of Sydney, Camperdown, NSW, AUSTRALIA; [4]Neuroscience Research Australia, Sydney, NSW, AUSTRALIA; [5]Applied Physiology and Wellness Southern Methodist University, Dallas, TX; [6]Neurology and Neurotherapeutics, University of Texas Southwestern Medical Center, Dallas, TX; and [7]Charles Perkins Centre, University of Sydney, Camperdown, NSW, AUSTRALIA

ABSTRACT

CHASELING, G. K., D. FILINGERI, M. BARNETT, P. HOANG, S. L. DAVIS, and O. JAY. Cold Water Ingestion Improves Exercise Tolerance of Heat-Sensitive People with MS. *Med. Sci. Sports Exerc.*, Vol. 50, No. 4, pp. 643–648, 2018. **Purpose**: Heat intolerance commonly affects the exercise capacity of people with multiple sclerosis (MS) during bouts of hot weather. Cold water ingestion is a simple cooling strategy, but its efficacy for prolonging exercise capacity with MS remains undetermined. We sought to identify whether cold water ingestion blunts exercise-induced rises in body temperature and improves exercise tolerance in heat-sensitive individuals with MS. **Methods**: On two separate occasions, 20 participants (10 relapsing–remitting MS (expanded disability status scale, 2–4.5); 10 age-matched healthy controls) cycled at ~40% $\dot{V}O_{2max}$ at 30°C and 30% relative humidity until volitional exhaustion (or a maximum of 60 min). Every 15 min, participants ingested 3.2 mL·kg^{-1} of either 1.5°C (CLD) or 37°C (NEU) water. Rectal (T_{re}) temperature, mean skin (T_{sk}) temperature, and heart rate (HR) were measured throughout. **Results**: All 10 controls but only 3 of 10 MS participants completed 60 min of exercise in NEU trial. The remaining 7 MS participants all cycled longer ($P = 0.006$) in CLD (46.4 ± 14.2 min) compared with NEU (32.7 ± 11.5 min), despite a similar absolute T_{re} (NEU: 37.32°C ± 0.34°C; CLD: 37.28°C ± 0.26°C; $P = 0.44$), change in T_{re} (NEU: 0.38°C ± 0.21°C; CLD: 0.34°C ± 0.24°C), absolute T_{sk} (NEU: 34.48°C ± 0.47°C; CLD: 34.44°C ± 0.54°C; $P = 0.82$), and HR (NEU: 114 ± 20 bpm; CLD: 113 ± 18 bpm; $P = 0.38$) for the same exercise volume. **Conclusions**: Cold water ingestion enhanced exercise tolerance of MS participants in the heat by ~30% despite no differences in T_{re}, T_{sk} or HR. These findings support the use of a simple cooling strategy for mitigating heat intolerance with MS and lend insight into the potential role of cold-afferent thermoreceptors that reside in the abdomen and oral cavity in the modulation of exercise tolerance with MS in the heat. **Key Words:** UHTHOFF'S PHENOMENON, FATIGUE, PHYSICAL ACTIVITY, HEAT SENSITIVITIES

It is well documented that during physical activity and/or exposure to hot environments, individuals with multiple sclerosis (MS) can experience heat intolerance (1), which is typically characterized by a rapid onset of fatigue (2). Despite its prevalence, the underlying mechanisms responsible for this phenomenon (Uhthoff's) remain somewhat inconclusive. Nevertheless, since the work by Davis and Jacobson (3) and Rasminsky (4), it has been generally considered that a rise in core temperature of ~0.5°C induces heat-related fatigue secondary to slowed or blocked conduction of demyelinated nerves. As such, people with MS are regularly advised to remain indoors during hot weather and limit physical activity, which can substantially affect employability and/or quality of life (5).

Some cooling strategies administered before and/or during heat exposure successfully mitigate the development of heat-related fatigue in people with MS (6). However, these methods, such as 30 min of lower body cold water immersion (7) or donning an ice vest (8), can prove impractical in the context of everyday life and incompatible with many jobs. Cold fluid ingestion during physical activity is a simple strategy that is presently recommended by, among others, the

Address for correspondence: Ollie Jay, Ph.D., Thermal Ergonomics Laboratory, Faculty of Health Sciences, University of Sydney, Lidcombe, NSW 2141, Australia; E-mail: ollie.jay@sydney.edu.au.
Submitted for publication July 2017.
Accepted for publication November 2017.

0195-9131/18/5004-0643/0
MEDICINE & SCIENCE IN SPORTS & EXERCISE®

DOI: 10.1249/MSS.0000000000001496

National MS Society (9), the MS Society (United Kingdom) (10), and MS Queensland (Australia). Indeed, drinking cold water could effectively mitigate elevations in core temperature and associated fatigue because it introduces an internal heat loss avenue (via conduction) in addition to evaporative and convective heat loss from the skin surface. Nevertheless, to the best of our knowledge, no study has yet assessed whether cold fluid ingestion during exercise in the heat can mitigate rises in core temperature and accompanying fatigue in people with MS.

The aim of this study was to examine the effect of ingesting cold (1.5°C) compared with thermoneutral (37°C) water on exercise tolerance at a fixed low relative intensity (~40% $\dot{V}O_{2max}$), and the elevation in core temperature of heat-sensitive relapsing–remitting MS participants in a warm (30°C) environment. It was hypothesized that with thermoneutral water ingestion, exercise time would be shorter for MS compared with age-matched control participants. It was also hypothesized that compared with thermoneutral water ingestion, exercise time of MS participants would be extended with cold water ingestion because of a blunted rise in core temperature.

METHODS

Participants. Twenty participants, 10 individuals with relapsing–remitting MS, an expanded disability status scale range of 2–4.5 (1, no disability, slight dysfunction in one area; 4.5, significant disability with some limitation of daily activities [11]), and 10 age-, height-, and weight-matched healthy controls with a similar estimated aerobic fitness (Table 1) were recruited for this study on the basis of a power calculation (Heinrich-Heine-Universität Düsseldorf, Germany) using an α of 0.05, a $1 - \beta$ of 0.95, and an effect size of 1.55 for the main outcome variable of exercise performance with cold fluid ingestion in the heat (12). All MS participants had a self-reported intolerance to the heat. All participants were informed of any risks associated with the study before providing written informed consent. The study was approved by the University of Sydney Human Research Ethics Committee (HREC No. 2016/214).

Measurements. Rectal (T_{re}) temperature was measured using a general-purpose pediatric thermistor (TM400; Covidien, Mansfield, MA) self-inserted to a depth of 12 cm past the anal sphincter. Skin temperature was measured at four sites on the right side using thermistors (Concept Engineering, Old Saybrook, CT) attached with hypoallergenic tape (Blenderm; 3M, Sydney, NSW, Australia). Mean skin temperature (T_{sk}) was estimated using a weighted average in accordance with Ramanathan (13). All thermometric measurements were sampled at 5-s intervals (NI cDAQ-91722 module; National Instruments, Austin, TX) and displayed in real-time using LabView (v7.0).

TABLE 1. Participant characteristics.

	MS (n = 10)	CON (n = 10)	P
Sex	4 M/6 F	5 M/5 F	
Age, yr	47 ± 9	44 ± 6	0.35
Weight, kg	82.5 ± 15.7	76.1 ± 15.7	0.41
Height, m	1.7 ± 0.1	1.7 ± 0.1	0.64
BSA, m^2	1.9 ± 0.2	1.9 ± 0.3	0.57
$\dot{V}O_{2max}$, $L \cdot min^{-1}$	2.4 ± 1.4	2.9 ± 0.9	0.27

BSA, body surface area; F, female; M, male; $\dot{V}O_{2max}$, estimated maximum rate of oxygen consumption; MS, multiple Sclerosis group; CON, control group.

Heart rate (HR) was measured using a wireless six-lead ECG (Quark T12x Asia Pacific PTY, Sydney, NSW, Australia) monitoring system. Electromagnetic gel was applied to four foam electrodes, which were then placed under the right and left clavicle, the right and left sixth intercostal, and then covered with tape. Before the placement of the electrodes, the skin surface was shaved and cleaned with alcohol to ensure minimal signal interference.

Protocol. Each participant completed one preliminary trial and two experimental trials. During the preliminary trial, participants performed an incremental submaximal exercise protocol (beginning at 45 W increasing 20 W every 3 min for a total of four stages) on a semirecumbent cycle ergometer (Corival Recumbent; Lode BV, Groningen, the Netherlands) in a 20°C room. HR and oxygen consumption (Quark CPET, Cosmed; Asia Pacific PTY, Sydney, NSW, Australia) were measured during each 3-min stage. 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) (14) to determine $\dot{V}O_{2max}$ using the Young Men's Christian Association (YMCA) protocol (15). Individualized workloads (40% of predicted $\dot{V}O_{2max}$) were calculated for the subsequent experimental trials.

Participants completed two experimental trials separated by a minimum of 48 h in a climate-controlled chamber at 30°C and 30% relative humidity exercising until (i) volitional exhaustion or (ii) a maximum of 60 min. Participants were required to complete both trials at the same time of day to avoid any disparity in resting core temperature due to circadian rhythm. If any participant presented with a resting T_{re} more than 0.2°C away from their previous trial, the trial would not commence. Participants cycled on a semirecumbent cycle ergometer at a fixed relative intensity (~40% $\dot{V}O_{2max}$) and consumed a 3.2 $mL \cdot kg^{-1}$ aliquot of water (in <1 min) after the 15th, 30th, and 45th minutes of exercise. Participants consumed either thermoneutral (37°C) water (NEU) or cold (1.5°C) water (CLD) during each experimental trial. The presentation of trials was balanced between participants. The temperature of the water ingested in the NEU trial was maintained using a hydrostatic-controlled water bath (DA05A; Polyscience, Niles, IL). The temperature of the water ingested in the CLD trial was maintained in a thermos filled with ice. Immediately before fluid ingestion, the temperature of the fluid was verified using a factory-calibrated glass precision thermometer (Durac Plus, Blue Spirit; Cole-Parmer, Vernon Hills, IL) with a certified range between −1°C and +100°C and with an accuracy of ±0.1°C, and the required mass of water was measured using a balance with a precision of 0.1 g (MS12001L; Mettler Toledo, Columbus, OH). Breath-by-breath oxygen consumption was continuously monitored to ensure that participants were exercising at the target rate of oxygen consumption associated with a fixed estimated relative intensity throughout both trials.

Statistical analysis. A two-way mixed ANOVA using the repeated factor of water temperature (CLD, NEU) and the non–repeated factor of group (MS participants (MS), controls (CON)) was used to examine exercise time to exhaustion (with a maximum of 60 min). The T_{re}, T_{sk}, and HR at the time of exhaustion in the shortest trial for each individual were also compared with the same time point in the other trial within the MS and CON groups using paired-sample *t*-tests. A within-group analysis of the effect of water temperature was used for these measures because of different exercise times between the CON and MS groups. Furthermore, within the CLD trial for the MS group, the T_{re} and T_{sk} values at the same time as the time of exhaustion in the NEU trial were compared with the values at end-exercise using a paired-sample *t*-test. Finally, an independent-samples *t*-test was used to examine HR between CON and MS participants at 30 min of exercise for both the NEU and CLD trials. All statistical analyses were performed using GraphPad Prism (v6.0, LA Jolla, CA).

RESULTS

Exercise time was shorter in the MS group compared with the CON group ($P = 0.002$); however an interaction was observed between water temperature and group ($P < 0.001$). Specifically, all 10 CON participants completed 60 min of exercise in both the NEU and CLD trials (Fig. 1). On the other hand, although only 3 of 10 participants in the MS group completed 60 min of exercise in the NEU trial, 5 of 10 MS participants completed 60 min of exercise in the CLD trial, and all 7 MS participants who could not complete the NEU trial cycled longer (Fig. 1) in the CLD trial (NEU: 32.7 ± 11.5 min; CLD: 46.4 ± 14.2 min; $P = 0.006$). After 30 min of exercise, HR responses in the NEU trial (MS: 104 ± 15 bpm; CON: 96 ± 10 bpm; $P = 0.22$) and the CLD trial (MS: 103 ± 17 bpm; CON: 92 ± 12 bpm; $P = 0.17$) were not different.

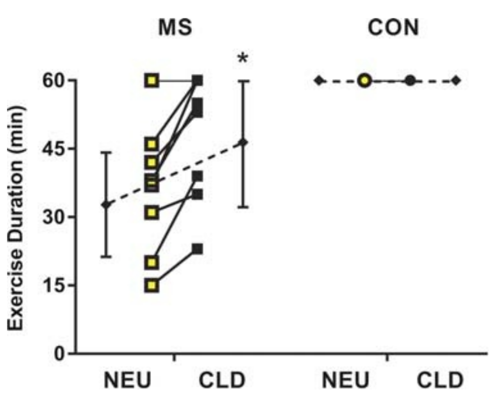

FIGURE 1—Individual data and group means (with SD) at the end of exercise in NEU (*yellow*) trial compared with the same time point in the CLD (*black*) trial for the MS (*squares*) and CON (*circles*) groups. Values given for exercise time to exhaustion with a maximum of 60 min. *$P < 0.05$.

In the MS group, at the time of exhaustion in the NEU trial, change in T_{re} ($P = 0.66$; Fig. 2A), absolute T_{re} ($P = 0.44$; Fig. 2C), T_{sk} ($P = 0.82$; Fig. 2E), and HR (NEU: 114 ± 19 bpm; CLD: 113 ± 17 bpm; $P = 0.45$) were not different after the same amount of exercise time elapsed in the CLD trial. All 7 MS participants who cycled for longer in the CLD trial did so despite T_{re} ($P = 0.001$) and T_{sk} ($P = 0.03$) rising to higher values above baseline when they did stop exercise (ΔT_{re}: 0.26°C ± 0.12°C vs 0.40°C ± 0.23°C; ΔT_{sk}: 1.27°C ± 0.72°C vs 1.47°C ± 0.79°C).

In the CON group, end-exercise (i.e., after 60 min in all CON participants) change in T_{re} ($P = 0.05$; Fig. 2B), absolute T_{re} ($P = 0.25$; Fig. 2D), T_{sk} ($P = 0.33$; Fig. 2F), and HR (NEU: 99 ± 11 bpm; CLD: 99 ± 13; $P = 0.33$) were not different between the NEU and CLD trial.

DISCUSSION

This study is the first to report the efficacy of cold water ingestion for improving exercise tolerance in the heat in people with MS. Importantly, all MS participants who could not complete 60 min of exercise with the ingestion of thermoneutral water (NEU trial) due to volitional exhaustion cycled for longer with ingestion of cold water (CLD trial). However, this longer exercise time in the CLD trial in the MS group was observed despite no influence of a lower ingested water temperature on core and skin temperatures as well as HR.

It is well documented that even small increases in body temperature are associated with a transient worsening of symptoms for individuals with MS (3,4), otherwise known as Uhthoff's phenomenon (16). The development of fatigue, manifested by sensations of tiredness, is a common characteristic associated with Uhthoff's phenomenon and explains the shorter exercise time for 7 of the 10 MS participants who could not complete 60 min of exercise compared with the CON group in the NEU trial. Although we attempted to match groups for aerobic fitness, it is evident that the MS group had an end-exercise HR that was ~15 bpm higher compared with the CON group in both trials. As such, it is likely that $\dot{V}O_{2max}$ of the MS group was slightly overestimated, and therefore, this group worked at a slightly higher relative intensity than the 40% $\dot{V}O_{2max}$ target intensity. Nevertheless, 60 min of exercise at intensities as high as 60% $\dot{V}O_{2max}$ are sustainable even for older individuals (>60 yr) with heart failure in the same environmental conditions as the present study (17). Therefore, the large difference in exercise duration in the MS group compared with the CON group cannot be attributed to any differences in aerobic fitness; rather, they can be primarily ascribed to the well-documented effects of MS on exercise capacity in the heat (1). Furthermore, given that relative exercise intensity and HR were consistent within the MS group

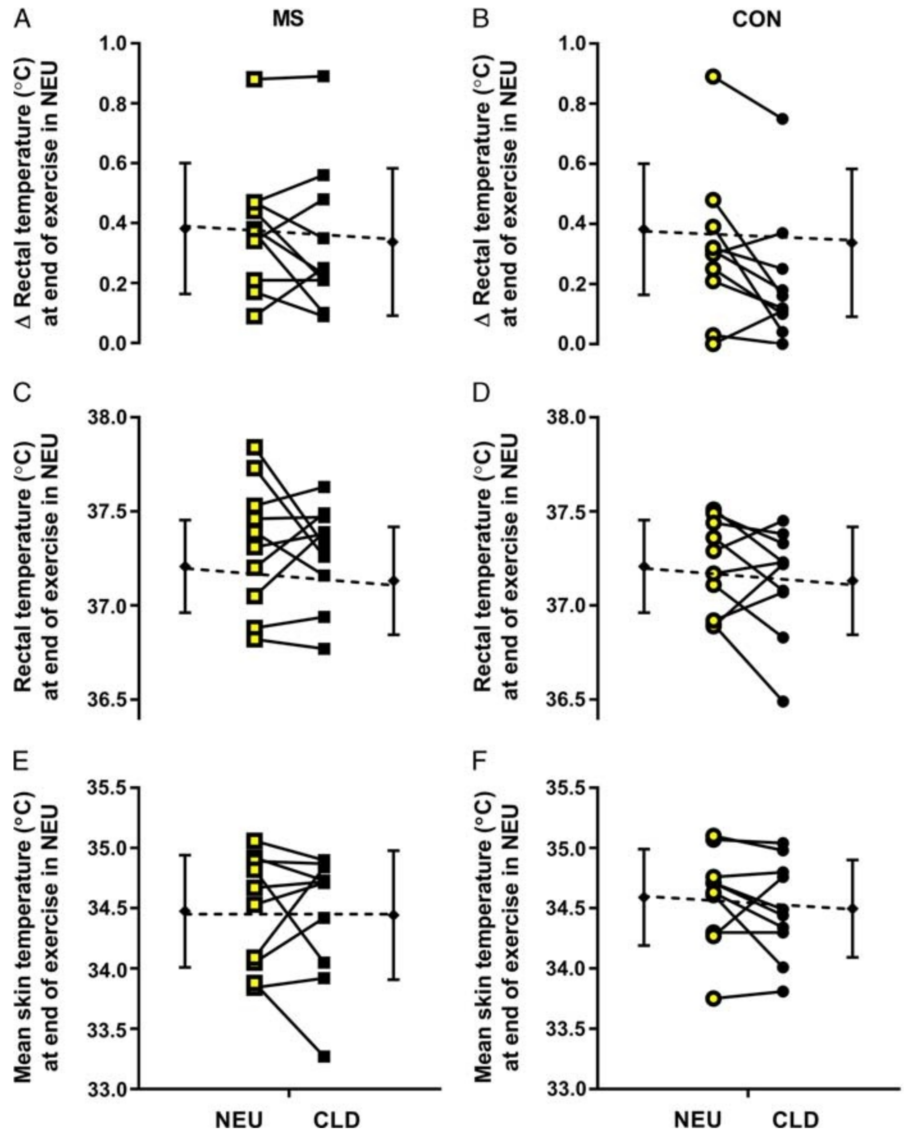

FIGURE 2—Individual data and group means (with SD) at the end of exercise in NEU (*yellow*) trial compared with the same time point in the CLD (*black*) trial for the MS (*squares*) and CON (*circles*) groups. Values given for change in T_{re} from baseline (A–B), absolute T_{re} (C–D), and absolute T_{sk} (E–F). *$P < 0.05$.

between the NEU and CLD trials (NEU: 114 ± 19 bpm; CLD: 113 ± 17 bpm), the main finding that a longer exercise time occurs with cold water ingestion remains independent of any potential differences in fitness.

Within the MS group, the longer exercise time to exhaustion in the CLD trial occurred despite a similar T_{re}, T_{sk}, and HR at a comparable time point (i.e., same volume of exercise) in the NEU trial. In other words, exercise tolerance in the heat was improved in the MS group with cold water ingestion despite no independent influence of ingested water temperature on the development of thermal and cardiovascular strain with exercise time. Indeed, from the time point at which exercise exhaustion was reached in the NEU trial, T_{re} and T_{sk} in the CLD trial continued to rise to higher values by the time exercise stopped. It has been previously suggested that the underlying mechanism responsible for heat-related reduction in exercise performance in healthy athletes is potentially similar to heat sensitivity with MS, but with fatigue onset occurring alongside much smaller rises in body temperature with MS (18). It follows that heat-related decrements in the aerobic performance of healthy athletes can potentially be attenuated via the stimulation of cold-afferent receptors located in the oral cavity (12) and on the skin surface (19), without necessarily lowering core temperature. The present findings potentially support the notion that research examining the mitigation of heat-related decrements in exercise performance in healthy athletes may, at least to an extent, be translatable to the management of Uhthoff's phenomenon in the MS population.

Irrespective of participant group, the same volume of exercise core and skin temperature were altered negligibly by ingested fluid temperature (Figs. 2A–F), despite the greater internal heat loss via conduction with cold fluid ingestion. A recent series of studies (20–22) described fluid temperature–dependent alterations in sweating during exercise that are modulated, independently of core and skin temperatures, by visceral thermoreceptors located in the abdomen. Ultimately, the reduction in evaporative heat loss from the skin surface with cold fluid ingestion was found to approximately counterbalance the greater internal heat loss, thereby yielding similar changes in whole-body heat storage and thus similar changes in core temperature, irrespective of ingested fluid temperature (20). Although sweating rates are not reported in the present study, a similar fluid temperature–dependent modulation of skin surface evaporation could explain the similar levels of thermal strain between the NEU and CLD trials within both the MS and CON groups. Another consideration is that the absolute amount of heat transfer generated by each 3.2 $mL \cdot kg^{-1}$ aliquot of 1.5°C water, even without any parallel alterations of skin surface evaporation, would only be ~35 kJ, which for a 82.5-kg individual with a mean body specific heat of 3.49 $kJ \cdot kg^{-1} \cdot {}^{\circ}C^{-1}$ would yield a reduction in mean body temperature of only ~0.1°C.

Despite the profound effect of regular exercise on the physical and psychological health of individuals with MS (23), it has been reported that people with MS are less physically active (24), partly to avoid a temporary worsening of symptoms associated with an elevation in body temperature. Moreover, heat intolerance has been shown to greatly affect the capacity for many people with MS to remain among the workforce (5). Cold water ingestion is a simple strategy for improving exercise tolerance in the heat, which could be used as an alternative to other less practical but currently recommended cooling strategies such as partial immersion in cold water before heat exposure (7), or donning an ice vest (25). It should be noted though that for individuals with MS susceptible to urinary incontinence, additional fluid ingestion might not prove an optimal solution. Therefore, future research must establish whether independently stimulating cold-afferent thermoreceptors in the oral cavity, via a cold mouth rinse, would be sufficient to mitigate heat-related decrements in exercise tolerance with MS, as reported with complete cold water ingestion in the present study.

LIMITATIONS

The present study does not include subjective measures such as whole-body thermal sensation or rating of perceived exertion (RPE). As such, it is unclear whether alterations in whole-body thermal sensation and/or RPE contributed to the longer exercise duration in the heat with cold water ingestion. Similarly the onset and severity of MS-related symptoms were not specifically assessed during or after exercise, and we therefore cannot rule out that the longer exercise duration, which was apparently promoted by cold water ingestion, resulted in any prolonged symptom worsening after exercise. Future research should therefore investigate whether prolonged exercise duration affects heat-related MS symptoms and if ingesting cold water mitigates the development of MS symptom severity during exercise in the heat. Because some participants reported some transient mild discomfort during cold fluid ingestion, future research should also assess the efficacy of ingesting slightly warmer fluid temperatures.

The exercise time to exhaustion protocol with a fixed end point of 60 min was selected to assess the capacity of an easily fatigued, nonathletic population. However, because of the large variability that is typically demonstrated in time to exhaustion studies, future research should examine the reliability of a different study design to assess performance in MS individuals such as a fixed RPE (26) or a time trial protocol (27). Finally, $\dot{V}O_{2max}$ values were estimated using HR and $\dot{V}O_2$ responses at submaximal workloads that were then extrapolated to age-predicted maximum HR levels. However, to the best of our knowledge, this formula has not been validated in an MS population and therefore merits further investigation, particularly given that $\dot{V}O_{2max}$ seems to be slightly overestimated in the MS group in the present study.

CONCLUSIONS

In conclusion, the present study examined the influence of ingesting cold compared with thermoneutral water on exercise performance at a fixed low relative intensity (~40% $\dot{V}O_{2max}$), and the concurrent elevation in core and skin temperature of heat-sensitive relapsing–remitting MS participants in a warm (30°C) environment. With thermoneutral water ingestion, exercise time was shorter in the MS group compared with age-matched controls, presumably because of the development of fatigue associated with Uhthoff's phenomenon. Cold water ingestion resulted in a ~30% longer exercise time in the MS participants who could not complete 60 min of exercise in the thermoneutral water ingestion trial. However, although cold water ingestion seemed to improve the exercise tolerance of the MS group in the heat, it did not blunt the rise in T_{re} or T_{sk} with time. These findings provide a practical and simple strategy for individuals with MS performing physical activity in hot environments, and lend insight into the potential role of cold-afferent thermoreceptors that reside in the abdomen and oral cavity in the modulation of exercise tolerance with MS in the heat.

This research was supported by a Multiple Sclerosis Research Australia Incubator Grant (grant holders: Jay, Davis, Barnett, and Hoang; grant no. 14-009), a Multiple Sclerosis Research Australia Postgraduate Fellowship (grant holders: Chaseling and Jay; grant no. 15-087), and an Australian Government, Department of Education, Endeavour Post-Doctoral Research Fellowship (grant holder: Filingeri). All results in this study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation. Results of the present study do not constitute endorsement by the American College of Sports Medicine.

The authors have no conflicts of interest to disclose.

REFERENCES

1. Nelson DA, McDowell F. The effects of induced hyperthermia on patients with multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 1959;22(2):113.
2. Simmons RD, Ponsonby AL, Van Der Mei IA, Sheridan P. What affects your MS? Responses to an anonymous, Internet-based epidemiological survey. *Mult Scler*. 2004;10(2):202–11.
3. Davis FA, Jacobson S. Altered thermal sensitivity in injured and demyelinated nerve. A possible model of temperature effects in multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 1971;34(5):551–61.
4. Rasminsky M. The effects of temperature on conduction in demyelinated single nerve fibers. *Arch Neurol*. 1973;28(5):287–92.
5. Julian LJ, Vella L, Vollmer T, Hadjimichael O, Mohr DC. Employment in multiple sclerosis. Exiting and re-entering the work force. *J Neurol*. 2008;255(9):1354–60.
6. Watson CW. Effect of lowering of body temperature on the symptoms and signs of multiple sclerosis. *N Engl Journal of Medicine*. 1959;261(25):1253–9.
7. White A, Wilson T, Davis S, Petajan J. Effect of precooling on physical performance in multiple sclerosis. *Mult Scler*. 2000;6(3):176–80.
8. Meyer-Heim A, Rothmaier M, Weder M, Kool J, Schenk P, Kesselring J. Advanced lightweight cooling-garment technology: functional improvements in thermosensitive patients with multiple sclerosis. *Mult Scler*. 2007;13(2):232–7.
9. Society NMS. Heat and Temperature Sensitivity 2004 [updated December 4, 2015]. Available from: http://www.nationalmssociety.org/Living-Well-With-MS/Health-Wellness/Heat-Temperature-Sensitivity-section-3.
10. Society MS. Hot and Cold 2013. [4 p.]. Available from: https://www.mssociety.org.uk/sites/default/files/Documents/Essentials/Hot-and-cold-temperature-factsheet-Feb-13.pdf.
11. Kurtzke JF. Rating neurologic impairment in multiple sclerosis an expanded disability status scale (EDSS). *Neurology*. 1983;33(11):1444–52.
12. Burdon CA, Hoon MW, Johnson NA, Chapman PG, O'Connor HT. The effect of ice slushy ingestion and mouthwash on thermoregulation and endurance performance in the heat. *Int J Sport Nutr Exerc Metab*. 2013;23(5):458–69.
13. Ramanathan NL. A new weighting system for mean surface temperature of the human body. *J Appl Physiol*. 1964;19(3):531–3.
14. Astrand P, Rodahl K. Evaluation of physical work capacity on the basis of tests. In: *Textbook of Work Physiology: Physiological Basis of Exercise*. Champaign (IL): Human Kinetics; 1977. pp. 333–65.
15. Fitchett MA. Predictability of $\dot{V}O_2$max from submaximal cycle ergometer and bench stepping tests. *Br J Sports Med*. 1985;19(2):85–8.
16. Uhthoff W. Studies on the occurring in multiple sclerosis stove eye disorders. *Arch Psychiat Nervenkr*. 1889;21:303.
17. Balmain BN, Jay O, Sabapathy S, et al. Altered thermoregulatory responses in heart failure patients exercising in the heat. *Physiol Rep*. 2016;4(21):e13022.
18. Marino FE. Heat reactions in multiple sclerosis: an overlooked paradigm in the study of comparative fatigue. *Int J Hyperthermia*. 2009;25(1):34–40.
19. Tyler CJ, Sunderland C, Cheung SS. The effect of cooling prior to and during exercise on exercise performance and capacity in the heat: a meta-analysis. *Br J Sports Med*. 2015;49(1):7–13.
20. Morris NB, Bain AR, Cramer MN, Jay O. Evidence that transient changes in sudomotor output with cold and warm fluid ingestion are independently modulated by abdominal, but not oral thermoreceptors. *J Appl Physiol (1985)*. 2014;116(8):1088–95.
21. Morris NB, Coombs G, Jay O. Ice slurry ingestion leads to a lower net heat loss during exercise in the heat. *Med Sci Sports Exerc*. 2016;48(1):114–22.
22. Bain AR, Lesperance NC, Jay O. Body heat storage during physical activity is lower with hot fluid ingestion under conditions that permit full evaporation. *Acta Physiol (Oxf)*. 2012;206(2):98–108.
23. Sandroff BM, Dlugonski D, Weikert M, Suh Y, Balantrapu S, Motl RW. Physical activity and multiple sclerosis: new insights regarding inactivity. *Acta Neurol Scand*. 2012;126(4):256–62.
24. Motl RW, McAuley E, Snook EM. Physical activity and multiple sclerosis: a meta-analysis. *Mult Scler*. 2005;11(4):459–63.
25. Beenakker E, Oparina T, Hartgring A, Teelken A, Arutjunyan A, De Keyser J. Cooling garment treatment in MS: clinical improvement and decrease in leukocyte NO production. *Neurology*. 2001;57(5):892–4.
26. Ravanelli NM, Cramer MN, Molgat-Seon Y, Carlsen AN, Jay O. Do greater rates of body heat storage precede the accelerated reduction of self-paced exercise intensity in the heat? *Eur J Appl Physiol*. 2014;114(11):2399–410.
27. Ely BR, Cheuvront SN, Kenefick RW, Sawka MN. Aerobic performance is degraded, despite modest hyperthermia, in hot environments. *Med Sci Sports Exerc*. 2010;42(1):135–41.