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Review article

The effect of cooling garments to improve physical function in people with multiple sclerosis: A systematic review and meta-analysis

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ABSTRACT

Background: There is strong evidence for the benefits of exercise for people with Multiple Sclerosis (MS), however, up to 80% of people with MS report experiencing exacerbated symptoms with elevated body temperatures. A range of cooling garments to assist people with MS manage symptoms of heat sensitivity have been investigated. Therefore, the aim of this systematic review was to assess the effect of cooling garments to improve physical function in people with MS, and to determine any associated physiological and perceptual responses.
Method: A systematic review adhering to the PRISMA guidelines was performed. The eligibility criteria required investigations to have conducted a randomized controlled trial or cross-over study to assess the effect of a cooling garment to improve physical function, or a related physiological or perceptual measure, in people with MS.
Results: Thirteen empirical studies were identified, compromising of acute cross-over designs (61.5%), longitudinal parallel group designs (23.1%) or a combination of both (15.4%). The studies included 384 participants with MS with an expanded disability status scale range of 1–7.5. Garments included liquid-perfused cooling vests/tops/hoods (50.0%), phase-change cooling vests (38.9%), a cooling thigh-cuff (5.6%) and a palm cooling device (5.6%). The cooling garments were effective at improving walking capacity and functional mobility, and some studies demonstrated improvements in muscular strength and balance, but not manual dexterity. The garments also resulted in improved core temperature, skin temperature, thermal sensation and subjective fatigue. Improvements occurred in temperate and warm conditions, and both with and without an exercise stimulus.
Discussion: Cooling garments can improve physical function for people with MS. Since none of the cooling garments caused harm, and no particular cooling garment could be identified as being superior, people with MS should experiment with different cooling garments to determine their preference, and industry should focus on cooling garments that are effective, accessible and user-friendly.

1. Introduction

Multiple sclerosis (MS) is an autoimmune neurodegenerative disease affecting an estimated 2.3 million people worldwide (Browne et al., 2014). Physiologically, MS is characterized by demyelination of the sheath that surrounds nerve fibres within the central nervous system, which reduces the efficiency of action potentials and can lead to incorrect signal transmission at the synaptic cleft (Fuhr and Schindler, 2015). The symptoms associated with the disease vary and are often dependant on the severity and location of the affected nerve fibres, but common symptoms include sensory disturbances such as pain and fatigue, motor weakness, impaired gait, lack of coordination and optic neuritis (Saguil et al., 2022). These symptoms can have a profound impact on physical function, which can hinder activities of daily living and employment (Vitturi et al., 2022), social participation (Mikula et al., 2015) and quality of life (Li et al., 2022). Disease modifying drugs such as corticosteroids and immunomodulator medications are the first line pharmacological management strategy for MS (Robertson and Moreo, 2016), however, people with MS should be treated by a multidisciplinary team to promote good health, manage symptoms and maintain

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functional capacity (Saguil et al., 2022).

There is strong evidence for the benefits of physical activity and exercise for people with MS (Halabchi et al., 2017; Hoang et al., 2022). Traditionally, exercise was thought to exacerbate MS symptoms such as fatigue (Halabchi et al., 2017), however, exercise is now considered safe and effective for people with MS, as well-controlled studies have demonstrated that exercise interventions can improve functional capacity (Rampello et al., 2007; White et al., 2004) and reduce fatigue (Petajan et al., 1996; Pilutti et al., 2013). Exercise recommendations for people with mild-moderate MS include at least 30 min of moderate intensity aerobic exercise twice per week, muscle strengthening exercises twice per week, as well as balance training exercises (Hoang et al., 2022). Those with low levels of disability can also progress to programs incorporating high-intensity interval training (Campbell et al., 2018; Hoang et al., 2022), which can have greater benefit than lower intensity training, but may not be as well-tolerated (Collett et al., 2011). Regardless of these published recommendations, people with MS can be discouraged from engaging in physical activity and exercise programs due to initially experiencing post-exercise fatigue and other symptoms that may be related to increased body temperatures (Hoang et al., 2022).

Up to 80% of people with MS report experiencing heat sensitivity, where MS symptoms are exacerbated by elevated body temperatures (Syndulko et al., 1996). "Uhthoff's Phenomenon" was first used to describe the transient blurring of vision that people with MS experience during physical activity and exercise, but has since expanded to describe a range of neurological symptoms that are temporarily exacerbated by environmental- or exercise-induced increases in body temperature (Jain et al., 2019), including fatigue, pain, concentration difficulty and urination urgency (Christogianni et al., 2018; Flensner et al., 2011). While it is understood that these symptoms are primarily caused by temperature-dependant slowing or blocking of neural conduction within the central nervous system (Christogianni et al., 2018), it has also been reported that cooling garments may improve physical function and capacity irrespective of substantial increases in body temperature in MS cohorts (Beenakker et al., 2001; Meyer-Heim et al., 2007; Reynolds et al., 2011). Moreover, it was recently reported that increases in ambient temperature alone (i.e., hot days) can result in augmented symptomology, especially fatigue (Christogianni et al., 2022). People with MS are known to predominantly use air-conditioning to keep cool on hot days to attenuate heat sensitivity symptoms (Christogianni et al., 2022), but when air-conditioning is not available, heat sensitivity poses a substantial barrier to physical function, which could reduce engagement in physical activity, exercise and activities of daily living. Therefore, effective and accessible strategies are needed for people with MS who want to be active, especially in warmer outdoor environments.

A range of cooling strategies designed to assist people with MS to improve physical function have been investigated, predominantly cold-water immersion and the application of specialized liquid-perfused cooling garments (Kaltsatou and Flouris, 2019). A large focus of this MS research has been on the use of 'pre-cooling', which involves cooling the body prior to exercise to delay the negative effects of increased body temperature. A systematic review demonstrated that pre-cooling strategies were effective in reducing core temperature by 0.4–1.0 °C after 30–60 min of cold exposure, which was enough to significantly improve subsequent physical performance and functional capacity in people with MS (Kaltsatou and Flouris, 2019). However, pre-cooling protocols are arduous and can be impractical to incorporate into daily life, and as such, more practical and user-friendly methods have been researched, predominantly 'phase-change' cooling garments with removable cooling packs, which are lightweight and can be worn during exercise. These phase-change cooling garments have received recent research interest (Buoite Stella et al., 2020; Gonzales et al., 2017; Özkan Tuncay and Mollaoğlu, 2017), and potentially present an effective cooling strategy for people with MS to overcome heat sensitivity and better engage in exercise and physical activity. There is a growing number of cooling garments commercially available that are marketed specifically toward people with MS, and some of these garments are included in medical rebate schemes that can be accessed by people with MS in some countries. As such, health professionals should be aware of the effects of these cooling garments in order to provide recommendations, however, no systematic review has been performed on the topic and no guidelines currently exist. Therefore, the primary aim of this systematic review was to assess the effect of cooling garments to improve physical function in people with MS, and the secondary aim was to determine any associated physiological and perceptual responses, which may provide insights into the mechanisms of any improvements.

2. Method

2.1. Protocol

This systematic review was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO; ID number: CRD42022354560) and adhered to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines (Page et al., 2021). One deviation from the PROSPERO registration was made, to use the terminology 'improve physical function' in place of 'aid exercise therapy' to better reflect the scope of the systematic review. This deviation had no impact on the eligibility of studies or on the outcomes and results reported within the review.

2.2. Eligibility criteria

Studies eligible for inclusion in this review were randomized controlled trials or randomized cross-over trials which assessed the effect of a cooling garment to improve physical function in people with MS. For the purpose of this review, a 'cooling garment' was defined as any cooling device that could be worn on the body or head immediately before and/or during a task. Improving 'physical function' was defined as an improvement in a direct measure of physical function including cardio-respiratory endurance, walking distance or speed, functional mobility, muscular strength, balance or manual dexterity. Related physiological and perceptual measures were also included such as body temperatures, heart rate, sweat loss, skin blood flow, thermal sensation, thermal comfort, subjective fatigue, MS symptoms, motivation, rating of perceived exertion, and exercise engagement/adherence. We did not require studies to have implemented an exercise or other heating stimulus in an attempt to induce heat sensitivity symptoms, as we aimed to determine how cooling garments could improve physical function in all situations. Studies must have contained empirical data and been published in a peer-reviewed journal. Conference abstracts and theses were excluded.

2.3. Information sources and search strategy

An electronic database search was conducted in Academic Search Premier, Medline, SPORTdiscus, CINAHL, AMED, PEDro, EMBASE, The Cochrane Library, Web of Science (Core Collection) and Scopus. Preliminary searches were performed between the 16th and 17th August 2022, with the final search conducted on 18th August 2022. The search string was extensively piloted to ensure that the search was comprehensive (Siddaway et al., 2019). A search strategy based on PICO was initially piloted but ultimately many terms were deemed redundant and removed as they did not increase the number of search returns. The final search string was: ("multiple sclerosis") and (cooling). Retrieved titles and abstracts were imported into Endnote X9 reference management software (Clarivate, United Kingdom) before the results were imported into Covidence screening software (Covidence, Australia).

2.4. Screening process

Two authors (CS and GS) independently screened all titles, abstracts, and full-texts to determine if studies met the eligibility criteria. Any disagreements regarding eligibility of the studies were resolved following arbitration with a third reviewer (BP). One author (CS) also conducted a manual search for any articles not retrieved by the database search, which involved screening the reference lists of studies identified until no further studies were discovered.

2.5. Quality assessment

The Cochrane RoB2 tool for randomized trials and the Cochrane RoB2 tool for cross-over trials were deemed applicable to assess the risk of bias in the included studies, which were selected in accordance with Cochrane guidelines (Sterne et al., 2019). These tools involved a series of questions being answered independently by two reviewers (CS and GS) and arbitration carried out by a third reviewer (BP) when required. The individual domains within the RoB2 tool address potential sources of bias relating to randomization procedures, deviations from intended interventions, statistical methods, missing outcome data, measurement techniques, and selective reporting of results. Each domain proposed a judgement risk as either 'low', 'high' or 'some concerns' based on a standardized assessment framework.

2.6. Data extraction and analysis

Data extraction was performed with a custom data extraction tool by one author (CS) and checked by a second author (GS). Extracted data included: authors; study design; participant characteristics including sample size, heat sensitivity status, MS type, sex, age and expanded disability status scale (EDSS) score; intervention(s); protocol; outcome measures; environmental conditions; and results. When articles had

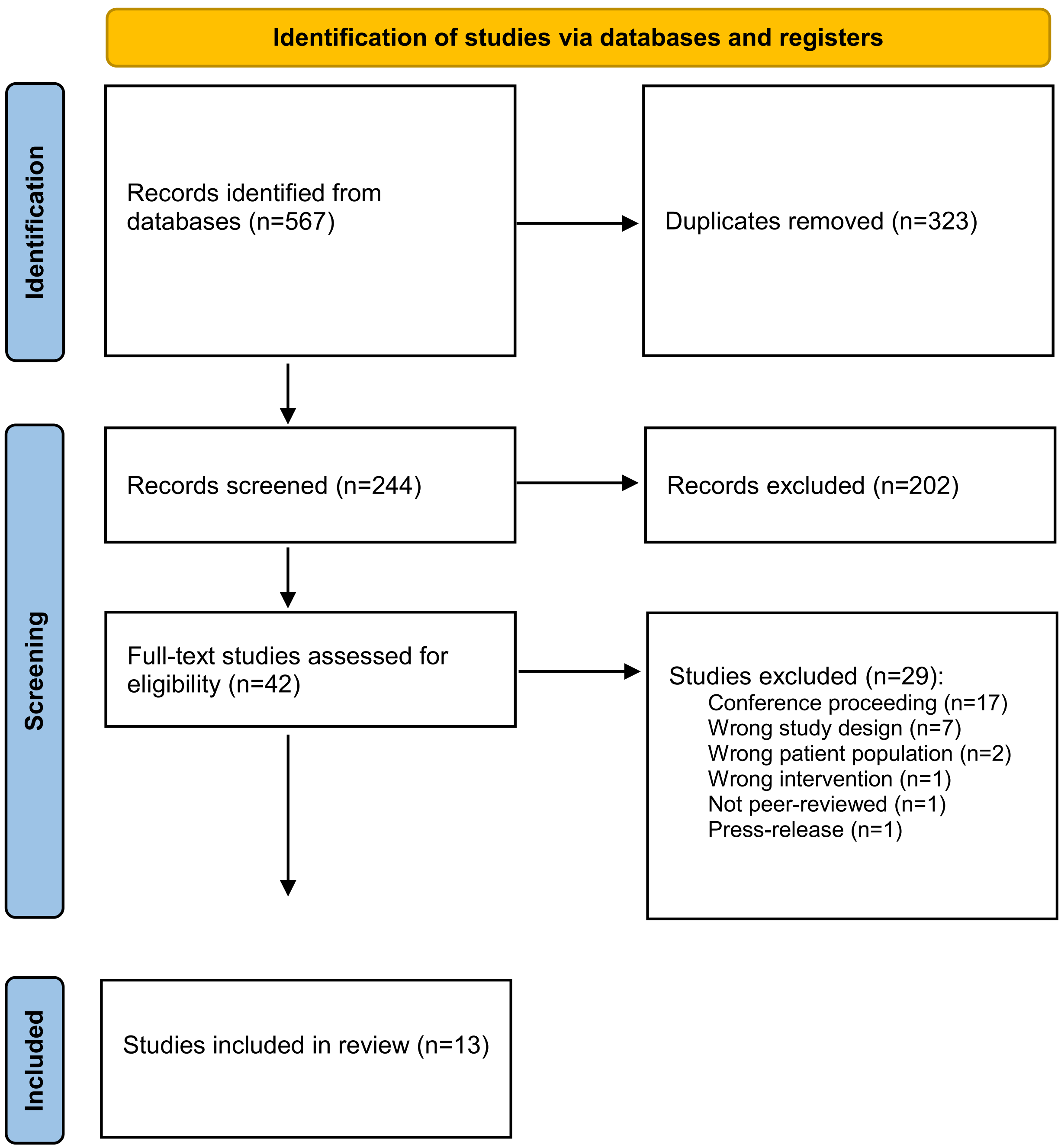

Fig. 1. Prisma flow diagram of the screening results.

missing or ambiguous data, the authors of the articles were contacted to see if the data could be acquired.

Meta-analyses were conducted using Review Manager 5.4.1 (The Cochrane Collaboration, Denmark) where possible and the remaining data were analysed by narrative synthesis. Meta-analyses were performed when at least two of the studies with the same research design assessed the same outcome variable, and where the required data could be acquired. In cases of multi-armed trials with one control group and multiple intervention groups, or where studies reported the same physiological responses at multiple sites, a sensitivity analysis was performed and the data which resulted in the lowest level of statistical heterogeneity between studies (based on the I^2 statistic) was included in the meta-analysis. This conservative approach was taken to avoid contamination effects due to non-independence of patient group data whilst also taking a standardized approach to data selection and inclusion. Standard deviations were calculated from standard errors where required. Meta-analyses used weighted mean differences in instances where all studies reported the outcome using the same scale, otherwise, standardized mean differences were used. Unadjusted estimates were used in each analysis. Magnitudes of standardized mean differences were interpreted according to Hopkins' modified version of Cohen's scale: <0.20 = trivial effect, 0.20 to 0.59 = small effect, 0.60 to 1.19 = moderate effect, and >1.19 = large effect (Hopkins et al., 2009).

3. Results

3.1. Study characteristics

A Prisma flow diagram of the screening results is illustrated in Fig. 1 and the characteristics of the 13 included studies are presented in Table 1. Search returns that were excluded after full-text screening are listed in Supplementary File 1. Included studies comprised of a total of 384 participants, and for studies that reported sex ($n = 12$), 63.4% were female and 36.6% were male. For studies that reported MS type ($n = 9$), 70.8% were relapsing remitting, 16.3% were primary progressive and 12.9% were secondary progressive. Participants had an EDSS range of 1–7.5. All participants were reported to be heat-sensitive, except for one study which did not report heat sensitivity status (Özkan Tuncay and Mollaoğlu, 2017). None of the studies excluded participants based on experiencing cold sensitivity symptoms, nor did they report if any of the included participants experienced cold-sensitivity symptoms. A total of 18 cooling garments were investigated including active liquid-perfused cooling vests/tops/hoods (50.0%), phase change cooling vests (38.9%), a cooling thigh-cuff (5.6%) and a palm cooling device (5.6%). The studies had either an acute (single session) cross-over design (61.5%), a longitudinal (multiple session) parallel or cross-over design (23.1%), or a combination of both acute and longitudinal phases (15.4%). In the acute studies, outcomes were measured while wearing the cooling garment (Buoite Stella et al., 2020; Grahn et al., 2008; Meyer-Heim et al., 2007; Vargas et al., 2021), or shortly after wearing the cooling garment (Beenakker et al., 2001; Coyle et al., 1996; Ku et al., 2000; Nilsagård et al., 2006; Reynolds et al., 2011; Schwid et al., 2003; Syndulko et al., 1995), and were compared to a control and/or other cooling garment(s). In the longitudinal studies, outcomes were measured pre/-post a 4- to 8-week intervention period involving regular use of the cooling garment, and were compared to a control (Gonzales et al., 2017; Özkan Tuncay and Mollaoğlu, 2017; Schwid et al., 2003; Syndulko et al., 1995). Three of the studies performed assessments in situations where the participants had an elevated body temperature due to the protocol involving prolonged walking or cycling (Buoite Stella et al., 2020; Grahn et al., 2008; Vargas et al., 2021). None of the other included studies involved enough exercise or any other type of heating stimulus to increase body temperature in the participants.

3.2. Quality appraisal

A summary of the quality appraisal results is presented in Table 2. Overall, 8/13 studies returned a low risk of bias, 3/13 studies returned some concerns due to a lack of information reported regarding Domain S1, and 2/13 studies returned a high risk of bias due to issues with the selection of the reported result or missing outcome data.

3.3. Meta-analysis

The results for the meta-analyses that could be performed are presented in forest plots in Figs. 2 and 3, for the acute and longitudinal comparisons, respectively. A limited number of meta-analyses with a limited number of studies could be conducted due to differences in study design, inconsistency in the outcome variables assessed and inadequate and inconsistent data reporting. The meta-analyses demonstrate that the use of cooling garments significantly improved walking time to exhaustion, thermal sensation, core temperature (i.e. rectal, gastrointestinal, oral, tympanic), skin temperature and subjective fatigue, while having no effect on timed 25 ft walk, postural sway or 9-hole peg test time. No sub-group analyses could be performed to make comparisons between different types of cooling garments. Standardized mean differences were used for the pooled analyses of timed 25 ft walk, 9-hole peg test and core temperature due to the inclusion of absolute and change from baseline data (Fig. 2), and for subjective fatigue, due to the different measurement instruments used (Fig. 3). The pooled analysis for skin temperature had high heterogeneity (Fig. 2G), which is explained by one study reporting the mean skin temperature across ten sites (Vargas et al., 2021) and the other reporting data for individual sites (Buoite Stella et al., 2020). The pooled analysis for subjective fatigue also had high heterogeneity (Fig. 3), which is likely explained by the studies using different measurement instruments.

3.4. Narrative synthesis

A summary of the results reported in each study is presented in Supplementary File 2.

3.4.1. Walking capacity and functional mobility

Eight studies investigated the effect of cooling garments on walking capacity and/or functional mobility. For longer walking protocols as a measure of endurance, acute cooling garment use significantly increased walking time to exhaustion by 35–36% (in protocols of ~30 min duration) while wearing a phase change cooling vest (Buoite Stella et al., 2020) or a palm cooling device (Grahn et al., 2008). A further study demonstrated a significant increase (11%) in 6-min walk test distance following the acute use of a liquid-perfused cooling hood (Reynolds et al., 2011), and similarly, a significant increase (27%) in 6-min walk test distance was reported compared to control after longitudinal use of a phase change cooling garment within a 7-week exercise program (Gonzales et al., 2017). For shorter walking tests that represent functional mobility, there have been significant (3%) improvements in both 10 m and 30 m walking times with a phase change cooling vest (Nilsagård et al., 2006), and significant 4–11% improvements in the 'timed up and go test' with a phase change cooling vest (Nilsagård et al., 2006) and liquid-perfused cooling hood (Reynolds et al., 2011). There were mixed results in the timed 25 ft walk test, where an acute cooling garment resulted in significant 21–22% improvements across two studies (Coyle et al., 1996; Meyer-Heim et al., 2007), whereas two other acute studies demonstrated no change (Reynolds et al., 2011; Schwid et al., 2003). A separate study also reported no change in timed 25 ft walk following longitudinal use of a liquid-perfused head-vest cooling garment over 4 weeks (Schwid et al., 2003). Hence, all studies that assessed walking capacity and functional mobility in tests ≥10 m demonstrated significant improvements, indicating that the cooling garments were effective at improving walking capacity and functional mobility in people with

Table 1
The characteristics of the included studies.

Authors	Design	Participants	Intervention(s)	Protocol and outcome measures	Environmental conditions
Beenakker et al., 2001	Randomised cross-over (acute)	10 people with MS with heat sensitivity (MS type NR, female=5, age=41 ± 9, EDSS=3.5–6.5)	Liquid head-vest cooling garment (Life Enhancement Technologies) that was active (7 °C) vs. sham active (26 °C), worn during passive sitting	60 min of passive sitting with pre/post assessment of leg muscle strength, postural sway with eyes open and closed and subjective fatigue. Tympanic temp. measured across protocol and at 3 h post	NR
Buoite Stella et al., 2020	Randomised cross-over (acute)	10 people with MS with heat sensitivity (RR=8, PP=2, female=10, age=59 ± 9 y, EDSS=3–5.5)	Phase change cooling vest (CryoVest Comfort) vs. sham vest with menthol, worn during exercise	Walking time to exhaustion at 20% above 'comfortable speed' with assessment of thermal sensation, skin temp., and heart rate	29–30 °C, 30% RH
Coyle et al., 1996	Randomised cross-over (acute)	11 people with MS with heat sensitivity (RR=11, female=5, age=44 ± 8 y, EDSS=2.7 ± 0.6)	Liquid head-vest cooling garment (Life Support Systems) that was active (temp. NR) vs. sham active (temp. NR), worn during passive sitting	45 min of passive sitting with pre/post assessment of timed 25 ft walk and muscle strength	NR
Gonzales et al., 2017	Parallel groups (longitudinal)	18 people with MS with heat sensitivity (PP=7, SP=11, female=12, age=50 ± 8 y, EDSS=5.1 ± 1)	Phase change cooling vest (Vtherm Inc) vs. cotton t-shirt, worn during exercise sessions	7-week exercise program with pre/post assessment of 6 min walk distance and subjective fatigue, activity and motivation	20–22 °C, RH NR
Grahn et al., 2008	Randomised cross-over (acute)	10 people with MS with heat sensitivity (RR=8, SP=2, female=4, age=52 ± 6 y, EDSS=3.5–6)	Palm cooling device (AVAcore Technologies) worn on hand with palm on a metal surface at 18–22 °C vs. control with no device, worn during exercise	Walking time to exhaustion at 65% of maximum with assessment of heart rate	23 ± 1 °C, 10–25% RH
Ku et al., 2000	Independent groups (acute)	78 people with MS with heat sensitivity (MS type NR, female=39, age=31–67 y, EDSS=5–7.5)	Liquid head-vest cooling garment (Life Enhancement Technologies; LET) that was active (10 °C) vs. phase change cooling vest (MicroClimate Systems; MCS) vs. phase change cooling vest (Steele), worn during passive sitting	60 min of passive sitting with pre/post assessment of handgrip strength, manual dexterity and subjective energy and muscle strength. Body temps. measured across protocol	22 °C, RH NR
Meyer-Heim et al., 2007	Randomised cross-over (acute)	20 people with MS with heat sensitivity (MS type NR, female=10, age=27–66 y, EDSS=1.5–6.5)	Cooling thigh cuff vs. sham thigh cuff, worn throughout protocol	10 min of passive sitting with post assessment of timed 25 ft walk, muscle strength, balance, 9-hole peg test and subjective feelings. Tympanic temp. measured across protocol	23–24 °C, RH NR
Nilsagard et al., 2006	Randomised cross-over (acute)	43 people with MS with heat sensitivity (RR=22, SP=13, PP=8, female=30, age=52 ± 9, EDSS=3.0–6.0)	Phase change cooling vest (Rehband) that was frozen in freezer at −20 °C vs. not frozen (22 °C), worn during passive sitting	45 min of passive sitting with pre/post assessment of 10 m and 30 m timed walk, timed up and go, balance, 9-hole peg test and subjective measures. Oral temp. measured across protocol	22–23 °C, RH NR
Ozkan Tuncay et al., 2017	Parallel groups (longitudinal)	75 people with MS (heat sensitivity NR, RR=57, SP=8, PP=8, female=57, age experimental group=36 ± 8, age control group=38 ± 7, EDSS≤6)	Ice pack cooling vest (brand NR) vs. observation control, worn once daily for 40 min during passive sitting	8-week period with assessment of Fatigue Impact Scale, Fatigue Severity Scale and Modified Barthel Index at 0, 4 and 8 weeks	Mean daily temp.: 25–29 °C
Reynolds et al., 2011	Randomised cross-over (acute)	6 people with MS with heat sensitivity (MS type NR, female=6, age=41 ± 7, EDSS=2.5–6.5)	Liquid head and neck cooling hood (Life Enhancement Technologies) that was active (10 °C) vs. sham (24 °C, with periods of 10 °C) vs. control worn during passive sitting	60 min of passive sitting with post assessment of timed 25 ft walk, 6 min walk distance, timed up and go and muscle strength. Rectal temp. and thermal sensation measured across protocol	22 °C, 40% RH
Schwid et al., 2003	(a) Randomised cross-over (acute)	84 people with MS with heat sensitivity (RR=74, PP=6, MS type NR=4, female=52, age=48 ± 1, EDSS=3.3 ± 0.2)	Liquid head-vest cooling garment (Life Enhancement Technologies) that was active (13 °C) vs. sham active (21 °C), worn during passive sitting	60 min of passive sitting with pre/post assessment of timed 25 ft walk and 9-hole peg test. Oral temp. measured across protocol	NR
	(b) Randomised crossover (longitudinal)	84 people with MS with heat sensitivity (RR=74, PP=6, MS type NR=4, female=52, age=48 ± 1, EDSS=3.3 ± 0.2)	Liquid head-vest cooling garment (Life Enhancement Technologies) that was active (13 °C) vs. observation control, worn once daily for 60 min during passive sitting	4-weeks with daily assessment of subjective fatigue and subjective strength	NR
Syndulko et al., 1995	(a) Randomised cross-over (acute)	9 people with MS with heat sensitivity (PP=4, SP=1, RR=4, female=5, age=43 ± 7, EDSS=4.9 ± 1.6)	Liquid head-vest cooling garment (Life Support Systems; LSS) that was active (temp. NR) vs. phase change cooling vest (Steele) vs. no cooling, worn during passive sitting	90 min of passive sitting with pre/post assessment of tandem gait with parallel bars, balance and peg rotation test. Tympanic temp. measured pre/post protocol	21 °C, RH NR
	(b) Parallel groups (longitudinal)	12 people with MS with heat sensitivity (PP=12, female=NR, age=50 ± 10, EDSS=5.9 ± 0.6)	Liquid head-vest cooling garment (Life Support Systems) that was active (temp. NR) vs. no cooling, worn twice daily for 60 min during passive sitting	6-weeks with weekly assessment of; tandem gait with parallel bars, balance and peg rotation test. Fatigue Severity Scale, Incapacity Status Scale and EDSS were assessed at 0, 3 and 6 weeks	NR

(continued on next page)

Table 1 (*continued*)

Authors	Design	Participants	Intervention(s)	Protocol and outcome measures	Environmental conditions
Vargas et al., 2021	Randomised cross-over (acute)	7 people with MS with heat sensitivity (RR=7, female=6, age=34 ± 7 y, EDSS=1–3.5)	Liquid cooling top (Med-Eng) covering full arms and torso (with compression top worn over to ensure skin contact) that was active on demand (2 °C) vs. control-active (34 °C), worn during exercise	40 min of cycling at 3.5 $W \cdot kg^{-1}$ metabolic heat production with measures of gastro and skin temp., local sweat rate, heart rate, thermal perceptions, RPE, subjective fatigue and MS symptoms	27 °C, 38–43% RH

Key: EDSS=Expanded Disability Status Scale, MS=Multiple Sclerosis, NR=not reported, PP=primary progressive, RH=relative humidity, RPE = rating of perceived exertion, RR=relapsing remitting, sig.=significant, SP=secondary progressive, temp.=temperature.

Table 2
A summary of the quality appraisal results.

Authors	Randomisation	Period and carryover effects	Deviations from the intended intervention	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall risk of bias
Beenakker et al., 2001	Low risk	Some concerns	Low risk	Low risk	Low risk	High risk	High risk
Buoite Stella et al., 2020	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Coyle et al., 1996	Low risk	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns
Gonzales et al., 2017	Low risk	N/A	Low risk	Low risk	Low risk	Low risk	Low risk
Grahn et al., 2008	Low risk	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns
Ku et al., 2000	Low risk	N/A	Low risk	Low risk	Low risk	Low risk	Low risk
Meyer-Heim et al., 2007	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Nilsagard et al., 2006	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Özkan Tuncay and Mollaoğlu, 2017	Low risk	N/A	Low risk	High risk	Low risk	Low risk	High risk
Reynolds et al., 2011	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Schwid et al., 2003	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Syndulko et al., 1995	Low risk	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns
Vargas et al., 2021	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

MS, regardless of whether they were used in an acute or longitudinal setting.

3.4.2. Muscular strength

Five of the studies included objective measures of muscular strength with isometric dynamometry (Beenakker et al., 2001; Ku et al., 2000; Meyer-Heim et al., 2007; Reynolds et al., 2011) or manual muscle testing (Coyle et al., 1996), all following acute use of a cooling garment. Pre-cooling with a liquid-perfused head-vest cooling garment significantly improved summed muscle strength of the legs (hip flexion, knee flexion and extension, and ankle dorsiflexion) by 8.2% (Beenakker et al., 2001). Similarly, the use of a cooling thigh-cuff significantly increased ankle dorsiflexion and knee extension strength by 3.4% and 8.4%, respectively, but no effect was demonstrated for hand-grip strength (Meyer-Heim et al., 2007). In a separate study that compared three different cooling vests (without a control), hand-grip strength significantly improved following cooling in all conditions, but there were no differences between vests (Ku et al., 2000), nor were there improvements in hand-grip strength following head cooling (Reynolds et al., 2011). When muscular strength was assessed by manual muscle testing following acute use of a liquid-perfused head-vest cooling garment, there was a significant 9.7% improvement in the British system rating scale (Coyle et al., 1996). Hence, the majority of evidence demonstrates that acute cooling garments improve objective measures of muscular strength in people with MS. Muscular strength following longitudinal use of a cooling garment was not assessed in any of the included studies.

3.4.3. Balance

Assessments of balance have occasionally been included in the testing batteries of studies to determine the effect of cooling garments on physical function in people with MS (Beenakker et al., 2001; Meyer-Heim et al., 2007; Nilsagård et al., 2006; Syndulko et al., 1995). Following the acute use of a phase change cooling vest, the time to hold challenging positions of tandem stance and one-legged stance were significantly improved by 3–35% compared to control (Nilsagård et al., 2006). However, there were no improvements in standing balance on one or two legs (with eyes open or closed) following the acute or longitudinal use of a liquid-perfused head-vest cooling garment (Syndulko et al., 1995). Two separate studies also demonstrated no improvements in postural sway on a force platform with eyes open following acute use of a cooling garment compared to control (Beenakker et al., 2001; Meyer-Heim et al., 2007), however, one of the studies demonstrated a significant 18.1% improvement in postural sway with the cooling garment compared to control when the eyes were closed (Beenakker et al., 2001). Hence, there is mixed evidence based on individual studies for the effectiveness of cooling garments to improve balance in people with MS.

3.4.4. Manual dexterity

Assessments of manual dexterity have also been included in the testing batteries of studies to determine the effect of cooling garments on physical function in people with MS. Most of the studies that have included this component (4/5) have assessed performance in the 9-hole peg test (or other similar peg manipulation tests), with the majority reporting no improvement in this test following both acute and longitudinal use of cooling garments (Nilsagård et al., 2006; Schwid et al., 2003; Syndulko et al., 1995). There was one exception, however, where an acute cooling thigh-cuff improved 9-hole peg test performance by 14% (Meyer-Heim et al., 2007). One study assessed manual dexterity through ‘finger to nose’ and ‘finger tapping’ tests, and reported no significant differences between the acute use of three different types of cooling garment, but no comparison was made to a control (Ku et al.,

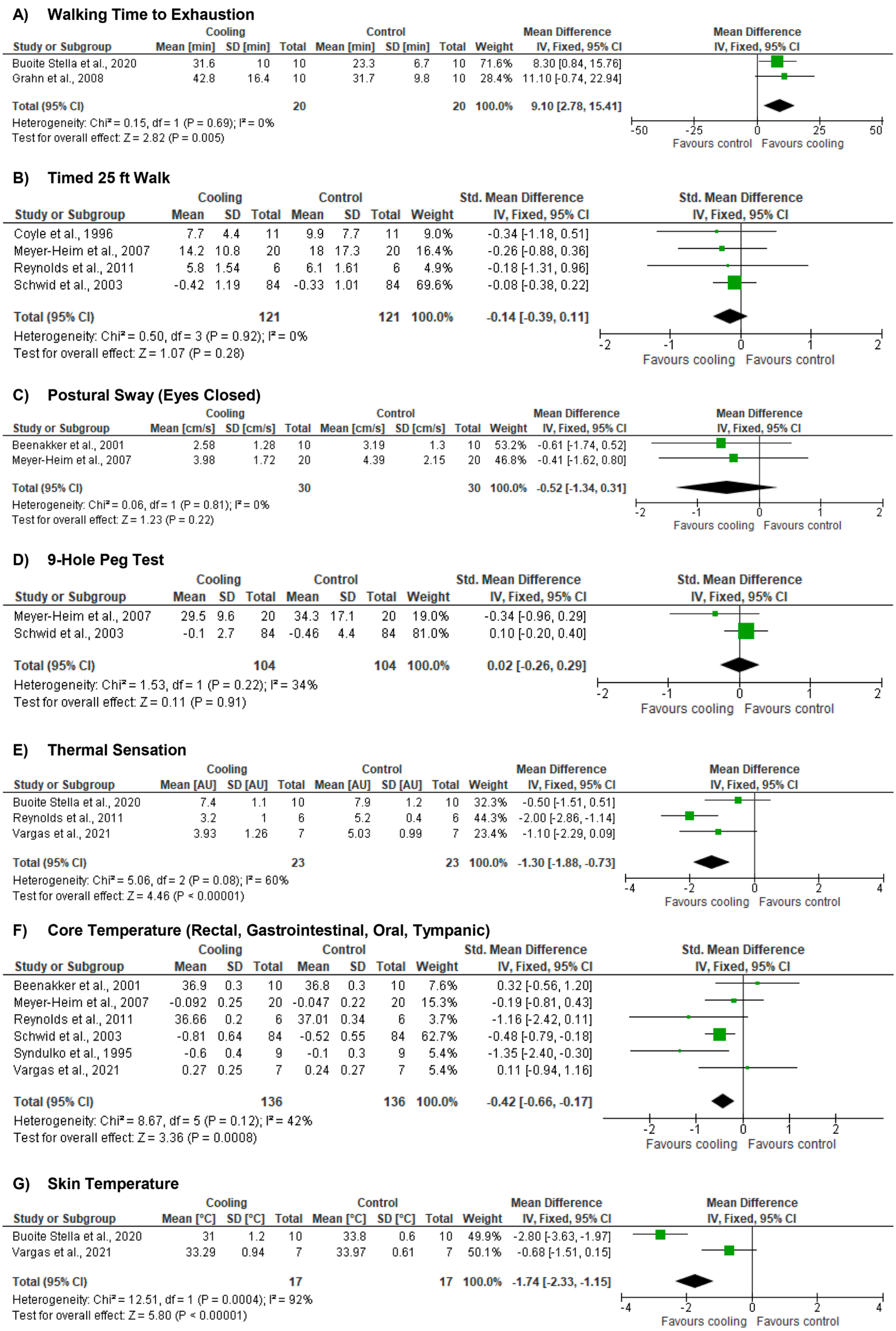

Fig. 2. Forest plots of meta-analysis results for the acute studies.

2000). Therefore, the majority of studies pointed toward no improvement in manual dexterity from cooling garment use.

3.4.5. *Physiological responses*

Several physiological responses have been included as outcome measures across the included studies. Eight studies measured core (i.e. rectal, gastrointestinal, oral, tympanic) or skin temperatures. Tympanic

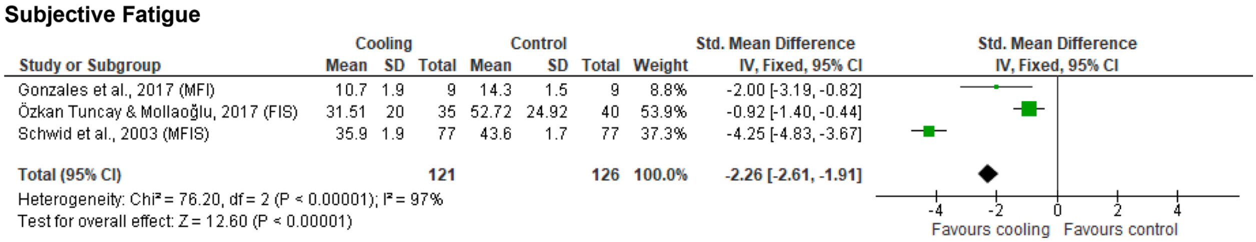

Fig. 3. Forest plots of meta-analysis results for the longitudinal studies (FIS = Fatigue Impact Scale; MFI = Multidimensional Fatigue Inventory, MFIS = Modified Fatigue Impact Scale).

or oral temperatures were significantly lower after exposure to an acute cooling thigh-cuff (Meyer-Heim et al., 2007), acute liquid-perfused head-vest garments (Schwid et al., 2003; Syndulko et al., 1995), and an acute phase change cooling vest (Syndulko et al., 1995), compared to controls. In contrast, there was no significant difference in tympanic temperature with an acute liquid-perfused head-vest (Beenakker et al., 2001), oral temperature with a phase change cooling vest (Nilsagård et al., 2006), or rectal temperature with a head and neck cooling hood (Reynolds et al., 2011), compared to controls. Further, there was no significant change in gastrointestinal temperature or sweat rate reported with an acute liquid-perfused cooling top compared to control, despite significantly lower mean skin temperature (Vargas et al., 2021). A further study also reported significantly lower chest and back skin temperatures with an acute phase change cooling vest (Buoite Stella et al., 2020). In a separate study, while there were no significant differences in skin temperature between three different acute cooling vests, a liquid-perfused vest produced the lowest skin temperatures compared to two types of phase change vest (Ku et al., 2000). Three studies also measured heart rate after the use of an acute cooling garment (Buoite Stella et al., 2020; Grahn et al., 2008; Vargas et al., 2021) and while one reported a significantly lower heart rate with the use of a phase-change cooling vest, it was only by 2 bpm, which is not a meaningful difference (Buoite Stella et al., 2020). Overall, studies demonstrated that the cooling garments can reduce various measures of body temperature.

3.4.6. Perceptual responses

A range of perceptual responses have been included across the studies to gain more understanding of the perceived benefits of the cooling garments. Both an acute phase-change cooling garment and an acute liquid-perfused head-vest cooling garment significantly improved subjective fatigue (Beenakker et al., 2001; Nilsagård et al., 2006). The acute phase-change cooling garment was also reported to significantly improve feelings of spasticity, weakness, balance, gait, transfers and time to recover (Nilsagård et al., 2006). However, an acute liquid-perfused cooling top did not improve subjective fatigue or overall composite symptom scores, which included measures of vision, dizziness, bladder/bowl, sensory, speech or cognitive symptoms (Vargas et al., 2021). For studies with a longitudinal design, there were significant improvements in subjective fatigue (including global scores and subscales for cognitive, physical and social fatigue) across a range of validated instruments with both phase change cooling garments (Gonzales et al., 2017; Özkan Tuncay and Mollaoğlu, 2017) and a liquid-perfused head-vest cooling garment (Schwid et al., 2003), but no improvement in subjective mental fatigue or motivation (Gonzales et al., 2017; Syndulko et al., 1995). Lastly, various cooling garments significantly improved thermal sensation and thermal comfort in an acute setting (Buoite Stella et al., 2020; Reynolds et al., 2011; Vargas et al., 2021). Overall, subjective fatigue and thermal perception were improved following the use of cooling garments used in both acute and longitudinal settings, and some MS symptoms were improved in one study.

3.4.7. Exercise engagement and adherence

A measure of exercise engagement was only investigated in one study, in the form of the number of exercise sessions completed throughout a longitudinal study, and there was no difference between cooling and control groups (Gonzales et al., 2017). It should be noted that this outcome was designed to be standardized between groups and therefore, the effect of cooling garments on exercise engagement and adherence in people with MS is unclear.

4. Discussion

The primary aim of this systematic review was to assess the effect of cooling garments to improve physical function in people with MS. The main findings were that the cooling garments were effective at improving walking capacity and functional mobility, and some studies demonstrated improvements in muscular strength and balance, but not manual dexterity, in MS participants with a broad range in disability (EDSS=1–7.5). The secondary aim was to determine any associated physiological and perceptual responses. There were beneficial responses associated with the use of the cooling garments, including improved core temperature, skin temperature, thermal sensation and subjective fatigue. Importantly, there were no harmful outcomes reported in relation to any of the cooling garments. These findings are consistent with other systematic reviews that assessed the effect of pre-cooling on physical performance and functional capacity (Kaltsatou and Flouris, 2019) and cooling on subjective fatigue in people with MS (Bilgin et al., 2022; Campbell et al., 2019).

The cooling garments significantly improved measures of walking capacity and functional mobility, and some studies demonstrated improvements in muscular strength and balance. These measures are closely related to one another, for example, strength and balance are known to influence walking performance in people with MS (Fritz et al., 2015; Thoumie et al., 2005). Hence, small improvements in strength and balance could accumulate and translate to larger improvements in walking capacity, which is in line with the large improvement demonstrated for walking time to exhaustion in this review (Fig. 2A). The functional improvements demonstrated suggest that the cooling garments can be used by people with MS in different scenarios where improved physical function could enhance quality of life, most notably, to support engagement in exercise, physical activity, work or social activities. While no study was designed in a way to measure the effect of a cooling garment on the latter outcomes, one study did report improved independence in activities of daily living following daily use of a phase change cooling vest over 8 weeks (Özkan Tuncay and Mollaoğlu, 2017). This suggests that a cooling garment could encourage movement when functional problems or fatigue may otherwise encourage sedentary behaviour. Indeed, significantly improved subjective fatigue was a common finding across the studies in a range of validated questionnaires, both acutely and longitudinally. Interestingly, the cooling garments had benefits for physical function in both temperate and warm environmental conditions, and during both long and short duration tasks. Therefore, cooling garments can improve physical function even without the presence of increased body temperatures or prolonged exercise, which suggests that improved subjective fatigue is a predominate mechanism contributing to this improved physical function.

The meta-analyses demonstrated that the cooling garments significantly improved core temperature, skin temperature and thermal sensation (Fig. 2). Therefore, these variables are also likely involved in the mechanism that allowed the cooling garments to improve physical function. Reducing body temperature, especially the skin temperature, reduces thermoregulatory and cardiovascular strain (Sawka et al., 2012), and separately, improving thermal perception can improve endurance independently of any changes in physical body temperature (Stevens et al., 2018). As such, improvements in both body temperature and thermal perception likely allowed the participants to walk for a longer duration and at a faster speed in the various walking tasks assessed. Both the active liquid perfused cooling garments and the phase change cooling garments resulted in significant improvements in body temperature and thermal perception in different studies, and as such, one type of garment does not appear to have a greater cooling benefit than another. Nevertheless, the phase change material in the phase change cooling garments would eventually heat up and act as an insulator, whereas the liquid-perfused garments can maintain their temperature and cooling capacity indefinitely. In the majority of studies, reduced body temperature was reported close to the cooling site, for example, a phase change cooling vest significantly reduced chest and back skin temperature (Buoite Stella et al., 2020), however, there was one exception, where a head and neck cooling hood significantly reduced rectal temperature (Reynolds et al., 2011), which suggests that this garment had a high cooling capacity.

A description of each cooling garment and details regarding their accessibility and practicality is summarized in Table 3. These cooling garments can be classified as accessible or inaccessible. Accessible garments were those that were low cost and could be easily purchased and used in daily life (i.e., a phase change cooling vest), while inaccessible garments were those that were high cost (i.e., active liquid-perfused cooling garments and the palm cooling device) or not commercially available (e.g., the thigh-cuff). Hence, only seven (38.9%) of the cooling garments investigated were accessible for people with MS, which limits the practical applications that can be drawn from the research. Further, many of the practical issues associated with using the garments were not considered within the research, for example, which garments were the most comfortable, and best to facilitate unrestricted movement. Similarly, considerations around the added mass on the metabolic rate and thus heat production of the user, or the time taken for phase change garments to heat up and start acting as an insulator, were not considered either. Nevertheless, benefits were reported with both the accessible and inaccessible garments separately, and while two studies directly compared the accessible and inaccessible garments (Ku et al., 2000; Syndulko et al., 1995), there was no clear evidence to suggest that one outperformed the other. As such, recommendations for people with MS should focus on phase-change cooling garments that are effective, accessible, and user-friendly, alongside other practical cooling strategies such as cold fluid ingestion (Chaseling et al., 2018) and air-conditioning (Christogianni et al., 2022).

Table 3
A description of the different types of cooling garments and details regarding their accessibility and practicality.

Type of cooling garment	Description	Accessibility and practicality
Active liquid-perfused cooling vest/top/hood	Garments coupled to a cooling unit and pump system with chargeable batteries to circulate coolant fluid through tubes in the garment. Outlet temperature can be manipulated to maintain a desired temperature.	High cost (i.e. >$1000 USD), difficult to purchase but simple to use after initial set-up. Movement is highly restricted when worn.
Phase change cooling vest	Vests with ice or gel packs that are frozen and then inserted into the vest in various locations.	Low cost (i.e. $100-$300 USD), freely available to purchase and simple to use. Some brands are also included in medical rebate schemes in some countries. Movement mostly unrestricted when worn.
Palm cooling device	A custom-built chamber allowing for insertion of one hand through an elastic sleeve with an airtight seal around wrist. Chamber connected to a pressure sensor and vacuum pump at −40 mmHg.	High cost (i.e. >$1000 USD), difficult to purchase but simple to use after initial set-up. Movement is highly restricted when worn.
Cooling thigh-cuff	Waterproof but vapour-permeable polyester membranes that coat hydrophilic fabric and provide evaporative cooling at skin surface.	Not commercially available. Movement mostly unrestricted when worn.

The findings of this systematic review should be interpreted in the context of certain limitations. We have identified a lack of well-designed research that has assessed the effect of cooling garments to improve physical function in people with MS. A strength of this review was that only randomized and controlled studies were included, however, this also meant that six studies were excluded due to study design (Fig. 1). There were 60 unique outcome variables assessed across the included studies, which when combined with different study designs, and inadequate reporting in some instances, precluded pooling the vast majority of results, and performing sub-group analyses to compare between different garments. Another limitation was that only three of the thirteen included studies assessed the effect of a cooling garment in response to an exercise bout that increased body temperature. Hence, many of the trials tested the effect of the garments when participants were not exercising for a prolonged duration (i.e., >6 min) and therefore not likely to experience heat sensitivity symptoms. Therefore, only three studies were designed to determine the ability of the cooling garments to mitigate increases in body temperatures, which is a key underlying premise for increased symptomology during and after exercise in people with MS. Nevertheless, a valuable outcome of this review was the beneficial effect of the cooling garments for people with MS to improve physical function in short functional tasks.

Future research is needed in this area. A key recommendation for future research is to simulate real-world scenarios, most importantly, protocols that simulate ecologically valid exercise sessions, such as traditional physical therapy, other novel therapies that have similar benefits, such as Pilates (Kalron et al., 2017), and exercise prescription according to published recommendations for people with MS (Halabchi et al., 2017; Hoang et al., 2022). There is also a lack of controlled research on the effect of cooling garments to promote exercise and physical activity engagement in people with MS. Indeed, it is currently unclear if a freely available cooling garment increases exercise or incidental physical activity prospectively. There are a range of cooling garments available commercially which claim to have large effects on core temperature, and these should be investigated independently to test these claims, and ensure that misinformation is not used within marketing targeted toward people with MS. In order to increase opportunities for more comprehensive pooled analyses within future reviews, authors should ensure that they report absolute data in full including means and standard deviations (not just change from baseline data). Researchers should also consider individual experiences by ensuring that each participant's unique set of heat sensitivity (and cold sensitivity) symptoms are measured, as well as the acceptability of the garments with outcomes such as comfort, movement restriction, heaviness and concealability, which are factors that would likely contribute to ongoing use of the garments. On a related note, the potential for cooling garments to cause harm for people with MS with cold-sensitivity is also worthy of investigation.

The main practical application of this review is that cooling garments are beneficial for a range of outcomes of improved physical function. The cooling garments had benefits for physical function in both temperate and warm environmental conditions, and in both short and long duration tasks. Therefore, cooling garments can improve physical function even without the presence of increased body temperatures or prolonged exercise. Out of the cooling garments that have been assessed as captured within this review, none have been reported to cause harm, however, many factors relating to the acceptability of the garments have not been reported on, nor have the garments been assessed specifically in people with MS that experience both hot and cold sensitivity. At this time, no particular cooling garment can be identified as more beneficial than another. Therefore, people with MS should experiment with different cooling garments and determine what suits their needs and preferences, and industry should focus on the production of cooling garments that are effective, accessible and user-friendly.

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CRediT authorship contribution statement

Christopher J. Stevens: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Resources, Software, Visualization, Writing – original draft, Writing – review & editing. **Gurpreet Singh:** Methodology, Writing – original draft. **Benjamin Peterson:** Methodology, Writing – review & editing. **Nicole T. Vargas:** Conceptualization, Methodology, Writing – review & editing. **Julien D. Périard:** Conceptualization, Methodology, Writing – review & editing.

Declaration of Competing Interest

The authors declare that there were no competing interests.

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Supplementary materials

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References

Beenakker, E.A.C., Oparina, T.I., Hartgring, A., Teelken, A., Arutjunyan, A.V., De Keyser, J., 2001. Cooling garment treatment in MS: clinical improvement and decrease in leukocyte NO production. Neurology 57 (5), 892. https://doi.org/10.1212/WNL.57.5.892.

Bilgin, A., Kesik, G., Ozdemir, L., 2022. The effects of cooling therapies on fatigue, physical activity, and quality of life in Multiple Sclerosis: a meta-analysis. Rehabil. Nurs. 47 (6), 228–236. https://doi.org/10.1097/rnj.0000000000000388.

Browne, P., Chandraratna, D., Angood, C., Tremlett, H., Baker, C., Taylor, B.V., Thompson, A.J., 2014. Atlas of Multiple Sclerosis 2013: a growing global problem with widespread inequity. Neurology 83 (11), 1022–1024. https://doi.org/10.1212/wnl.0000000000000768.

Buoite Stella, A., Pasquin, F., Morrison, S.A., Morelli, M.E., Dinoto, A., Bratina, A., 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. https://doi.org/10.1007/s00421-020-04478-3.

Campbell, A., Killen, B., Cialone, S., Scruggs, M., Lauderdale, M., 2019. Cryotherapy and self-reported fatigue in individuals with multiple sclerosis: a systematic review. Phys. Ther. Rev. 24 (5), 259–267. https://doi.org/10.1080/10833196.2019.1674546.

Campbell, E., Coulter, E.H., Paul, L., 2018. High intensity interval training for people with multiple sclerosis: a systematic review. Mult. Scler. Relat. Disord. 24, 55–63. https://doi.org/10.1016/j.msard.2018.06.005.

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. https://doi.org/10.1249/mss.0000000000001496.

Christogianni, A., Bibb, R., Davis, S.L., Jay, O., Barnett, M., Evangelou, N., Filingeri, D., 2018. Temperature sensitivity in multiple sclerosis: an overview of its impact on sensory and cognitive symptoms. Temperature 5 (3), 208–223. https://doi.org/10.1080/23328940.2018.1475831 (Austin).

Christogianni, A., O'Garro, J., Bibb, R., Filtness, A., Filingeri, D., 2022. Heat and cold sensitivity in multiple sclerosis: a patient-centred perspective on triggers, symptoms, and thermal resilience practices. Mult. Scler. Relat. Disord. 67, 104075 https://doi.org/10.1016/j.msard.2022.104075.

Collett, J., Dawes, H., Meaney, A., Sackley, C., Barker, K., Wade, D., Buckingham, E., 2011. Exercise for multiple sclerosis: a single-blind randomized trial comparing three exercise intensities. Mult. Scler. J. 17 (5), 594–603. https://doi.org/10.1177/1352458510391836.

Coyle, P.K., Krupp, L.B., Doscher, C., Deng, Z., Milazzo, A., 1996. Clinical and immunological effects of cooling in Multiple Sclerosis. Neurorehabil. Neural Repair 10 (1), 9–15. https://doi.org/10.1177/154596839601000102.

Flensner, G., Ek, A.C., Söderhamn, O., Landtblom, A.M., 2011. Sensitivity to heat in MS patients: a factor strongly influencing symptomology–an explorative survey. BMC Neurol. 11, 27. https://doi.org/10.1186/1471-2377-11-27.

Fritz, N.E., Marasigan, R.E.R., Calabresi, P.A., Newsome, S.D., Zackowski, K.M., 2015. The impact of dynamic balance measures on walking performance in multiple sclerosis. Neurorehabil Neural Repair 29 (1), 62–69.

Fuhr, P., Schindler, C., 2015. Clinical neurophysiology in multiple sclerosis–from diagnostic tool to biomarker. Clin. Neurophysiol. 126 (1), 7–9. https://doi.org/10.1016/j.clinph.2014.06.003.

Gonzales, B., Chopard, G., Charry, B., Berger, E., Tripard, J., Magnin, E., Groslambert, A., 2017. Effects of a training program involving body cooling on physical and cognitive capacities and quality of life in Multiple Sclerosis patients: a pilot study. Eur. Neurol. 78 (1–2), 71–77. https://doi.org/10.1159/000477580.

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. https://doi.org/10.1186/1471-2377-8-14.

Halabchi, F., Alizadeh, Z., Sahraian, M.A., Abolhasani, M., 2017. Exercise prescription for patients with multiple sclerosis; potential benefits and practical recommendations. BMC Neurol. 17 (1), 185. https://doi.org/10.1186/s12883-017-0960-9.

Hoang, P.D., Lord, S., Gandevia, S., Menant, J., 2022. Exercise and Sports Science Australia (ESSA) position statement on exercise for people with mild to moderate multiple sclerosis. J. Sci. Med. Sport 25 (2), 146–154. https://doi.org/10.1016/j.jsams.2021.08.015.

Hopkins, W.G., Marshall, S.W., Batterham, A.M., Hanin, J., 2009. Progressive statistics for studies in sports medicine and exercise science. Med. Sci. Sports Exerc. 41 (1), 3–13.

Jain, A., Rosso, M., Santoro, J.D., 2019. Wilhelm Uhthoff and Uhthoff's phenomenon. Mult. Scler. J. 26 (13), 1790–1796. https://doi.org/10.1177/1352458519881950.

Kalron, A., Rosenblum, U., Frid, L., Achiron, A., 2017. Pilates exercise training vs. physical therapy for improving walking and balance in people with multiple sclerosis: a randomized controlled trial. Clin. Rehabil. 31 (3), 319–328. https://doi.org/10.1177/0269215516637202.

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. https://doi.org/10.1016/j.msard.2018.11.013.

Ku, Y.T., Montgomery, L.D., Lee, H.C., Luna, B., Webbon, B.W., 2000. Physiologic and functional responses of MS patients to body cooling. Am. J. Phys. Med. Rehabil. 79 (5), 427–434.

Li, J., Zakeri, M., Hutton, G.J., Aparasu, R.R., 2022. Health-related quality of life of patients with multiple sclerosis: analysis of ten years of national data. Mult. Scler. Relat. Disord. 66, 104019 https://doi.org/10.1016/j.msard.2022.104019.

Meyer-Heim, A., Rothmaier, M., Weder, M., Kool, J., Schenk, P., Kesselring, J., 2007. Advanced lightweight cooling-garment technology: functional improvements in thermosensitive patients with multiple sclerosis. Mult. Scler. J. 13 (2), 232–237. https://doi.org/10.1177/1352458506070648.

Mikula, P., Nagyova, I., Krokavcova, M., Vitkova, M., Rosenberger, J., Szilasiova, J., van Dijk, J.P., 2015. Social participation and health-related quality of life in people with multiple sclerosis. Disabil. Health J. 8 (1), 29–34. https://doi.org/10.1016/j.dhjo.2014.07.002.

Nilsagård, Y., Denison, E., Gunnarsson, L.G., 2006. Evaluation of a single session with cooling garment for persons with multiple sclerosis – a randomized trial. Disabil. Rehabil. Assist. Technol. 1 (4), 225–233. https://doi.org/10.1080/09638280500493696.

Özkan Tuncay, F., Mollaoğlu, M., 2017. Effect of the cooling suit method applied to individuals with multiple sclerosis on fatigue and activities of daily living. J. Clin. Nurs. 26 (23–24), 4527–4536. https://doi.org/10.1111/jocn.13788.

Page, M.J., Moher, D., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., …, McKenzie, J.E., 2021. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. Br. Med. J. 372, n160. https://doi.org/10.1136/bmj.n160.

Petajan, J.H., Gappmaier, E., White, A.T., Spencer, M.K., Mino, L., Hicks, R.W., 1996. Impact of aerobic training on fitness and quality of life in multiple sclerosis. Ann. Neurol. 39 (4), 432–441. https://doi.org/10.1002/ana.410390405.

Pilutti, L.A., Greenlee, T.A., Motl, R.W., Nickrent, M.S., Petruzzello, S.J., 2013. Effects of exercise training on fatigue in Multiple Sclerosis: a meta-analysis. Psychosom. Med. 75 (6), 575–580.

Rampello, A., Franceschini, M., Piepoli, M., Antenucci, R., Lenti, G., Olivieri, D., Chetta, A., 2007. Effect of aerobic training on walking capacity and maximal exercise tolerance in patients with multiple sclerosis: a randomized crossover

controlled study. Phys. Ther. 87 (5), 545–555. https://doi.org/10.2522/ptj.20060085.
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. https://doi.org/10.1017/s0317167100011136.
Robertson, D., Moreo, N., 2016. Disease-modifying therapies in Multiple Sclerosis: overview and treatment considerations. Fed. Pract. 33 (6), 28–34.
Saguil, A., Farnell Iv, E.A., Jordan, T.S., 2022. Multiple Sclerosis: a primary care perspective. Am. Fam. Physician 106 (2), 173–183.
Sawka, M.N., Cheuvront, S.N., Kenefick, R.W., 2012. High skin temperature and hypohydration impair aerobic performance. Exp. Physiol. 97 (3), 327–332. https://doi.org/10.1113/expphysiol.2011.061002.
Schwid, S.R., Petrie, M.D., Murray, R., Leitch, J., Bowen, J., Alquist, A., Webbon, B., 2003. A randomized controlled study of the acute and chronic effects of cooling therapy for MS. Neurology 60 (12), 1955–1960. https://doi.org/10.1212/01.wnl.0000070183.30517.2f.
Siddaway, A.P., Wood, A.M., Hedges, L.V., 2019. How to do a systematic review: a best practice guide for conducting and reporting narrative reviews, meta-analyses, and meta-syntheses. Annu. Rev. Psychol. 70, 747–770. https://doi.org/10.1146/annurev-psych-010418-102803.
Sterne, J.A.C., Savović, J., Page, M.J., Elbers, R.G., Blencowe, N.S., Boutron, I., Higgins, J.P.T., 2019. RoB 2: a revised tool for assessing risk of bias in randomised trials. Br. Med. J. 366, l4898. https://doi.org/10.1136/bmj.l4898.
Stevens, C.J., Mauger, A.R., Hassmèn, P., Taylor, L., 2018. Endurance performance is influenced by perceptions of pain and temperature: theory, applications and safety considerations. Sports Med. 48 (3), 525–537. https://doi.org/10.1007/s40279-017-0852-6.
Syndulko, K., Jafari, M., Woldanski, A., Baumhefner, R.W., Tourtellotte, W.W., 1996. Effects of temperature in multiple sclerosis: a review of the literature. Neurorehabil. Neural Repair 10 (1), 23–34.
Syndulko, K., Woldanski, A., Baumhefner, R.W., Tourtellotte, W.W., 1995. Preliminary evaluation of lowering tympanic temperature for the symptomatic treatment of Multiple Sclerosis. Neurorehabil. Neural Repair 9 (4), 205–215. https://doi.org/10.1177/154596839500900403.
Thoumie, P., Lamotte, D., Cantalloube, S., Faucher, M., Amarenco, G., 2005. Motor determinants of gait in 100 ambulatory patients with multiple sclerosis. Mult. Scler. J. 11 (4), 485–491.
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.
Vitturi, B.K., Rahmani, A., Dini, G., Montecucco, A., Debarbieri, N., Sbragia, E., Durando, P., 2022. Occupational outcomes of people with multiple sclerosis: a scoping review. Br. Med. J. Open 12 (7), e058948. https://doi.org/10.1136/bmjopen-2021-058948.
White, L.J., McCoy, S.C., Castellano, V., Gutierrez, G., Stevens, J.E., Walter, G.A., Vandenborne, K., 2004. Resistance training improves strength and functional capacity in persons with multiple sclerosis. Mul. Scler. 10 (6), 668–674. https://doi.org/10.1191/1352458504ms1088oa.