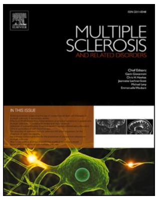
Multiple Sclerosis and Related Disorders 91 (2024) 105833

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard



Original article

Head and neck cooling enhance exercise tolerance in individuals with multiple sclerosis

George Apostolou [a], Andreas D. Flouris [a], Evangelia Kouidi [b], Athanasios Z. Jamurtas [c], Glen P. Kenny [d], Antonia Kaltsatou [a,*]

[a] FAME Laboratory, Department of Physical Education and Sport Science, University of Thessaly, Greece
[b] Sports Medicine Laboratory, Department of Physical Education and Sport Science, Aristotle University of Thessaloniki, Greece
[c] Smart Lab, Department of Physical Education and Sport Science, University of Thessaly, Greece
[d] Human and Environmental Physiology Research Unit, School of Human Kinetics, University of Ottawa, Ottawa, Canada

ARTICLE INFO

Keywords:
Cooling
Functional capacity
Thermoregulation
Exercise
Quality of life
Chronic disease

ABSTRACT

Background: Individuals with Multiple Sclerosis (MS) experience impairments in heat dissipation, compromising core temperature regulation during exercise.

Objective: To examine the efficacy of combined head-and-neck cooling as administered via a commercially available cooling cap and neck wrap in mitigating increases in core temperature during exercise.

Methods: On separate days, ten (7 females) adults (46.1 ± 11.6 years) with relapsing-remitting MS performed semi-recumbent cycling consisting of an incremental exercise bout to volitional fatigue in a temperate environment (23 °C, 50 % relative humidity) while undergoing head-and-neck cooling using a cooling cap and neck wrap maintained at 10 °C (COLD) or 24–26 °C (NEUTRAL). Prior to and following a 30-minute post-exercise recovery, functional capacity was assessed by a battery of tests consisting of a 2-minute walk test, Timed 25-Foot Walk test, sit-to-stand test, and Berg Balance Scale. Core (ingestible pill) and skin temperatures were recorded continuously. The level of fatigue was measured with questionnaires.

Results: The duration of the incremental exercise test increased with the application of COLD (28.4 ± 5.1 min) versus NEUTRAL water (vs 20.8 ± 5.1 min) ($p = 0.001$) and was paralleled by a significant reduction in body temperatures (∼1 °C, $p < 0.05$). The distance covered during the 2-min walk test performed after the incremental exercise test increased with the COLD (176.5 ± 0.6 m), relative to the NEUTRAL condition (147.7 ± 43.5 m) ($p = 0.01$). Fatigue levels did not change between conditions.

Conclusion: We show that head-and-neck cooling with cold water effectively enhances exercise tolerance and mitigates increases in core temperature during exercise in individuals with MS.

1. Introduction

Multiple Sclerosis (MS) is a progressive neurological disease that disrupts axonal myelin in the central nervous system, leading to a broad spectrum of physical disabilities (Smith and McDonald, 1999). While MS can occur at any age, it is most often diagnosed in young adults (Howard et al., 2016), leading to the potential risk of permanent disability and premature death (Koch-Henriksen and Sorensen, 2010). Increased fatigue and fatigability, which occur in 70–75 % of MS individuals, are the most common and debilitating disease symptoms (Krupp, 2006, Enoka et al., 2021). These symptoms are associated with declines in both physical (e.g., weakness, motor dysfunction, altered gait and spasms) and psychological functioning that worsen with disease progression (Smith and McDonald, 1999).

It is generally accepted that centrally mediated fatigue observed in MS is associated with an inability to maintain central nervous system activation of spinal motoneurons, although peripheral factors (e.g., decreased muscle peak force output and delayed half-relaxation time) also influence this response (Lenman et al., 1989, Davis et al., 2010). Excessive fatigue combined with motor weakness, spasticity, and poor balance can limit engagement in activities of daily living or general exercise and, in more serious cases, make participation unlikely (Correale et al., 2022). In such cases, MS symptoms can compromise physical function, leading to physical inactivity and a sedentary

---

* Corresponding author at: FAME Laboratory, Department of Physical Education and Sport Science, University of Thessaly, Karies, Trikala, 42100, Greece.
E-mail address: akaltsat@gmail.com (A. Kaltsatou).

https://doi.org/10.1016/j.msard.2024.105833
Received 29 March 2024; Received in revised form 4 July 2024; Accepted 19 August 2024

lifestyle. In turn, this can increase the risk of secondary diseases such as coronary heart disease, obesity, diabetes mellitus and other health conditions (Marrie, 2017).

Relative to their healthy counterparts, individuals with MS have a reduced capacity to dissipate heat due to impaired thermoregulatory activity, including lower sweating thermosensitivity and delayed sweating onset, leading to a greater increase in core body temperature during moderate exercise (Allen et al., 2018). In turn, this can lead to a transient, short-term worsening of clinical and neurological symptoms (Davis et al., 2010, Frohman et al., 2013). Specifically, symptom worsening can be caused by exposure to hot environments (e.g., direct exposure to the sun or radiant heat sources, warm baths/showers), heat generated from exercise (increases in metabolic rate augments body heat production and core temperature), or a combination of these (Davis et al., 2010). Notably, elevated levels of heat stress can exacerbate impairments in functional capacity, negatively impacting patient well-being and safety and limiting their ability to perform routine activities of daily living (Huang et al., 2014). For this reason, MS patients tend to limit their participation in physical activity, especially in hot environments, to prevent overheating (Davis et al., 2010). While this may provide some degree of temporary comfort to the patient, over the long term, it can lead to a worsening of general health and well-being. In turn, physical inactivity can lead to physical deconditioning (e.g., muscle wasting), decrements in functional capacity (e.g., reduction in aerobic capacity), increased risk of injury (due to a gradual deterioration in functional and motor ability), and poor health (Marrie, 2017).

Despite the heat-induced physiological burden caused by physical activity, especially in hot environments, engagement in exercise is highly recommended for individuals with MS and should be incorporated into their overall disease management plan (Dalgas et al., 2019). Notably, incorporating structured exercise and lifestyle intervention programs can reduce the rate of decline in functional capacity and elicit improvements in overall quality of life. To enhance participation in both activities of daily living and exercise, cooling strategies (e.g., use of cooling devices, vests with ice packs, application of cold water on the body, others) have been recommended to mitigate potentially dangerous increases in body temperature during exercise which can lead to heat-related illness (Kaltsatou and Flouris, 2019, Buoite Stella et al., 2020). This includes enhancing exercise performance and reducing fatigue in individuals with MS (Stevens et al., 2023). For example, a recent study showed that a cooling vest improved exercise performance in a warm environment, as evidenced by an increase in total walking time and distance covered in heat-sensitive MS individuals (Buoite Stella et al., 2020). Moreover, another study by Reynolds et al. (2011), highlights the importance of both physiological and psychological benefits of cooling strategies in managing MS symptoms. They showed that head-and-neck cooling maintained at 10 °C with a custom-made cooling device significantly reduced core temperature and improved exercise performance in individuals with MS. Notably, sham cooling at 24 °C also enhanced perceptual responses and performed as measured by timed up-and-go performance (Reynolds et al., 2011). Similarly, even short-term head and neck cooling, i.e. 30 min set at < 10 °C, significantly reduced various body temperatures and heart rates of seated resting individuals with MS, providing symptomatic relief for both male and female patients (Ku et al., 1999). Further, localized head and neck pre-cooling (i.e., cooling the body prior to the start of exercise) has also been shown to limit fatigue following exercise in the heat (Gordon et al., 2020). Taken together, these findings demonstrate that mitigating increases in body temperature during exercise in individuals with MS can enhance engagement in safe exercise. In turn, this can translate into improvement in health and well-being if participation in exercise is maintained over the long-term.

To the best of our knowledge, no study has examined the effectiveness of body cooling applied both prior to (pre-cooling) and during (per-cooling) exercise in mitigating heat strain for the purposes of managing MS symptoms and improving physical performance. In the present study, we evaluated the efficacy of employing a commercially available, practical and inexpensive head-and-neck cooling system on exercise tolerance, functional capacity, physiological heat strain, and fatigue in individuals with MS. We assessed responses using the head-and-neck device cooled with either tap water (24–26 °C) or refrigerated water (10 °C) that can be easily applied in households in Greece.

2. Materials and methods

2.1. Ethical approval

This crossover laboratory-based study (ClinicalTrials.gov identifier: NCT04040010) was approved by the University of Thessaly Research Ethics Board (protocol no. 1300) and agreed with the latest version of the Declaration of Helsinki, except for registration in a database. Written and informed consent was obtained from all volunteers prior to their participation.

2.2. Participants

Participants were recruited from the Greek MS Society (https://gmss.gr/) via community outreach (i.e. visits to community centers). Prospective participants were eligible for the study if they met the following criteria: they had a confirmed diagnosis of MS according to the McDonald's criteria (Polman et al., 2011), had experienced no relapses in the past six months, possessed no musculoskeletal conditions that would hinder exercise, scored between 0 to 5.5 on the Expanded Disability Status Scale [indicating their ability to walk independently for at least 100 meters without a cane (Kurtzke, 1983)], had a history of heat sensitivity reported by their physician, and had not used cooling therapy for at least 4 months prior to participation in the study. Participants were excluded if they had health comorbidities (e.g., diabetes mellitus, hypertension, heart disease, or kidney disease), and use of medications to manage MS-related symptoms (e.g., antidepressants, psychostimulants, anticonvulsants, antispasmatic and anticholinergic) as well as previously diagnosed conditions known to impact physiological responses to heat exposure. Of the 52 patients screened for enrollment, 10 (7 female) adults with relapsing-remitting MS met the eligibility criteria and participated in the study (Fig. 1). None of the women were menstruating during the time of their test sequence. Participant characteristics are presented in Table 1.

3. Experimental design

3.1. Screening session

All participants underwent an initial screening session followed by two experimental trials in a counterbalanced order. During the preliminary visit, a multidimensional assessment was conducted, including a recording of demographic and social parameters to confirm their participation eligibility. Height and weight were measured using a stadiometer (Seca 206, Hamburg, Germany) and scale (Seca 877, Hamburg, Germany). Participants were also familiarized with the experimental testing procedures.

Prior to all visits, participants were asked to refrain from exercise, alcohol or caffeine and were instructed to consume ~200–500 mL of water ~2 h prior to their arrival at the laboratory to ensure they were euhydrated.

3.2. Experimental sessions

Participants were required to visit the lab for two separate trials. Upon arrival for each experimental trial, participants provided a urine sample to confirm euhydration (urine specific gravity: ≤1.025) and donned a t-shirt, shorts, socks, and sports shoes. Participants swallowed an ingestible temperature pill to record core (visceral) temperature and

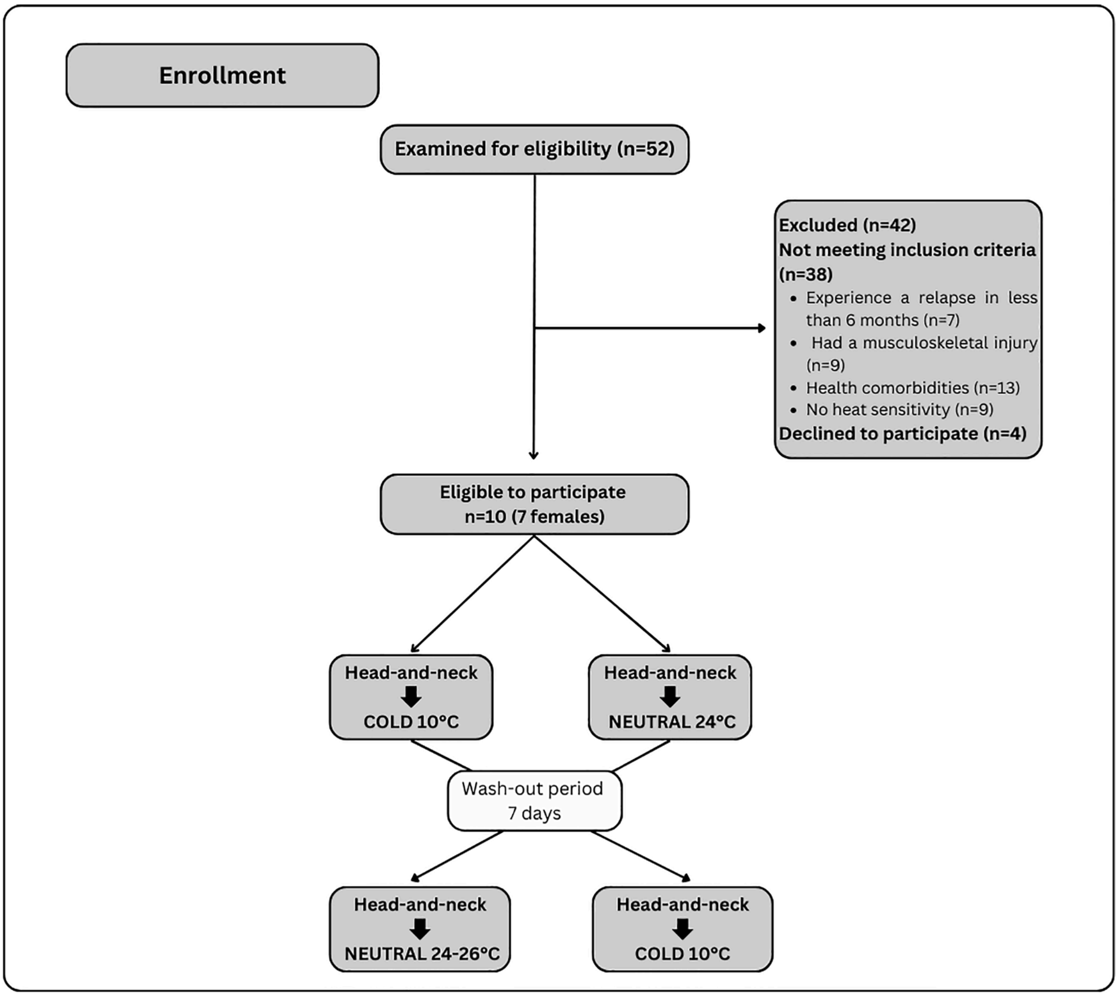


Fig. 1. Flowchart of the recruitment phase.

Table 1
Group characteristics (mean ± SD).

	Patients with MS
Age (years)	46.1 ± 11.6
Height (cm)	168.1 ± 0.1
Weight (kg)	71.8 ± 12.3
BMI	25.2 ± 2.3
Years of disease	10.3 ± 7.5
EDSS	5.1 ± 0.3

Key: BMI = body mass index; EDSS= Expanded Disability Status Scale.

skin temperature sensors were affixed to four skin sites (see below). The time elapsed between ingesting the capsule and the initial recording was 60 min. Previous research has demonstrated that the duration after capsule ingestion does not impact the accuracy of core temperature measurements during exercise (Notley et al., 2021). They were also instrumented with a heart rate monitor. Thereafter, they donned a cooling cap (Headcool Power, Inuteq, The Netherlands) and a neck wrap (Neckcool Tie, Inuteq, The Netherlands). The cooling intervention involved immersing the cooling cap and neck wrap in a water bath maintained at either 10 °C (i.e., COLD condition) or 24–26 °C (i.e., NEUTRAL condition), respectively, as measured using a thermometer. This ensured that the cooling cap and neck wrap were at the desired temperature before being applied to the participant, thus providing a consistent and controlled cooling effect. Furthermore, according to the manufacturer's specifications, these cooling products are designed to provide effective cooling for up to two hours. To ensure optimal performance and consistent cooling throughout the experimental intervention, we conducted our sessions for 1 h and 30 min. After this, they remained at rest for a 30-min pre-exercise period in a temperate environment (~23 °C and 50 % relative humidity). During this time, participants were required to undergo a series of functional capacity tests and complete two questionnaires to assess fatigue levels (see below). Thereafter, they performed an incremental semi-recumbent cycling (Monark, 837E Semi-recumbent Bike, Sweden) protocol commencing at an initial workload of 45 W, increasing by 10 W every 10 min till volitional fatigue. Volitional fatigue was defined as the point at which the participant could no longer continue exercising due to physical exhaustion despite encouragement from the study personnel. This protocol was employed to examine the participant's response to performing submaximal exercise at increasing intensities to reflect activities of daily living. This approach aligns with recommendations for exercise training in clinical populations, which emphasize the importance of submaximal exercise to safely enhance functional capacity and daily activity performance ACSM (2018). By design, we employed an exercise training session that reflects real-world exercise conditions that would permit the assessment of improvements in exercise tolerance and functional ability following the treatment period. Previous studies have shown that submaximal exercise protocols are effective in improving functional capacity and daily activity performance in chronic disease patients (Storer et al., 1990). Upon completion of exercise, a 30-min post-exercise recovery period was initiated, after which the participants completed the same series of functional capacity tests and questionnaires.

The head-and-neck cooling devices (i.e., cooling cap and the neck wrap) were worn during the entire data collection period and were set to COLD (i.e., cooling cap and neck wrap containing 10 °C water) temperature during one trial and to NEUTRAL (i.e., cooling cap and neck wrap containing thermoneutral 24–26 °C water) temperature during the other trial. This temperature was chosen because research has shown that a temperature range of 24 to 26 °C is generally considered to be within the comfortable range for humans, with 26 °C being the most comfortable (Sun et al., 2013). The cooling intervention involved immersing the cooling cap and neck wrap into cold water, which was set at 10 °C measured with a thermometer, while the control condition involved immersing them in neutral water (24–26 °C). This ensured that the cooling cap and neck wrap were at the desired temperature before being applied to the participants, providing a consistent and controlled cooling effect. Furthermore, according to the manufacturer's specifications, these cooling products are designed to provide effective cooling for up to two hours. To ensure optimal performance and consistent cooling throughout the experimental intervention, we conducted our sessions for 1 hour and 30 min. This approach allowed us to maintain the integrity of the cooling intervention and ensure that the participants experienced the intended thermal effects. Water (30–33 °C) was available to participants ad libitum. Trials were performed in a random order at the same time of the day (9:00 am) and separated by 7 days.

3.3. Physiological measurements

Core temperature was recorded continuously using a gastrointestinal telemetric capsule and receiver (e-Celsius Performance, BodyCap, Caen, France). Skin temperatures were recorded continuously at four sites using iButton sensors (type DS1921 H, Maxim/Dallas Semiconductor Corp., USA) to estimate mean skin temperature as follows, upper arm: 30 %, chest: 30 %, thigh: 20 %, and calf: 20 % (Ramanathan, 1964). Heart rate was continuously recorded via a Polar S810 (Kempele, Finland).

3.4. Functional capacity tests

Functional capacity was assessed with a series of four tests:

1) Two-minute walk test. The test required that all patients walk as far as possible over 2 minutes (Butland et al., 1982). The test is used to assess an individual's ability to perform activities of daily living independently.
2) Timed 25-Foot Walk (T25-FW) test. The test assesses walking speed achieved over a 25-foot (7.6 m) distance. It is a validated test that reflects the patient's mobility and lower limb function (Solari et al., 2005).
3) Sit-to-stand test (STS). Participants were encouraged to complete five successive full stands from a seated position. The test is used as an indicator of lower limb strength, balance and mobility (Whitney et al., 2005, de Melo et al., 2019). It has been reported that the STS times are associated with standing and leaning balance and mobility in older people. Slow STS times have also been found to predict subsequent disability, falls and hip fractures (Alosaimi et al., 2023).
4) Berg Balance Scale (BBS). The BBS evaluates the performance in 14 specific activities that require a balance function (Alosaimi et al., 2023) (picking up an object, standing on one leg, etc.) necessary for daily living activities. Participants are scored on a 5-point (0-4) ordinal scale depending on their ability to complete the requested actions. A score of 0 is assigned when the task could not be completed, and a score of 4 indicates independence. A total score of 45 or less over the 14 activities indicates a high risk for falls (Alosaimi et al., 2023).

The level of fatigue was assessed via the following two questionnaires:

1) Multidimensional Fatigue Inventory (MFI). The MFI is a self-report measure of fatigue (Lin et al., 2009, Aslani et al., 2019) and consists of 20 questions. Answers are scored on a 7-point scale where 1 = strongly disagree and 7 = strongly agree. The total score of the MFI ranges from 0 to 84. The ranges of scores for each subscale are as follows: physical, 0 to 36; cognitive, 0 to 40; and psychosocial, 0 to 8. Some studies use a total score of 38 as a cut-off to discriminate fatigued from non-fatigued individuals (Lin et al., 2009, Aslani et al., 2019).
2) Fatigue Severity Scale (FSS). The Fatigue Severity Scale (FSS) is a self-administered questionnaire consisting of nine questions that evaluate the severity of fatigue experienced during the preceding week. Each item is graded on a scale of 1 to 7 (Krupp et al., 1989). The Greek version of the FSS was employed as it has been translated and validated for the Greek population (Bakalidou et al., 2013). The inclusion of the FSS provides a comprehensive understanding of each participant's baseline fatigue status. This information is critical for interpreting the variability in acute exercise outcomes, as baseline fatigue can significantly influence exercise performance and recovery.

3.5. Statistical analysis

The sample size calculation was based on a prior study by Chaseling et al. (2018), which assessed the effects of cold (4 °C) versus neutral (37 °C) water ingestion at specific intervals, while performing the exercise protocol, on exercise time in individuals with MS (n = 10) and healthy controls (n = 10), performed up to 60 min semi-recumbent cycling. The control group completed 60 min of exercise in each condition, namely the neutral and cold conditions, respectively. In contrast, whereas mean exercise time was 32.7 ± 11.5 and 46.4 ± 14.2 min for the neutral and cold conditions for the individuals with MS, respectively. For the neutral condition, the effect size *d* was 3.22, indicating a very large effect. Based on this effect size, a sample size of 8 participants per group was deemed sufficient to achieve a statistical power of 0.95 with an α error probability of 0.05. For the cold condition, the effect size *d* was 1.30, which is also considered large. Accordingly, a sample size of 24 participants was required to achieve the same level of statistical power and α error probability. Given these considerations and aiming to balance feasibility with statistical rigour, our study included 20 participants, which we determined was sufficient to detect a large effect size as previously observed in cold conditions (Chaseling et al., 2018). Sample size calculations were conducted using G*Power 3.0 (Faul et al., 2007). Sample size calculations were conducted using G*Power 3.0 (Faul et al., 2007). We used a linear mixed model with a random effect for the participants to assess differences in the dependent variables between groups over time. This analysis was adjusted for the participants' years of disease and their baseline FSS score. The level of statistical significance was set at $p \leq 0.05$. All statistical analyses were performed using the Statistical Package for Social Sciences (version 26.0, IBM Inc, Chicago, IL, USA).

4. Results

4.1. Exercise tolerance

Exercise tolerance, measured by the duration participants were able to exercise, was significantly affected by the cooling condition. In the MS individuals, exercise time was significantly longer during the COLD condition compared to the NEUTRAL condition. Specifically, MS individuals exercised for 28.40 ± 5.10 minutes during the COLD condition [95 % CI: 24.7, 30.0] and for 20.08 ± 5.13 minutes during the NEUTRAL condition [95 % CI: 17.12, 24.47]. The mean difference between the two conditions was 7.6 ± 3.06 min [95 % CI: 3.0, 13.0], (p = 0.002). The effect size (Cohen's d) for this difference was 1.63, indicating a large effect.

4.2. Physiological responses

At the start and throughout the pre-exercise period, heart rate and core temperature were similar between COLD and NEUTRAL. During exercise, heart rate was higher in the NEUTRAL condition by 4.2 beats/min (95 %CI: 2.6, 5.7) ($p < 0.001$) while core temperature was significantly lower in the COLD as compared to NEUTRAL by ~0.9 °C ($p < 0.05$). A similar trend was observed in mean skin temperature, which was reduced by ~1.5 °C ($p < 0.05$) in the COLD. Exercise time increased by 36.5 % ($p < 0.05$) during the COLD condition. Core and skin temperatures returned to baseline resting levels at the end of the 30-min post-exercise recovery in the COLD condition, while they remained elevated in the NEUTRAL condition (Table 2).

4.3. Functional capacity and fatigue

At baseline, no differences in functional capacity were observed between COLD and NEUTRAL ($P > 0.05$). However, the distance covered during the two-minute walk test at the end of the post-exercise recovery was significantly increased by 19.7 % ($p = 0.01$) in the COLD compared to the NEUTRAL condition while the COLD condition showed a medium effect size (Cohen's $d = 0.60$), suggesting a moderate improvement in walking endurance compared to the NEUTRAL condition (Fig. 2). Similarly, the time taken to complete the STS test was significantly reduced by 25 % ($p = 0.02$) in the COLD compared to the NEUTRAL condition. Postural stability improved significantly in the COLD (13.5 %; $p = 0.003$) relative to the NEUTRAL condition (Fig. 2). However, no significant differences were observed in the T25-FW test (COLD 4.2 ± 1.2 sec vs NEUTRAL 4.4 ± 1.8 sec, $p = 0.34$). The STS test revealed a large effect size (Cohen's $d = 0.87$), indicating a significant enhancement in lower body strength and functional mobility under the COLD condition. Similarly, the BBS demonstrated a medium effect size (Cohen's $d = 0.52$), reflecting an improvement in balance performance with the cooling intervention. These effect sizes highlight the potential benefits of cooling on functional capacity in individuals with MS, with varying degrees of impact across different measures of physical performance.

Table 2
Descriptive statistics for core and skin temperatures at different time points (baseline, prior to exercise, during exercise, and recovery) between the two conditions with COLD and NEUTRAL water.

	NEUTRAL	COLD	Difference means [95 % CI]	*p-value*	*Effect Size (Cohen's d)*
Core Temperature (°C)					
Baseline	36.85 ± 0.14	36.91 ± 0.15	-0.05 [-0.15, 0.05]	0.30	-0.41
Pre-exercise resting	36.66 ± 0.12	36.36 ± 0.17	0.32 [0.22, 0.728]	0.04	1.94
Exercise					
10 min	37.20 ± 0.31	36.48 ± 0.34	0.75 [-0.50, 0.850]	0.03	2.18
20 min	37.43 ± 0.31	36.38 ± 0.48	1.13 [0.12, 1.23]	0.01	2.55
End of exercise (Neutral: 20.8 min, Cold: 28.4 min)	37.61 ± 0.28	36.37 ± 0.43	1.18 [-1.23, 0.12]	0.03	3.12
End of recovery	37.14 ± 0.37	36.38 ± 0.28	0.76 [0.33, 1.46]	0.01	2.16
Mean Skin Temperature (°C)					
Baseline	33.24 ± 0.85	32.86 ± 0.89	0.41 [0.11, 1.34]	0.20	0.43
Pre-exercise resting	33.33 ± 0.81	32.28 ± 0.81	1.01 [-0.51, 1.61]	0.006	1.30
Exercise					
10 min	33.71 ± 0.63	32.52 ± 0.56	1 [-1.60, 0.51]	0.03	1.87
20 min	34.94 ± 0.79	32.47 ± 0.54	1.44 [0.64, 1.73]	0.006	3.46
End of exercise (Neutral: 20.8 min, Cold: 28.4 min)	34.03 ± 0.59	32.70 ± 0.45	1.14 [0.11, 1.98]	0.01	2.48
End of recovery	33.90 ± 0.67	32.17 ± 0.66	1.8 [0.78, 2.09]	0.008	2.59

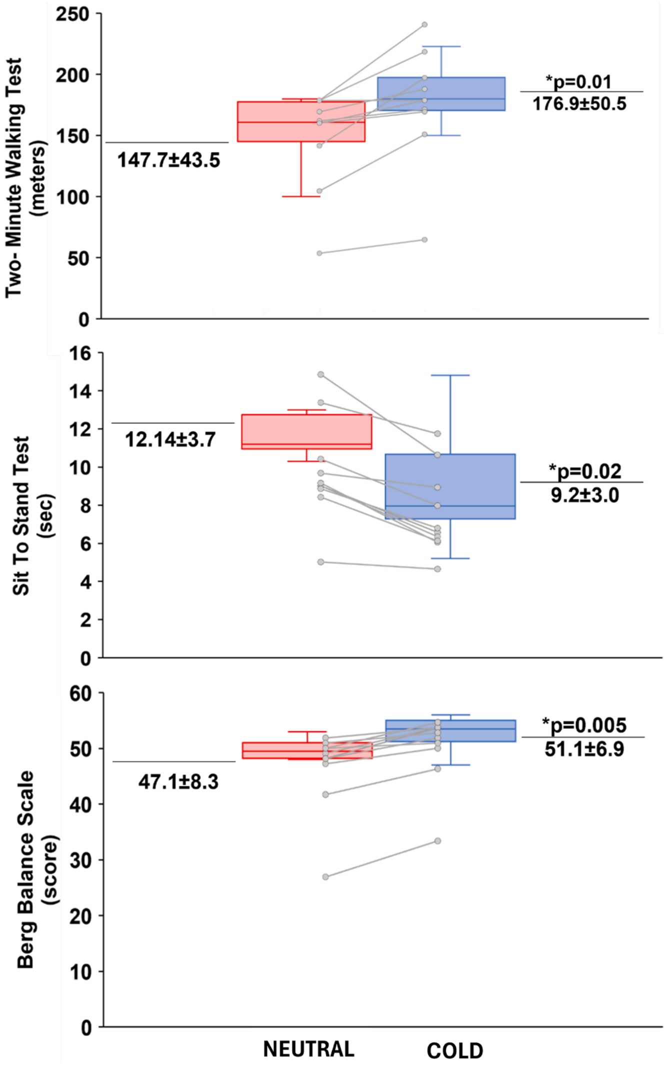


Fig. 2. Results of the three functional ability tests two-minute walking test (top panel), sit-to-stand test (middle panel) and Berg balance scale (bottom panel) performed prior to and at the end of the 30-min exercise recovery period for the COLD (blue) and NEUTRAL (red) conditions.
Individual data (gray lines) and group means.
Note: * = statistically significant ($p \leq 0.05$) differences between NEUTRAL and COLD conditions.

Fatigue levels were assessed using the MFIS and the FSS to determine any differences between conditions. The results indicated no significant differences in fatigue levels between the COLD and NEUTRAL conditions for either questionnaire. Specifically, the MFIS scores were 58.1 in the COLD condition and 58.0 in the NEUTRAL condition, while the FSS scores were 47.9 in the COLD condition and 47.5 in the NEUTRAL condition. Additionally, when baseline fatigue levels measured by the FSS were considered as a covariate in our analysis, we did not observe a significant effect on the acute exercise outcomes, indicating that baseline fatigue levels had no effect on the intervention results.

5. Discussion

We showed a practical and inexpensive commercial head-and-neck cooling system can significantly improve exercise tolerance and functional capacity, as well as reduce physiological heat strain without affecting fatigue levels in individuals with MS. This simple and practical method is particularly beneficial for MS individuals, as it can help manage their sensitivity to heat. Importantly, our observation of improvements in functional capacity and physical performance is particularly noteworthy, given that such improvements can benefit quality of life over the long term by enabling individuals with MS to engage more safely in physical activity, especially on warm to hot days (Schwid et al., 2002).

Relative to employing thermoneutral water, head-and-neck cooling with cold refrigerated water induced a reduction in core temperature. This was achieved by applying the head-and-neck cooling for 30 min prior to the start of (pre-cooling) exercise as well as during (per-cooling) the 30-min exercise bout. Previous studies employing cooling prior to an exercise rehabilitation intervention (i.e., pre-cooling) have reported reductions in core temperature of 0.4 to 1 °C (White et al., 2000, Reynolds et al., 2011). In these studies, pre-cooling consisted of lower limb immersion in a water bath maintained at 16-17 °C (26) or head-and-neck cooling with a hood maintained at 10 °C (27). While a greater overall reduction in core temperature was observed with lower limb cooling as compared to head-and-neck cooling, immersing one's lower limbs in a cold-water bath and having the capacity to regulate water at 16-17 °C may not be a viable option for many adults. On the other hand, employing head-and-neck cooling with head and neck cooling devices using cold water employed in the present study is a more practical option with similar effectiveness in mitigating exercise-induced increases in body temperature in individuals with MS. Moreover, the neutral temperature used (24–26 °C) might have induced a local cooling effect that was insufficient to produce significant improvements in functional capacity and exercise tolerance. Although local cooling has been shown to reduce fatigue and improve motor functions (Flensner and Lindencrona, 2002), its impact on sensory and cognitive processes is less clear and may not translate to enhanced exercise performance (Geisler et al., 1996).

In parallel to the reduction in core temperature, we observed a reduction in mean skin temperature of ~1.5 °C. While Buoite Stella et al. (2020) reported much greater reductions in skin temperature (i.e., 3.9 °C and 2.7 °C for the back and chest respectively), they employed a commercially available cooling vest with ice packs maintained at ~-0.4 °C to cool the body of MS patients during exercise in the heat (i.e., 30 °C, relative humidity of 30 %). Despite the less pronounced reduction in skin temperature in our study, our MS patients were able to extend their exercise duration by ~36 %, mirroring the findings of Buoite Stella et al. (2020) who observed a 36 % increase in total walk time. This suggests that, while the extent of temperature reduction varies with different cooling methods, the overall impact on enhancing exercise tolerance in MS individuals remains significant even at marginally higher skin temperatures.

A recent study by Vargas et al. (2021) investigated thermosensitive individuals with MS in cool-seeking behaviour (which involves voluntary cooling of the torso and arms using a tube-lined top set at around 2 °C) during exercise in a temperate environment. They showed that relative to their age-matched healthy counterparts, MS individuals spent more time in cooling during exercise (7 min vs 13 min), but voluntary cooling did not consistently alleviate perceptions of heat-related symptoms or subjective fatigue despite a reduction in mean skin temperature (by ~1.5 °C). While we recorded a similar reduction in skin temperature, we did not observe a concomitant reduction in fatigue. In the study by Vargas et al. (2021), the torso and arms were cooled with a tube-lined top set at around 2 °C in a temperate environment of 27 °C and 42 % humidity, whereas we cooled the head-and-neck region. This difference in the region of the body where cooling is applied may have been a mediating factor in terms of fatigue reduction.

An important observation of our study was the improvement in functional capacity with the application of head-and-neck cooling. This aligns with the findings of Grahn et al. (2008), who reported a significant 33 % increase in exercise duration when participants cooled one hand by placing it in a chamber maintained at 18–22 °C, during treadmill walking in a non-heat stress environment (i.e., 23 °C, relative humidity 10–25 %). In addition to benefits in exercise tolerance, we observed an improvement in functional capacity as evidenced by marked improvements in both STS (25.5 %) and BBS (13.5 %) tests. Previous studies have shown that cooling allows thermosensitive individuals with MS to participate more comfortably in exercise rehabilitation programs with fewer adverse effects caused by elevated level of heat stress (White et al., 2000, Davis et al., 2010, Kaltsatou and Flouris, 2019). Notably, Schwid et al. (2003) suggested that an improvement in functional capacity of less than 20 % may be insufficient to benefit MS patients. Consequently, our findings of marked improvements in functional capacity as assessed in the 2-minute walking test, STS, and the BBS suggest that head-and-neck cooling with a simple, commercially available system may benefit individuals with MS, potentially improving their quality of life through increased participation in exercise rehabilitation programs.

From a practical perspective, most if not all individuals with MS have access to the refrigerated water needed for the cooling system tested in our study, therefore making it easily accessible. With appropriate planning, individuals with MS could employ refrigerated water throughout the day, which in turn would provide greater improvements in functional ability and therefore quality of life. For those without access to refrigerated water, even employing tap water can mitigate increases in heat strain that may help facilitate greater engagement in activities of daily living and improve quality of life.

5.1. *Limitations*

Limitations of the current study include the relatively small sample size. Further research with larger cohorts and long-term follow-up is warranted to fully unravel the impacts of head-and-neck pre- and per-cooling during exercise as well as daily living activities. Additionally, alternative cooling methods should be assessed, including evaluating responses with the use of head-and-neck cooling to determine if more effective strategies may be available to individuals with MS. Finally, although, we tracked the participants' menstrual cycles and ensured that they were not in the menstrual phase during testing, we acknowledge that the different phases of their cycle may modulate thermoregulatory and perceptual response to heat. In summary, we show that employing a practical and inexpensive head-and-neck cooling method that can be easily applied in households significantly improved exercise tolerance and functional capacity, as well as reduced physiological heat strain without affecting fatigue levels in individuals with MS. In turn, this can help alleviate a heat-induced worsening of MS symptoms permitting individuals to engage more frequently in physical activity while reducing their risk of experiencing heat-related injuries. Given that exercise is recognized as an essential component of MS symptom management, individuals with MS should consider employing this simple and cost-effective strategy to enhance their participation in activities of daily living or general physical activity. Future studies should assess personalized cooling strategies based on factors such as the severity of MS, individual heat sensitivity, and lifestyle. Additionally, research should be conducted on the combined effects of cooling techniques with other therapeutic interventions in MS, such as exercise, behavioural techniques, and dietary modifications, to optimize patient outcomes.

CRediT authorship contribution statement

George Apostolou: Writing – original draft, Methodology, Investigation, Formal analysis. **Andreas D. Flouris:** Writing – review &

editing, Methodology, Formal analysis, Conceptualization. **Evangelia Kouidi:** Writing – review & editing, Supervision, Methodology. **Athanasios Z. Jamurtas:** Writing – review & editing, Supervision. **Glen P. Kenny:** Writing – review & editing. **Antonia Kaltsatou:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

None.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Acknowledgements

We would like to thank the Multiple Sclerosis Association of Kastoria and all the multiple sclerosis individuals who agreed to participate in the study.

Funding

This study received no funding.

References

(ACSM), A. C. O. S. M. S. (2018). Guidelines for exercise testing and prescription.

Allen, D.R., Huang, M.U., Morris, N.B., Chaseling, G.K., Jay, O., Davis, S.L., 2018. Impaired thermoregulatory function during dynamic exercise in multiple sclerosis. Med. Sci. Sports Exerc. 51, 395–404.

Alosaimi, R.M., Almegbas, N.R., Almutairi, G.R., Alqahtani, M.A., Batook, S.G., Alfageh, I.A., Alanazi, S.F., Alshehri, M.M., Alhowimel, A.S., Alqahtani, B.A., Alenazi, A.M., 2023. The five times sit-to-stand test is associated with both history of falls and fear of falling among community adults aged 50 years and older. Ir. J. Med. Sci. 192 (5), 2533–2540.

Aslani, E., Andriopoulos, P., Kattamis, A., Lyrakos, G.N., Tsironi, M., 2019. Reliability and validity of the greek version of the multidimensional fatigue inventory (MFI-20) in patients with hemoglobinopathies. Arch. Hell. Med. 36 (2), 245–253.

Bakalidou, D., Skordilis, E.K., Giannopoulos, S., Stamboulis, E., Voumvourakis, K., 2013. Validity and reliability of the FSS in Greek MS patients. Springerplus 2 (1), 304.

Buoite Stella, A., Pasquin, F., Morrison, S.A., Morelli, M.E., Dinoto, A., Bratina, A., Bosco, A., Sartori, A., Giudici, F., Manganotti, P., 2020. Effects of a cooling vest with sham condition on walking capacity in heat-sensitive people with Multiple Sclerosis. Eur. J. Appl. Physiol. 120 (11), 2467–2476.

Butland, R.J., Pang, J., Gross, E.R., Woodcock, A.A., Geddes, D.M., 1982. Two-, six-, and 12-minute walking tests in respiratory disease. Br. Med. J. (Clin. Res. Ed.) 29 (6329), 1607–1608.

Chaseling, G.K., Filingeri, D., Barnett, M., Hoang, P., Davis, S.L., Jay, O., 2018. Cold water ingestion improves exercise tolerance of heat-sensitive people with MS. Med. Sci. Sports Exerc. 50 (4), 643–648.

Correale, L., Martinis, L., Tavazzi, E., Pedulla, L., Mallucci, G., Brichetto, G., Bove, M., Ponzio, M., Borrelli, P., Monti, M.C., Bergamaschi, R., Montomoli, C., 2022. Barriers to exercise and the role of general practitioner: a cross-sectional survey among people with multiple sclerosis. Front. Neurol. 13, 1016143.

Dalgas, U., Langeskov-Christensen, M., Stenager, E., Riemenschneider, M., Hvid, L.G., 2019. Exercise as medicine in multiple sclerosis-time for a paradigm shift: preventive, symptomatic, and disease-modifying aspects and perspectives. Curr. Neurol. Neurosci. Rep. 19 (11), 88.

Davis, S.L., Wilson, T.E., White, A.T., Frohman, E.M., 2010. Thermoregulation in multiple sclerosis. J. Appl. Physiol. 109 (5), 1531–1537 (1985).

de Melo, T.A., Duarte, A.C., Bezerra, T.S., França, F., Soares, N.S., Brito, D., 2019. The five times sit-to-stand test: safety and reliability with older intensive care unit patients at discharge. Rev. Bras. Terapia Int. 31 (2), 27.

Enoka, R.M., Almuklass, A.M., Alenazy, M., Alvarez, E., Duchateau, J., 2021. Distinguishing between Fatigue and Fatigability in Multiple Sclerosis. Neurorehabil. Neural Repair. 35 (11), 960–973.

E. E. Faul, F., Lang, A.G., Buchner, A., 2007. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences Behav. Res. Methods 39 (2), 175–191.

Flensner, G., Lindencrona, C., 2002. The cooling-suit: case studies of its influence on fatigue among eight individuals with multiple sclerosis. J. Adv. Nurs. 37 (6), 541–550.

Frohman, T.C., Davis, S.L., Beh, S., Greenberg, B.M., Remington, G., Frohman, E.M., 2013. Uhthoff's phenomena in MS–clinical features and pathophysiology. Nat. Rev. Neurol. 9 (9), 535–540.

Geisler, M.W., Gaudino, E., Squires, N., Coyle, P., Doscher, C., Krupp, L., 1996. Cooling and multiple sclerosis: cognitive and sensory effects. J. Neuro Rehab. 10, 17–21.

Gordon, R., Tillin, N., Tyler, C.J., 2020. The effect of head and neck per-cooling on neuromuscular fatigue following exercise in the heat. Appl. Physiol. Nutr. Metab.

Grahn, D.A., Murray, J.V., Heller, H.C., 2008. Cooling via one hand improves physical performance in heat-sensitive individuals with multiple sclerosis: a preliminary study. BMC Neurol. 8, 14.

Howard, J., Trevick, S., Younger, D.S., 2016. Epidemiology of multiple sclerosis. Neurol. Clin. 34 (4), 919–939.

Huang, M., Morris, N., Jay, O., Davis, S., 2014. Thermoregulatory dysfunction in multiple sclerosis patients during moderate exercise in thermoneutral environment (1104.17). FASEB 28.

Kaltsatou, A., Flouris, A.D., 2019. Impact of pre-cooling therapy on the physical performance and functional capacity of multiple sclerosis patients: a systematic review. Mult. Scler. Relat. Disord. 27, 419–423.

Koch-Henriksen, N., Sorensen, P.S., 2010. The changing demographic pattern of multiple sclerosis epidemiology. Lancet Neurol. 9 (5), 520–532.

Krupp, L., 2006. Fatigue is intrinsic to multiple sclerosis (MS) and is the most commonly reported symptom of the disease. Mult. Scler. 12 (4), 367–368.

Krupp, L.B., LaRocca, N.G., Muir-Nash, J.R.N., Steinberg, A.D., 1989. The fatigue severity scale: application to patients with multiple sclerosis and systemic lupus erythematosus. Arch. Neurol. 46 (10), 1121–1123.

Ku, Y.T., Montgomery, L.D., Wenzel, K.C., Webbon, B.W., Burks, J.S., 1999. Physiologic and thermal responses of male and female patients with multiple sclerosis to head and neck cooling. Am. J. Phys. Med. Rehabil. 78 (5), 447–456.

Kurtzke, J.F., 1983. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 33 (11), 1444–1452.

Lenman, A.J., Tulley, F.M., Vrbova, G., Dimitrijevic, M.R., Towle, J.A., 1989. Muscle fatigue in some neurological disorders. Muscle Nerve 12 (11), 938–942.

Lin, J.M.S., Brimmer, D.J., Maloney, E.M., Nyarko, E., BeLue, R., Reeves, W.C., 2009. Further validation of the Multidimensional Fatigue Inventory in a US adult population sample. Popul. Health Metr. 7, 18.

Marrie, R.A., 2017. Comorbidity in multiple sclerosis: implications for patient care. Nat. Rev. Neurol. 13 (6), 375–382.

Notley, S.R., Meade, R.D., Kenny, G.P., 2021. Time following ingestion does not influence the validity of telemetry pill measurements of core temperature during exercise-heat stress: the journal Temperature toolbox. Temperature (Austin) 8 (1), 12–20.

Polman, C.H., Reingold, S.C., Banwell, B., Clanet, M., Cohen, J.A., Filippi, M., Fujihara, K., Havrdova, E., Hutchinson, M., Kappos, L., Lublin, F.D., Montalban, X., O'Connor, P., Sandberg-Wollheim, M., Thompson, A.J., Waubant, E., Weinshenker, B., Wolinsky, J.S., 2011. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann. Neurol. 69 (2), 292–302.

Ramanathan, N.L., 1964. A new weighting system for mean surface temperature of the human body. J. Appl. Physiol. 19, 531–533.

Reynolds, L.F., Short, C.A., Westwood, D.A., Cheung, S.S., 2011. Head pre-cooling improves symptoms of heat-sensitive multiple sclerosis patients. Can. J. Neurol. Sci. 38 (1), 106–111.

Schwid, S.R., Goodman, A.D., McDermott, M.P., Bever, C.F., Cook, S.D., 2002. Quantitative functional measures in MS: what is a reliable change? Neurology 58 (8), 1294–1296.

Schwid, S.R., Petrie, M.D., Murray, R., Leitch, J., Bowen, J., Alquist, A., Pelligrino, R., Roberts, A., Harper-Bennie, J., Milan, M.D., Guisado, R., Luna, B., Montgomery, L., Lamparter, R., Ku, Y.T., Lee, H., Goldwater, D., Cutter, G., Webbon, B., 2003. A randomized controlled study of the acute and chronic effects of cooling therapy for Multiple Sclerosis. Neurology 60 (12), 60–1955.

Smith, K.J., McDonald, W.I., 1999. The pathophysiology of multiple sclerosis: the mechanisms underlying the production of symptoms and the natural history of the disease. Philos. Trans. R. Soc. Lond. B Biol. Sci. 354 (1390), 1649–1673.

Solari, A., Radice, D., Manneschi, L., Motti, L., Montanari, E., 2005. The multiple sclerosis functional composite: different practice effects in the three test components. J. Neurol. Sci. 228 (1), 71–74.

Stevens, C.J., Singh, G., Peterson, B., Vargas, N.T., Periard, J.D., 2023. The effect of cooling garments to improve physical function in people with multiple sclerosis: a systematic review and meta-analysis. Mult. Scler. Relat. Disord. 78, 104912.

Storer, T.W., Davis, J.A., Caiozzo, V.J., 1990. Accurate prediction of VO2max in cycle ergometry. Med. Sci. Sports Exerc. 22 (5), 704–712.

Sun, C., Zhiwei, L., Lan, L., Zhang, H., 2013. Investigation on temperature range for thermal comfort in nonuniform environment. HVAC&R Res. 19 (2), 103–112.

Vargas, N.T., Chapman, C.L., Reed, E.L., Lizarraga, A., Fisher, N.M., Davis, S.L., Schlader, Z.J., 2021. Voluntary cooling during exercise is augmented in people with multiple sclerosis who experience heat sensitivity. Med. Sci. Sports Exerc. 53 (11), 2405–2418.

White, A.T., Wilson, T.E., Davis, S.L., Petajan, J.H., 2000. Effect of precooling on physical performance in multiple sclerosis. Mult. Scler. 6 (3), 176–180.

Whitney, S.L., Wrisley, D.M., Marchetti, G.F., Gee, M.A., Redfern, M.S., Furman, J.M., 2005. Clinical measurement of sit-to-stand performance in people with balance disorders: validity of data for the five-times-sit-to-stand test. Phys. Ther. 85 (10), 1034–1045.