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Cold water ingestion improves exercise tolerance of heat-sensitive people with MS

Georgia K Chaseling¹, Davide Filingeri^{1,2}, Michael Barnett³,
Phu Hoang⁴, Scott L Davis^{5,6}, Ollie Jay^{1,7}✉

¹Thermal Ergonomics Laboratory, Faculty of Health Sciences, University of Sydney, Lidcombe
NSW, Australia

²Environmental Ergonomics Research Centre, Loughborough University, Leicestershire, United
Kingdom

³Brain and Mind Research Centre, Sydney Medical School, University of Sydney, Camperdown,
NSW, Australia

⁴Neuroscience Research Australia, Sydney, NSW, Australia

⁵Applied Physiology & Wellness Southern Methodist University, Dallas, TX, United States

⁶Neurology and Neurotherapeutics, University of Texas Southwestern Medical Center, Dallas,
TX, United States

⁷Charles Perkins Centre, University of Sydney, Camperdown, NSW, Australia

Short title: *Cold drinks, Exercise and Multiple Sclerosis*

Address for correspondence:

Dr. O. Jay ✉

Thermal Ergonomics Laboratory,
Faculty of Health Sciences,
University of Sydney,
Lidcombe, NSW, 2141
AUSTRALIA

Tel: +61 2 93519328

Fax: +61 2 9351 9204

E-mail: ollie.jay@sydney.edu.au

1 **Abstract**

2 *Purpose:* Heat intolerance commonly affects the exercise capacity of people with multiple
3 sclerosis (MS) during bouts of hot weather. Cold-water ingestion is a simple cooling
4 strategy but its efficacy for prolonging exercise capacity with MS remains undetermined.
5 We sought to identify whether cold-water ingestion blunts exercise-induced rises in body
6 temperature and improves exercise tolerance in heat-sensitive individuals with MS.

7 *Methods:* On two separate occasions, 20 participants (10 relapsing-remitting MS (EDSS: 1-
8 5); 10 age- and fitness-matched healthy controls (CON)) cycled at 40% $\text{VO}_{2\text{max}}$ at 30°C,
9 30%RH until volitional exhaustion (or a maximum of 60 min). Every 15 minutes,
10 participants ingested 3.2 mL·kg⁻¹ of either 1.5°C (CLD) or 37°C (NEU) water. Rectal (T_{re})
11 temperature, mean skin (T_{sk}) temperature, and heart rate (HR) were measured throughout.

12 *Results:* All 10 CON, but only 3 of 10 MS participants completed 60 minutes of exercise in
13 NEU trial. The remaining 7 MS participants all cycled longer ($P=0.006$) in CLD
14 (46.4±14.2 min) compared to NEU (32.7±11.5 min), despite similar elevations in absolute
15 T_{re} (NEU: 37.32±0.34°C; CLD: 37.28±0.26°C; $P=0.44$), change in T_{re} (NEU: 0.38±0.21°C;
16 CLD: 0.34±0.24°C), absolute T_{sk} (NEU: 34.48±0.47°C; CLD: 34.44±0.54°C; $P=0.82$) and
17 HR (NEU: 114±20 b·pm⁻¹; CLD: 113±18 b·pm⁻¹; $P=0.38$) for the same exercise volume.

18 *Conclusions:* Cold-water ingestion enhanced exercise tolerance of MS participants in the
19 heat by ~30% despite no differences in core and mean skin temperatures or heart rate.
20 These findings support the use of a simple cooling strategy for mitigating heat intolerance
21 with MS, and lend insight into the potential role of cold-afferent thermoreceptors that
22 reside in the abdomen and oral cavity in the modulation of exercise tolerance with MS in
23 the heat.

24 **Keywords:** Uhthoff's phenomenon, fatigue, physical activity, heat sensitivities.

25 **Introduction**

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

35 Some cooling strategies administered before and/or during heat exposure
36 successfully mitigate the development of heat-related fatigue in people with MS (6).
37 However, these methods, such as 30 minutes of lower body cold water immersion (7) or
38 donning an ice vest (8) can prove impractical in the context of everyday life and
39 incompatible with many jobs. Cold fluid ingestion during physical activity is a simple
40 strategy that is presently recommended by, among others, the National MS Society (9) the
41 MS Society (UK) (10) and MS Queensland (Australia). Indeed, drinking cold water could
42 effectively mitigate elevations in core temperature and associated fatigue as it introduces
43 an internal heat loss avenue (via conduction) in addition to evaporative and convective heat
44 loss from the skin surface. Nevertheless, to the best of our knowledge, no study has yet
45 assessed whether cold fluid ingestion during exercise in the heat can mitigate rises in core
46 temperature and accompanying fatigue in people with MS.

47 The aim of this study was to examine the effect of ingesting cold (1.5°C) compared
48 to thermoneutral (37°C) water on exercise time to exhaustion at a fixed low relative
49 intensity (~40% $\text{VO}_{2\text{max}}$), and the elevation in core temperature of heat-sensitive relapsing-
50 remitting MS participants in a warm (30°C) environment. It was hypothesized that with
51 thermoneutral water ingestion, exercise time to exhaustion would be shorter for MS
52 compared to age- and fitness-matched control participants. It was also hypothesized that
53 compared to thermoneutral water ingestion exercise time to exhaustion in MS participants
54 would be extended with cold water ingestion due to a blunted rise in core temperature.

55 **Methods**

56 *Participants*

57 Twenty participants, 10 individuals with relapsing-remitting MS, an expanded
58 disability status scale (EDSS) range of 2-4.5 (1 = No disability, slight dysfunction in one
59 area, 4.5 = significant disability with some limitation of daily activities (11)) and 10 age,
60 height and weight-matched healthy controls (Table 1) were recruited for this study based
61 on a power calculation (Heinrich-Heine-Universität Düsseldorf, Germany) employing an α
62 of 0.05, a $1-\beta$ of 0.95 and an effect size of 1.55 for the main outcome variable of exercise
63 performance with cold fluid ingestion in the heat (12). All MS participants had a self-
64 reported intolerance to the heat. All participants were informed of any risks associated with
65 the study before providing written informed consent. The study was approved by the
66 University of Sydney Human Research Ethics Committee (HREC No: 2016/214).

67 *Measurements*

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

76 Heart rate (HR) was measured using a wireless 6-lead ECG (Quark T12x Asia
77 Pacific PTY, Sydney, NSW, Australia) monitoring system. Electromagnetic gel was

78 applied to 4 foam electrodes, which were then placed under the right and left clavicle, the
79 right and left 6th intercostal and then covered with tape. Prior to the placement of the
80 electrodes, the skin surface was shaved and cleaned with alcohol to ensure minimal signal
81 interference.

82 *Protocol*

83 Each participant completed one preliminary trial and two experimental trials.
84 During the preliminary trial, participants performed an incremental submaximal exercise
85 protocol (beginning at 45 W increasing 20 W every three minutes for a total of four stages)
86 on a semi-recumbent cycle ergometer (Corival Recumbent, Lode BV, Groningen,
87 Netherlands) in a 20°C room. Heart rate and oxygen consumption (Quark CPET, Cosmed,
88 Asia Pacific PTY, Sydney, NSW, Australia) were measured during each 3-min stage. A
89 least square regression equation was employed using sub-maximal heart rate and oxygen
90 consumption at the end of each stage and extrapolated to the maximum age-predictated
91 heart rate ($220 - \text{age}$) (14) to determine $\text{VO}_{2\text{max}}$ using the YMCA protocol (15).
92 Individualized workloads (40% of predicted $\text{VO}_{2\text{max}}$) were calculated for the subsequent
93 experimental trials.

94 Participants completed two experimental trials separated by a minimum of 48 h in a
95 climate-controlled chamber at 30°C and 30% relative humidity until i) volitional
96 exhaustion, or ii) a maximum of 60 minutes. Participants were required to complete both
97 trials at the same time of day to avoid any disparity in resting core temperature due to
98 circadian rhythm. If any participant presented with a resting T_{re} more than 0.2°C away from
99 the other trials, then the trial would not commence. Participants cycled on a semi-
100 recumbent cycle ergometer at a fixed relative intensity ($\sim 40\% \text{VO}_{2\text{max}}$) and consumed a 3.2

101 ml·kg⁻¹ aliquot of water (in <1 minute) after the 15th, 30th and 45th minute of exercise.
102 Participants consumed either thermoneutral (37°C) water (NEU) or cold (1.5°C) water
103 (CLD) during each experimental trial. The presentation of trials was balanced between
104 participants. The temperature of the water ingested in the NEU trial was maintained using
105 a hydrostatic controlled water bath (DA05A, Polyscience, Niles, IL, USA). The
106 temperature of the water ingested in the CLD trial was maintained in a thermos filled with
107 ice. Immediately prior to fluid ingestion, the temperature of the fluid was verified using a
108 factory-calibrated glass precision thermometer (Durac Plus, Blue Spirit, Cole-Parmer,
109 Vernon Hills, IL, USA) with a certified range between -1°C and +100°C and with an
110 accuracy of ±0.1°C, and the required mass of water was measured using a balance with a
111 precision of 0.1 g (MS12001L, Mettler Toledo, Columbus, OH, USA). Breath by breath
112 oxygen consumption was continuously monitored to ensure participants were performing
113 at the same relative intensity throughout both trials.

114 *Statistical Analysis*

115 A two-way mixed ANOVA employing the repeated factor of water temperature
116 (CLD, NEU) and the non-repeated factor of group (MS, Control) was used to examine
117 exercise time to exhaustion. The T_{re} , T_{sk} and HR at the time of exhaustion in the shortest
118 trial for each individual were also compared to the same time point in the other trial within
119 the MS and CON groups using paired sample t-tests. A within-group analysis was employed
120 for measures of T_{re} and T_{sk} due to the different exercise time between the con and MS groups.
121 Furthermore, within the CLD trial T_{re} and T_{sk} at the time of exhaustion in the NEU was
122 compared to the end-exercise values of the CLD within the MS group using a paired
123 sample t-test. Finally, an unpaired t-test was used to examine HR between control and MS

124 participants at 30 minutes of exercise for both the NEU and CLD trials..All statistical
125 analyses were performed using GraphPad Prism (v6.0, LA Jolla, CA, USA).

126

127 **Results**

128 Exercise time to exhaustion was shorter in the MS group compared to the CON
129 group ($P=0.002$), however an interaction was observed between water temperature and
130 group ($P<0.001$). Specifically, all 10 control participants completed 60 minutes of exercise
131 in both the NEU and CLD trials (Figure 1). On the other hand, while only 3 of 10
132 participants in the MS group completed 60 minutes of exercise in the NEU and CLD trial,
133 all 7 MS participants who could not complete the NEU trial cycled longer (Figure 1) in the
134 CLD trial (NEU: 32.7 ± 11.5 min; CLD: 46.4 ± 14.2 min; $P=0.006$). After 30 minutes of
135 exercise, HR responses in the NEU trial (MS: 104 ± 15 b•pm⁻¹; CON: 96 ± 10 b•pm⁻¹;
136 $P=0.22$) and the CLD trial (MS: 103 ± 17 b•pm⁻¹; CON: 92 ± 12 b•pm⁻¹; $P=0.17$) were not
137 different, despite being moderately higher for the MS group throughout exercise.

138 In the MS group, at the time of exhaustion in the NEU trial, T_{re} ($P=0.44$; Figure
139 2A), T_{sk} ($P=0.82$; Figure 2C) , change in T_{re} ($P=0.66$; Figure 2E) and HR (NEU: 114 ± 19
140 b•pm⁻¹; CLD: 113 ± 17 b•pm⁻¹; $P=0.45$) were not different after the same amount of
141 exercise time elapsed in the CLD trial. All 7 MS participants who cycled for longer in the
142 CLD trial did so despite T_{re} ($P=0.001$) and T_{sk} ($P=0.03$) rising to higher values above
143 baseline when they did stop exercise (ΔT_{re} : $0.26\pm0.12^{\circ}\text{C}$ vs. $0.40\pm0.23^{\circ}\text{C}$; ΔT_{sk} :
144 $1.27\pm0.72^{\circ}\text{C}$ vs. $1.47\pm0.79^{\circ}\text{C}$).

145 In the CON group, end-exercise (i.e. after 60 min in all CON participants) T_{re}
146 ($P=0.25$; Figure 2B), T_{sk} ($P=0.33$; Figure 2D) , change in T_{re} ($P=0.7$; Figure 2F) and HR
147 (NEU: 99 ± 11 bpm; CLD: 99 ± 13 ; $P=0.33$) were not different between the NEU and CLD
148 trial. Due to equipment problems, HR values are only displayed for 8 control participants.

149

150 Discussion

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

158 It is well documented that even small increases in body temperature are associated
159 with a transient worsening of symptoms for individuals with MS (3, 4), otherwise known
160 as Uhthoff's phenomenon (16). The development of fatigue, manifested by sensations of
161 tiredness, is a common characteristic associated with Uhthoff's phenomenon and explains
162 the shorter exercise time for 7 of the 10 MS who could not complete 60 minutes of exercise
163 compared to CON group in the NEU trial as both participant groups were matched for age
164 and aerobic fitness. In addition, the relative exercise intensity was moderately low
165 (~40% $\text{VO}_{2\text{max}}$) and should have been easily sustainable for 60 minutes, as evidenced by all
166 10 CON participants completing the exercise bout in both trials.

167 Within the MS group, the longer exercise to time to exhaustion in the CLD trial
168 occurred despite a similar T_{re} , T_{sk} , and HR at a comparable time point (i.e. same volume of
169 exercise) than the time to exhaustion in the NEU trial for each individual. In other words,
170 exercise tolerance in the heat was improved in the MS group with cold-water ingestion
171 despite no independent influence of ingested water temperature on the development of
172 thermal and cardiovascular strain with exercise time. Indeed, from the time point at which

173 exercise exhaustion was reached in the NEU trial, T_{re} and T_{sk} in the CLD trial continued to
174 rise to higher values by the time exercise stopped. It has been previously suggested that the
175 underlying mechanism responsible for heat-related reduction in exercise performance in
176 healthy athletes is potentially similar to heat sensitivity with MS, but with fatigue onset
177 occurring alongside much smaller rises in body temperature with MS (17). It follows that
178 heat-related decrements in the aerobic performance of healthy athletes can potentially be
179 attenuated via the stimulation of cold-afferent receptors located in the oral cavity (12) and
180 on the skin surface (18), without necessarily lowering core temperature. The present
181 findings potentially support the notion that research examining the mitigation of heat-
182 related decrements in exercise performance in healthy athletes may, at least to an extent, be
183 translatable to the management of Uhthoff's phenomenon in the MS population.

184 Irrespective of participant group, for the same volume of exercise, any alteration in
185 core and skin temperature due to the ingested fluid temperature were minimal (Fig. 2A, C
186 and E), despite the greater internal heat loss via conduction with cold fluid ingestion. A
187 recent series of studies (19-21) described fluid temperature-dependent alterations in
188 sweating during exercise that are modulated, independently of core and skin temperatures,
189 by visceral thermoreceptors located in the abdomen. Ultimately, the reduction in
190 evaporative heat loss from the skin surface with cold fluid ingestion was found to
191 counterbalance the greater internal heat loss, thereby yielding similar changes in whole
192 body heat storage and thus similar changes in core temperature, irrespective of ingested
193 fluid temperature (19). Although sweating rates are not reported in the present study, a
194 similar fluid temperature-dependent modulation of skin surface evaporation could explain
195 the similar levels of thermal strain between the NEU and CLD trials within both the MS

196 and CON group. Another consideration is that the absolute amount of heat transfer
197 generated by each $3.2 \text{ ml} \cdot \text{kg}^{-1}$ aliquot of 1.5°C water, even without any parallel alterations
198 of skin surface evaporation, would only be $\sim 35 \text{ kJ}$, which for a 82.5 kg individual with a
199 mean body specific heat of $3.49 \text{ kJ} \cdot \text{kg}^{-1} \cdot ^{\circ}\text{C}^{-1}$ would yield a reduction in mean body
200 temperature of only $\sim 0.1^{\circ}\text{C}$.

201 Despite the profound impact of regular exercise on the physical and psychological
202 health of individuals with MS (22), it has been reported that people with MS are less
203 physically active (23), partly to avoid a temporary worsening of symptoms associated with
204 an elevation in body temperature. Moreover, heat intolerance has been shown to greatly
205 impact the capacity for many people with MS to remain among the workforce (5). Cold
206 water ingestion is a simple strategy for improving exercise tolerance in the heat, which
207 could be used as an alternative to other less practical but currently recommended cooling
208 strategies such as partial immersion in cold water prior to heat exposure (7), or donning an
209 ice vest (24). It should be noted that for individuals with MS susceptible to urinary
210 incontinence, additional fluid ingestion might not prove an optimal solution. Therefore,
211 future research must establish whether independently stimulating cold-afferent
212 thermoreceptors in the oral cavity, via a cold mouth rinse, would be sufficient to mitigate
213 heat-related decrements in exercise tolerance with MS, as reported with complete cold-
214 water ingestion in the present study.

215 **Limitations**

216 The present study does not include subjective measures such as whole body thermal
217 sensation (WBTS) or rate of perceived exertion (RPE). If a lower WBTS and RPE were
218 observed for the same exercise load for the MS participants, this may have explained the

improved exercise tolerance. Furthermore, there was no measure taken to assess the onset of symptoms, if any, for the MS participants. Therefore, we are unsure whether cold fluid ingestion mitigated the onset of heat related symptoms, or temporarily dampened sensations of heat intolerance. Future research should investigate whether prolonged exercise time affects heat related symptoms, or whether ingesting cold water is sufficient to mitigate the onset of symptoms during exercise in a hot environment. As some participants reported a mild discomfort with the cold fluid ingestion future research should assess similar outcome variables to this current research, however with slightly warmer fluid temperatures.

The exercise time to exhaustion protocol was selected to assess the capacity of an easily fatigued, non-athletic population. However, due to the large variability that is typically demonstrated in time to exhaustion studies, future research should look at investigating aerobic performance for MS individuals using a more reliable protocol such as a time trial (25). Using heart rate to predict VO_{2max} for MS individuals has not yet been validated for this population. Given that heart rate responses to exercise were quite variable for the MS group, there is a possibility that VO_{2max} results were either under or overestimated. Despite this, the relative workload was consistent within each participant, and therefore the main outcome of this study is not affected.

Conclusion

In conclusion, the present study examined the influence of ingesting cold compared to thermoneutral water on exercise time to exhaustion at a fixed low relative intensity (~40% VO_{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

242 water ingestion, exercise time to exhaustion was shorter in the MS group compared to age-
243 matched controls, presumably due to the development of fatigue associated with Uhthoff's
244 phenomenon. Cold-water ingestion resulted in a ~30% longer exercise time to exhaustion
245 in the MS participants that could not complete 60 minutes of exercise in the thermoneutral
246 water ingestion trial. However while cold-water ingestion appeared to improve the exercise
247 tolerance of the MS group in the heat, it did not blunt the rise in core and mean skin
248 temperature with time. These findings provide a practical and simple cooling strategy for
249 individuals with MS performing physical activity in hot environments, and lend insight
250 into the potential role of cold-afferent thermoreceptors that reside in the abdomen and oral
251 cavity in the modulation of exercise tolerance with MS in the heat.

252

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259 study are presented clearly, honestly and without fabrication, falsification or inappropriate
260 data manipulation. Results of the present study do not constitute endorsement by the
261 American College of Sports Medicine.

262

263 **Conflicts of Interest**

264 There are no conflicts of interest to declare.

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327

328 **Figure Legends**

329 **Figure 1.** Individual data and group means (with SD) at the end of exercise in NEU
330 (yellow) trial compared to the same time point in the CLD (black) trial for multiple
331 sclerosis (MS: squares) and healthy controls (CON: circles). Values given for: Exercise
332 time to exhaustion with a maximum of 60 min. Asterisk (*) indicates $P \leq 0.05$.

333 **Figure 2.** Individual data and group means (with SD) at the end of exercise in NEU
334 (yellow) trial compared to the same time point in the CLD (black) trial for multiple
335 sclerosis (MS: squares) and healthy controls (CON: circles). Values given for: Rectal
336 temperature (Panels A-B), mean skin temperature (Panel C-D) and heart rate (Panel E-F)
337 Asterisk (*) indicates $P \leq 0.05$.

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Figure 1.

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359 Figure 2.