



Heat and cold sensitivity in multiple sclerosis: A patient-centred perspective on triggers, symptoms, and thermal resilience practices

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ABSTRACT

Background: The negative effects of heat and cold on Multiple Sclerosis (MS) have been known for ~100 years. Yet, we lack patient-centred investigations on temperature sensitivity in persons with MS (pwMS).

Objectives: To evaluate triggers, symptoms, and thermal resilience practices of temperature sensitivity pwMS via a dedicated survey.

Methods: 757 pwMS completed an online survey assessing the subjective experience of temperature sensitivity. We performed descriptive statistics and regression analyses to evaluate association between individual factors and susceptibility/resilience to thermal stress.

Results: Temperature sensitivity varied significantly in pwMS, with 58% of participants being heat sensitive only; 29% heat and cold sensitive; and 13% cold sensitive only ($p < 0.001$). Yet, all pwMS: i) experienced hot and cold days as primary triggers; ii) reported fatigue as the most common worsening symptom, impacting walking and concentration; iii) used air conditioning and changes in clothing insulation as primary thermal resilience practices. Furthermore, certain individual factors (i.e. age, level of motor disability, experience of fatigue) were predictive of greater susceptibility to certain triggers (e.g. hot days) and symptoms (e.g. fatigue).

Conclusion: Patient-centred evidence on the impact of and response to temperature sensitivity could play an important role in the development of individualised healthcare plans for temperature-sensitive pwMS.

1. Introduction

Global warming, and the related increase in extreme weather events such as heatwaves and cold spells, is now the greatest threat to human survival ([Internet] 2018). Over the past few years, all-time high temperature records have been broken across the world (Capon et al., 2019), resulting in a significant increase in excess mortality due to heat stress (The Guardian 2019). Patients affected by chronic illness such as neurodegenerative diseases are the most vulnerable to extreme heat and cold. Yet, whilst our knowledge on the impact of heat and cold on healthy individuals has expanded significantly (Ebi et al., 2021), neurological patients such as those affected by Multiple Sclerosis (MS), continue to be underrepresented in heat and cold stress research.

MS is the most common neurodegenerative disease in young adults. There is no cure, and with an increasing 2.5 M people affected worldwide, MS represents a significant public health challenge (Trisolini et al.,

2010). It is commonly reported that up to 80% of MS patients may experience heat sensitivity (Frohman et al., 2013), i.e. a worsening of neurological symptoms when body temperature increases, typically induced by warm environments and in exercise (Davis et al., 2010, V Leavitt et al., 2012). Heat sensitivity is an “invisible MS symptom” (National Multiple Sclerosis Society 2018, MS Australia), yet it predisposes individuals to significant morbidity and mortality. In severe cases, increases in body temperature can induce sudden loss of motor control to the extent that MS patients become physically incapacitated and can suffer fatal hyperthermia, for example through sun exposure (Harbison et al., 1989, Avis and Pryse-Phillips, 1995) or hot water immersion (Waxman and Geschwind, 1983). In less severe cases, exposure to warm ambient temperatures decreases postural stability (Poh et al., 2017) and worsens cognitive status (V Leavitt et al., 2012), both of which increase the risk of falls in MS (Mazumder et al., 2014, Nilsagård et al., 2009). These issues have severe consequences for quality of life

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and healthcare costs (Trisolini et al., 2010). Exercise-induced elevations in body temperature also increase the number and severity of MS symptoms (Skjærbæk et al., 2013). Having MS and being vulnerable to the heat creates barriers for maintaining appropriate physical activity levels (Fjeldstad et al., 2010) and conducting normal working activities (Huang et al., 2015, Coyne et al., 2015), with employment loss and early retirement (and the related cost burden) (Trisolini et al., 2010) due to heat intolerance highly prevalent worldwide (Trisolini et al., 2010, Coyne et al., 2015, Ahmad et al., 2018).

Whilst MS is commonly worsened by the heat, it is also commonly reported that ~15% of persons with MS (pwMS) experience deterioration of their symptoms during winter and cold ambient temperatures, while 5% of the patients report cold sensitivity during cold baths (Simmons et al., 2004). The primary driver of cold sensitivity in MS seems to be associated with the presence of demyelinating lesions within the hypothalamus (i.e. the main area within the nervous system controlling body temperature), which result in thermoregulatory dysfunction in the form of blunted autonomic responses (i.e. vasoconstriction, shivering) to cold stress (Sullivan et al., 1987). While the incidence rates of cold sensitivity in MS are believed to be generally smaller (~20%) than that of heat sensitivity (Grahn et al., 2008, Syndulko et al., 1995), cold-induced pseudo-exacerbations still play a major role in determining patients' quality of life.

The negative effects of heat and cold on MS have been known for over 100 years (Frohman et al., 2013), and empirical evidence is now available on some likely pathophysiological mechanisms (e.g. temperature-dependant slowing of neural conduction within demyelinated nerves) and the relative effectiveness of some interventions (e.g. body cooling for heat sensitivity). However, we still know very little about what drives vulnerability to the heat and cold at the level of the individual MS patient (Hajat et al., 2010); how heat and cold sensitivity affects MS symptoms in relation to people own' experience of MS; and what actual strategies pwMS have developed to increase their thermal resilience and reduce the negative impact of heat and cold stress. This lack of knowledge is due to both a broad individual variability in heat and cold sensitivity amongst pwMS (Davis et al., 2010, Forsyth et al., 2019, Coon and Low, 2018), as well as to a lack of large patient-centred approaches that comprehensively characterise the triggers, the impact on symptoms and life quality, and the thermal resilience practices adopted by temperature sensitive pwMS.

The often temporary and reversible nature of temperature sensitivity makes it difficult to reliably assess symptom worsening and understand its impact in MS. This often overlooks the patient's subjective experience. The patients' personal views and input about how much they are impacted by temperature sensitivity would be a valuable source of information about the condition for both carers and healthcare providers. Furthermore, the impact of heat and cold stress on vulnerable groups such as pwMS and health services is already significant and projected to increase, with an estimated global direct damage cost to health of USD 3 billion/year by 2030 (IPCC, 2018). If we do not develop a better understanding of what drives heat and cold sensitivity at the MS patient level, along with ways to predict and mitigate heat and cold vulnerability effectively, the burden on people and pressure on health services will inevitably increase (Arbuthnott and Hajat, 2017).

The aim of this study was therefore to evaluate the triggers, the impact on symptoms and life quality, and the thermal resilience practices adopted by a large, international cohort of temperature sensitive pwMS, and to determine association with individual factors. We hypothesised that certain triggers may be more prevalent than others and vary in specific temperature sensitive MS sub-groups (e.g., heat vs. cold sensitive); that specific symptoms (e.g. fatigue) and parameters relevant to life quality (e.g. reasoning) would be more affected by temperature sensitivity; and that a variety of thermal resilience practice may have been developed by pwMS to mitigate the impact of heat and cold.

2. Methods

2.1. Ethical approval

We collected both quantitative and qualitative data on temperature sensitivity in pwMS via an anonymous online survey, following best practice design. A similar online survey, investigating phantom skin wetness in the same study cohort, was recently published by Christogianni et al. (2022). Participant recruitment occurred via social media posting supported by MS charities and MS groups worldwide (e.g., National MS Society, the MS organization in the Netherlands, the MS society in South Africa and MS Research Australia). All participants provided an anonymous informed consent prior to participation, the latter being a pre-requisite to access the online survey. The study received full ethical approval by the Human Participants Sub-Committee of Loughborough University (proposal #R18-P200). Data collection took place between the 23rd of January and 9th of August 2019 and included only pwMS who had experienced heat and/or cold sensitivity. A copy of the survey is provided in Supplementary Material 1.

2.2. Study design

The minimum sample size (n) for the online survey was calculated using the following equation (Israel, 1992):

$$n = \left\{ z^2 \times p \times \left[\frac{1-p}{e^2} \right] \right\} / \left\{ 1 + \left[z^2 \times p \times \left[\frac{1-p}{e^2 \times N} \right] \right] \right\}$$

where $z = 1.96$ for a confidence level (α) of 95%; p = proportion (expressed as a decimal) of pwMS experiencing heat and cold sensitivity (~50% of pwMS); N = MS population size (~2.5 M); e = margin of error of 0.05. Therefore, the minimum sample size for this study was determined to be 385.

The online survey consisted of two main sections, i.e. (A) demographics and (B) temperature sensitivity.

The demographic section was based on previous online surveys that investigated self-reported factors affecting the experience of MS (Flensner et al., 2011) and included questions about participants' age; biological sex; country of origin and residence; type of MS [relapsing-remitting (RR), secondary progressive (SP), primary progressive (PP), unknown]; years since MS diagnosis; presence and level of motor disability; and whether taking disease modifying drugs (DMD). Furthermore, respondents were asked to report their fatigue levels by answering the questions in the Fatigue Severity Scale (Krupp, 1989), i.e. a 9-item scale which measures the severity of fatigue (min score: 9; max score: 63). Finally, respondents were asked to report any mental health symptoms (i.e., stress, anxiety, and depression).

The Temperature sensitivity section included two initial key questions:

- 1 "Have you ever experienced a worsening of your MS symptoms when you get hot or cold?" (Answer: Yes/No);
- 2 "Which worsens your symptoms more?" (Answer: Heat/Cold/Both heat and cold);

The questions above were followed by a series of multiple-choice questions, for which participants had to select:

- a The heat or cold triggers that worsen their symptoms the most (e.g., fever, exercise, hot/cold days, humidity, sunlight, etc.);
- b The symptoms that worsen the most when becoming hot or cold (e.g., fatigue, spasticity, numbness, etc.);
- c The thermal resilience strategies used to mitigate the negative impact of heat and cold (e.g., use of fans, air conditioning/heating, cooling garments, etc.)

Finally, participants responded one open-answer question, for which they described:

- a Activities and/or things they could not do when experiencing temperature sensitivity;

A copy of the survey is provided as *Supplementary Material 1*.

3. Data analysis

First, we performed descriptive statistics for the demographics section data in order to characterise the sample surveyed.

Second, we separated participants' responses into 3 groups (i.e. Heat/Cold/Both Heat and Cold), based on participants' answer to the question "Which worsens your symptoms more?". Frequency statistics were then performed separately for each group to identify the most frequent triggers, symptoms worsening, and thermal resilience practices. Furthermore, we calculated a chi-square goodness-of-fit test (LoRe, 2016) to evaluate differences in the frequency distribution of responses to triggers, symptoms worsening, and thermal resilience practices amongst the 3 groups (i.e. Heat/Cold/Both Heat and Cold). This analytical approach aimed at identifying both the prevalence and relative characteristics of heat vs. cold vs. concurrent heat and cold sensitivity in pwMS.

Third, we used a content analysis method (Krippendorff, 2018) to explore themes reported as part of the open-answer questions (i.e. things pwMS cannot do as a result of temperature sensitivity). We then used those themes to assess individual responses and assign a score to each of them (i.e. theme present= 1; theme not present= 0). Two researchers (AC and DF) performed, reviewed, and agreed the combination and refinement of themes. Additionally, all respondents' answers to the open questions are provided in *Supplementary Material 2*. Data processing occurred in MS Excel, where those coded data were reported in frequency rates.

Fourth, we performed separate binary logistic regressions (Kleinbaum et al., 2002) to examine the association between individual MS characteristics [i.e. i) biological sex; ii) age; iii) residence expressed as latitude; iv) type of MS expressed as Relapsing-remitting (RRMS), secondary progressive (SPMS), primary progressive (PPMS); v) presence and level of motor disability; vi) DMD; vii) Fatigue Severity Scale score; viii) mental health status (i.e. depression, anxiety, stress)], and the three primary triggers, symptoms worsening, and thermal resilience practices (note: these dependant variables were treated as dichotomous variables, i.e. presence/absence), for the Heat, Cold, and Both Heat and Cold groups. This analytical approach aimed to identify whether individual characteristics would be predictive of increased susceptibility to particular triggers; of worsening of specific symptoms; and of endorsement of specific thermal resilience practices, within heats and cold-sensitive groups of pwMS. For the purpose of this analysis, we merged responses from Heat and Both heat and cold groups, in order to consider the impact of heat sensitivity. Similarly, we merged responses from Cold and Both heat and cold groups, in order to consider the impact of cold sensitivity. Regression analyses were performed in SPSS (IBM Corp 2020) (IBM, USA). Statistical significance for all analyses was set a $p \leq 0.05$.

4. Results

4.1. Demographics

A total of 788 pwMS accessed the online survey. Following data screening for incomplete reporting, we confirmed a final sample size of 757 available for analysis.

Tables 1, 2 and 3 present summary data on demographics, the DMDs taken by pwMS who reported being on such treatment regimes, and country of residence, respectively.

Table 1

Summary of demographic data for the 757 responders (RR=relapsing remitting, SP=secondary progressive, PP=primary progressive).

Factor	Number of participants(% of total)
Sex	
Female	600 (79%)
Male	157 (21%)
Age	
19–25	25 (3%)
26–30	48 (6%)
31–35	77 (10%)
36–40	93 (12%)
41–45	125 (16%)
46–50	106 (14%)
51–55	114 (15%)
56–60	88 (12%)
61–65	51 (7%)
66–70	18 (2%)
71–75	10 (1%)
76 and above	2 (<1%)
Years with MS	
0–12	477 (63%)
13–25	226 (30%)
26–38	48 (6%)
39–47	6 (1%)
Type of MS	
RR	455 (60%)
SP	148 (20%)
PP	89 (12%)
Unknown	65 (8%)
Motor disability	
No disability	157 (21%)
Signs of disability (walk without aid)	297 (39%)
Require walking aid (e.g., cane)	234 (31%)
Unable to walk, restricted to wheelchair	57 (7%)
Restricted to bed	12 (2%)
Mental health	
Stress	641 (85%)
Anxiety	579 (76%)
Depression	519 (69%)

Table 2

Summary data of the disease modifying drugs (DMDs) that 407 participants were taking at the time of the survey (note: only DMDs reported by more than 10 participants are reported here).

DMDs	Number of participants(% of total)
Dimethyl fumarate	100 (13%)
Fingolimod	71 (9%)
Natalizumab	54 (7%)
Glatiramer acetate	53 (7%)
Ocrelizumab	51 (7%)
Alemtuzumab	24 (3%)
Teriflunomide	24 (3%)
Interferon beta 1a	16 (2%)
Peginterferon 1a	14 (2%)

Regarding the general characteristics of our sample (Table 1), we observed a greater proportion of females (79%) than males. Most respondents fell within the age bracket of 41 to 55 years old (45%), they were affected by RR MS (60%), and they had been diagnosed with the disease in the past 12 years (63%). Most respondents also presented signs of motor disability resulting in either unassisted (39%) or assisted walking (30%). Finally, we observed a high prevalence of mental health problems such as stress (85%), anxiety (76%), and depression (69%), amongst the sample surveyed.

Regarding DMD (Table 2), 54% of respondents were taking various DMDs at the time of the survey. Geographically (Table 3), most pwMS were residents of either the United Kingdom (37%), Greece (20%), or the USA (20%).

Table 3

Summary of the countries of residence of the 757 participants [note: only countries reported by more than 10 participants are reported here; “Other countries” include: Canada [Frohman et al., 2013], Luxembourg [Trisolini et al., 2010], Germany [Trisolini et al., 2010], Ireland [Ebi et al., 2021], Italy [Capon et al., 2019], Belgium [[Internet] 2018], Brazil [[Internet] 2018], India [[Internet] 2018], Kenya [[Internet] 2018], Poland [[Internet] 2018], Russia [[Internet] 2018], Saudi Arabia [[Internet] 2018], Spain [[Internet] 2018], Sweden [[Internet] 2018], Switzerland [[Internet] 2018], Trinidad [[Internet] 2018], Turkey [Internet] 2018].

Country	Number of participants(% of total)
United Kingdom	282 (37%)
Greece	155 (20%)
USA	148 (20%)
The Netherlands	46 (6%)
Australia	28 (4%)
South Africa	20 (3%)
France	19 (2%)
Cyprus	14 (2%)
New Zealand	10 (1%)
Other countries	35 (5%)

4.2. Temperature sensitivity

4.2.1. General characteristics

Regarding the presence and type of temperature sensitivity, we found that 438 respondents (58%) reported to be heat sensitive (hereby referred to as “Heat group”); 97 of respondents (13%) reported to be cold sensitive (hereby referred to as “Cold group”); 222 of respondents (29%) reported to be both heat and cold sensitive (hereby referred to as “Heat+Cold group”). The chi-square goodness-of-fit test indicated that the frequency distribution of respondents to the three groups (i.e., Heat/Cold/Both heat and cold) differed to a level that reached statistical significance ($\chi^2=235.88$, $df=2$, $p<0.001$). This observation highlighted an uneven distribution in the type of temperature sensitivity amongst temperature-sensitive pwMS, such that there was a higher frequency of pwMS affected by the heat; followed by pwMS affected by both heat and cold; and lastly pwMS affected by cold only.

4.2.2. Triggers

Table 4 presents an overview of the triggers of temperature sensitivity for each group. When considering the Heat group ($N = 438$), we found that the 3 most prevalent triggers of symptoms worsening were “hot days” ($N = 198$; 45%), “high humidity” ($N = 73$; 17%), and “hot baths” ($N = 42$; 10%). When considering the Cold group ($N = 97$), we found that the 3 most prevalent triggers of symptoms worsening were

Table 4
Triggers in heat and cold sensitivity.

Heat sensitivity	Heat Group	No. of participants	%	Heat+Cold group	No. of participants	%
	Hot days	198	45.20%	Hot days	82	36.90%
	High humidity	73	16.70%	High humidity	42	18.90%
	Hot baths	42	9.60%	Changes in weather	37	16.70%
	Sunlight	40	9.10%	Fever	26	11.70%
	Changes in weather	32	7.30%	Hot baths	26	11.70%
	Exercise	29	6.60%	Warm showers	19	8.60%
	Fever	28	6.40%	Exercise	16	7.20%
	Warm showers	22	5.00%	Your occupation	16	7.20%
	Housekeeping / gardening	16	3.70%	Sunlight	15	6.80%
	Your occupation	15	3.40%	Housekeeping / gardening	15	6.80%
Cold sensitivity	Cold Group	No. of participants	%	Heat+Cold group	No. of participants	%
	Cold days	29	29.90%	Cold days	76	34.20%
	Changes in weather	18	18.60%	Changes in weather	39	17.60%
	Lack of sunlight	10	10.30%	High humidity	23	10.40%
	High humidity	4	4.10%	Long periods of inactivity	18	8.10%
	Long periods of inactivity	3	3.10%	Lack of sunlight	13	5.90%
	Cold baths	2	2.10%	Cold showers	12	5.40%
	Cold showers	2	2.10%	Cold baths	8	3.60%

“cold days” ($N = 29$; 30%), “changes in weather” ($N = 18$; 19%), and “lack of sunlight” ($N = 10$; 10%). When considering the Heat+Cold group ($N = 222$), we found that the most prevalent triggers of symptoms worsening were “hot days” ($N = 82$; 40%); and “cold days” ($N = 76$; 34%).

When considering individual characteristics that could be predictive of increased susceptibility to particular triggers, we found that the pwMS who are more likely to be triggered by hot days are the ones who are older and live at lower latitudes (Table 5). Specifically, in the Heat group the trigger “hot days” showed weak model of fit in the Hosmer and Lemeshow Test ($\chi^2=10.19$, $df=8$, $p = 0.25$) with Age (Wald=7.07, $df=1$, $p = 0.01$) and Latitude (Wald=4.17, $df=1$, $p = 0.04$) being significant [*Predicted logit of Hot days* = $-1.59 + 0.02*(Age) - 0.01*(Latitude)$].

Also, we found that pwMS who are more likely to be triggered by cold days are the ones who are older, suffer from RRMS, and experience fatigue. Specifically, in the Cold group the trigger “cold days” showed weak model of fit in the Hosmer and Lemeshow Test ($\chi^2=5.17$, $df=8$, $p = 0.74$) with Age (Wald=4.29, $df=1$, $p = 0.04$) being significant [*Predicted logit of Cold days* = $-6.10 + 0.06*(Age)$]. Furthermore, in the Heat+Cold group the trigger “cold days” showed good model of fit in the Hosmer and Lemeshow Test ($\chi^2=16.98$, $df=8$, $p = 0.03$) with Relapsing-remitting (Wald=3.83, $df=1$, $p = 0.05$) and Fatigue (Wald=7.67, $df=1$, $p<0.01$) being significant [*Predicted logit of Cold days* = $-3.99 + 1.57*(Relapsing-remitting) + 0.31*(Fatigue)$].

4.2.2. Symptoms worsening

Table 6 presents an overview of the symptoms experienced by each group when becoming hot and/or cold. When considering the Heat group ($N = 438$), we found that the 3 most prevalent symptoms experienced were “fatigue” ($N = 291$; 66%), “weakness” ($N = 126$; 29%), and “poor walking” ($N = 102$; 23%). When considering the Cold group ($N = 97$), we found that the 3 most prevalent symptoms experienced were “fatigue” ($N = 38$; 39%), “muscle cramping” ($N = 22$; 22%), and “poor walking” ($N = 22$; 23%). When considering the Heat+Cold group ($N = 222$), we found that the most prevalent symptom experienced when becoming both hot ($N = 149$; 67%) and cold ($N = 83$; 37%) was “fatigue”.

When considering individual characteristics that could be predictive of specific symptoms worsening, we found that the pwMS who are more likely to be experience fatigue worsening and poor walking when becoming either hot or cold are the ones who already present high levels of fatigue and motor disability (Table 7). Specifically, in Heat group the symptom “fatigue” showed weak model of fit in the Hosmer and Lemeshow Test ($\chi^2=7.45$, $df=8$, $p = 0.49$) with Motor disability (Wald=5.23, $df=1$, $p = 0.02$) and the general Fatigue (Wald=13.08,

Table 5
Significant triggers' predictor variables under heat and cold sensitivity conditions (* $p < 0.05$).

Triggers		Heat Conditions			Cold Conditions			
		<i>Hot days</i>		<i>Hot baths</i>	<i>Changes in weather</i>		<i>Changes in weather</i>	
		Heat group	Heat group	Heat+Cold group	Cold group	Heat+Cold group	Cold group	Heat+Cold group
Predictors	Age	*	*		*		*	*
	Latitude	*						
	Remitting relapsing					*		
	Primary progressive							*
	DMD			*				*
	Fatigue					*		

Table 6
Reported symptoms during heat and cold sensitivity (reports include >5% in answer selection).

Heat sensitivity	Heat Group	No. of participants	%	Heat+Cold group	No. of participants	%
		Fatigue	291	66.40%	Fatigue	149
	Weakness	126	28.80%	Weakness	58	26.10%
	Poor walking	102	23.30%	Balance difficulties	49	22.10%
	Balance difficulties	89	20.30%	Poor walking	41	18.50%
	Perfused sweating	86	19.60%	Perfused sweating	40	18.00%
	Coordination difficulties	50	11.40%	Spasticity	26	11.70%
	Concentration	40	9.10%	Coordination difficulties	21	9.50%
	Loss of full control of bodily movements	33	7.50%	Muscle cramping	20	9.50%
	Spasticity	33	7.50%	Lack of sleep	20	9.50%
	Numbness	33	7.50%	Issues with decision making / information processing	17	7.70%
	Lack of sleep	32	7.30%	Intense pain	14	6.30%
	Muscle cramping	29	6.60%	Concentration	13	5.90%
	Issues with decision making / information processing	27	6.20%	Loss of full control of bodily movements	13	5.60%
	Burning	24	5.50%	Numbness	12	5.40%
				Attention deficits	12	5.40%
				Limited sweating	11	5.00%
				Memory deficits	11	5.00%

Cold sensitivity	Cold Group	No. of participants	%	Heat+Cold group	No. of participants	%
		Fatigue	38	39.20%	Fatigue	83
	Muscle cramping	22	22.70%	Muscle cramping	67	30.20%
	Poor walking	22	22.70%	Spasticity	60	27.00%
	Balance difficulties	20	20.60%	Poor walking	51	23.00%
	Weakness	16	16.50%	Balance difficulties	39	17.60%
	Intense pain	14	14.40%	Weakness	39	17.60%
	Numbness	13	13.40%	Intense pain	30	13.50%
	Spasticity	12	12.40%	Loss of full control of bodily movements	21	9.50%
	Pins and needles	12	12.40%	Coordination difficulties	21	9.50%
	Altered sensations	11	11.30%	Tremor	20	9.00%
	Coordination difficulties	10	10.30%	Numbness	20	9.00%
	Loss of full control of bodily movements	7	7.20%	Lack of sleep	17	7.70%
	Depression	7	7.20%	Immobility	12	5.40%
	Spontaneous pain	6	6.20%	Pins and needles	12	5.40%
	Concentration	6	6.20%	Tightness	12	5.40%
	Tremor	5	5.20%			
	Lack of sleep	5	5.20%			
	Burning	5	5.20%			

Table 7
Significant symptoms' predictor variables under heat and cold sensitivity conditions (* $p < 0.05$).

Symptoms		Heat Conditions			Cold Conditions				
		<i>Fatigue</i>		<i>Weakness</i>	<i>Poor walking</i>		<i>Fatigue</i>	<i>Poor walking</i>	<i>Muscle cramping</i>
		Heat group	Heat+Cold group	Heat group	Heat group	Cold group	Heat+Cold group	Cold group	Heat+Cold group
Predictors	Fatigue	*	*			*		*	
	Depression			*			*		
	Stress		*						
	Motor disability	*			*		*	*	

df=1, $p < 0.001$) being significant [*Predicted logit of Fatigue (general MS symptom)* = $-0.31 * (\text{Motor disability}) + 0.25 * (\text{Fatigue symptom worsening})$].

Furthermore, in the Cold group the symptom “fatigue” showed weak model of fit in the Hosmer and Lemeshow Test ($\chi^2=5.86$, df=8, $p = 0.66$) with Fatigue (Wald=6.60, df=1, $p = 0.01$) being significant [*Predicted logit of Fatigue* = $0.49 * (\text{Fatigue})$]. Finally, in the Cold group the symptom “poor walking” showed weak model of fit in the Hosmer and Lemeshow Test ($\chi^2=7.35$, df=8, $p = 0.50$) with Motor disability (Wald=3.83, df=1, $p = 0.05$) being significant [*Predicted logit of Poor walking* = $0.84 * (\text{Motor disability})$].

4.2.3. Thermal resilience practices

Table 8 presents an overview of the thermal resilience practices adopted by each group when becoming hot and/or cold. When considering the Heat group ($N = 438$), we found that the 3 most prevalent thermal resilience practices were “wearing lightweight clothing” ($N = 360$; 82%), “using air conditioning” ($N = 335$; 76%), and “using fans” ($N = 320$; 73%). When considering the Cold group ($N = 97$), we found that the 3 most prevalent thermal resilience practices were “staying in a heated environment” ($N = 88$; 91%), “wear layers of clothes” ($N = 79$; 81%), and “warming the house” ($N = 78$; 80%). When considering the Heat+Cold group ($N = 222$), we found that the most prevalent thermal resilience practice when becoming hot was “wearing lightweight clothing” ($N = 190$; 86%) and “staying in a heated environment” when becoming cold ($N = 188$; 85%).

When considering individual characteristics that could be predictive of the adoption of specific thermal resilience practices, we found that the pwMS who are more likely to use air conditioning and fans when becoming hot were the ones experiencing greater levels of fatigue and motor disability (Table 9). Specifically, in the Heat group the strategy “air-conditioning” showed a good model of fit in the Hosmer and Lemeshow Test ($\chi^2=16.48$, df=8, $p = 0.04$) with Latitude (Wald=7.75, df=1, $p < 0.005$), Motor disability (Wald=9.60, df=1, $p = 0.002$) and Anxiety (Wald=6.19, df=1, $p = 0.01$) being significant [*Predicted logit of Air-conditioning* = $4.20 - 0.02 * (\text{Latitude}) - 0.48 * (\text{Motor disability}) - 0.786 * (\text{Anxiety})$]. Furthermore, in the Heat group the strategy “using fan” showed a good model of fit in the Hosmer and Lemeshow Test ($\chi^2=14.99$, df=8, $p = 0.06$) with fatigue (Wald=5.28, df=1, $p = 0.02$)

being significant [*Predicted logit of Using fan* = $0.16 * (\text{Fatigue})$].

Also, we found that pwMS who are more likely to use house warming when becoming cold are the ones who experience greater stress levels. Specifically, in the Cold group the strategy “warming the house” showed weak model of fit in the Hosmer and Lemeshow Test ($\chi^2=4.96$, df=8, $p = 0.76$) with stress (Wald=6.35, df=1, $p = 0.01$) to be significant [*Predicted logit of Warming the house* = $-2.04 * (\text{Stress})$].

4.2.4. Effects on life activities

Tables 10 and 11 present an overview of themes related to the things pwMS cannot do as a result of temperature sensitivity. When considering the things pwMS cannot do as a result of becoming hot, we found that “walk” ($N = 202$; 27%), “concentrate” ($N = 105$; 14%), and “think” ($N = 84$; 11%), were the most prevalent themes. When considering the things pwMS cannot do as a result of becoming cold, we found that “walk” ($N = 86$; 11%), “use limbs” ($N = 63$; 8%), and “move” ($N = 45$; 6%), were the most prevalent themes.

5. Discussion

The aim of this study was to evaluate the triggers, symptoms’ worsening, and thermal resilience practices adopted by a large, international cohort of temperature sensitive pwM, and to determine associations with individual factors. Leveraging a large database of responses ($N = 757$), our survey results indicated that: 1) temperature-sensitive pwMS can be categorised under 3 sub-groups, i.e. heat sensitive only (58%); heat and cold sensitive (29%); cold sensitive only (13%); 2) regardless of their type of temperature sensitivity, pwMS experience environmental conditions (i.e. hot and cold days) as primary triggers, and report fatigue as the most common worsening symptom; 3) when becoming either hot or cold, pwMS adopt changes in clothing insulation and use of air conditioning (i.e. via air cooling, heating, and fanning) as their primary thermal resilience practices; 4) “walk” and “concentrate” are the most likely things pwMS cannot do when becoming hot or cold; 5) some individual factors (e.g. age, level of motor disability, experience of fatigue) may be predictive of susceptibility to certain triggers, symptoms, and endorsement of thermal resilience practices.

The first relevant finding of this study is that contrary to what

Table 8
Resilience practices in heat and cold sensitivity.

Heat sensitivity	Heat Group	No. of participants	%	Heat+Cold group	No. of participants	%
		Wearing lightweight, loose, breathable clothing	360	82.20%	Wearing lightweight, loose, breathable clothing	190
	Using air-conditioning	335	76.50%	Drinking icy/cold drinks or popsicles	174	78.40%
	Using fan	320	73.10%	Using fan	173	77.90%
	Drinking icy/cold drinks or popsicles	318	72.60%	Picking cooler times of the day (early morning or evening)	156	70.30%
	Picking cooler times of the day (early morning or evening)	304	69.40%	Using air-conditioning	142	64.00%
	Using cooling products such as vests and neck wraps	169	38.60%	Using cooling products such as vests and neck wraps	84	37.80%
	Bathing in a bathtub of cool water	144	32.90%	Exercising in a cool pool or a cool environment	57	25.70%
	Exercising in a cool pool or a cool environment	114	26.00%	Bathing in a bathtub of cool water	54	24.30%
Cold sensitivity	Cold Group	No. of participants	%	Heat+Cold group	No. of participants	%
	Staying in a heated environment	88	90.70%	Staying in a heated environment	188	84.70%
	Wear layers of clothes	79	81.40%	Wear layers of clothes	175	78.80%
	Warming the house by closing windows and shutting internal doors	78	80.40%	Warming the house by closing windows and shutting internal doors	166	74.80%
	Eating hot food and drinking warm drinks	69	71.10%	Eating hot food and drinking warm drinks	158	71.20%
	Using hot water bottles, electric blankets or heat pads	63	64.90%	Using hot water bottles, electric blankets or heat pads	109	49.10%
	Staying in the sun	62	63.90%	Using heating assistive devices	107	48.20%
	Taking a holiday somewhere warm	51	52.60%	Staying in the sun	85	38.30%
	Using heating assistive devices	40	41.20%	Taking a holiday somewhere warm	37	16.70%

Table 9
Significant thermal resilience practices' predictor variables under heat and cold sensitivity conditions (* $p < 0.05$).

Strategies		Heat Conditions				Cold Conditions				
		Using air-conditioning	Wearing lightweight, loose, breathable clothing	Using fan	Cold drinks	Warming the house by closing windows and shutting internal doors	Staying in a heated environment	Wear layers of clothes		
		Heat group	Heat+Cold group	Heat group	Heat+Cold group	Heat+Cold group	Cold group	Heat+Cold group	Heat+Cold group	Heat+Cold group
Predictors	Biological sex		*				*			*
	Latitude	*								*
	Secondary progressive						*			
	Stress							*		
	Anxiety	*			*					
	Motor disability	*	*		*			*		
	Fatigue		*	*		*				

Table 10
What people with MS cannot do due heat sensitivity.

What people with MS cannot do in heat sensitivity	number of participants	%
Walk	202	26.70%
Concentrate	105	13.90%
Think	84	11.10%
Physical activity	75	9.90%
Go outside	66	8.70%
Move	61	8.10%
Exercise	58	7.70%
Function	53	7.00%
Sleep/rest	49	6.50%
Work	47	6.20%
Housework	47	6.20%
Talk	42	5.50%
Stand	41	5.40%
Balance	24	3.20%
Use limbs	21	2.80%
See	21	2.80%
No energy	19	2.50%
Eat/swallow	17	2.20%
Read/study	16	2.10%
Stay awake	14	1.80%
Sunbath/stay in sun	14	1.80%
Breath	14	1.80%
Socialize	13	1.70%
Drive	12	1.60%
Relax	11	1.50%

Table 11
What people with MS cannot do due to cold sensitivity.

What people with MS cannot do in cold sensitivity	number of participants	%
Walk	86	11.40%
Use limbs	63	8.30%
Move	45	5.90%
Concentrate	41	5.40%
Go outside	37	4.90%
Sleep	25	3.30%
Warm up	24	3.20%
Function	18	2.40%
Exercise	17	2.20%
Think	16	2.10%
Be active	12	1.60%
Talk	11	1.50%
Work	11	1.50%
Stop shaking/spasms	10	1.30%
Stop pain	10	1.30%

commonly reported, temperature-sensitive pwMS do not simply differentiate between those who suffer from either heat or cold sensitivity; in fact, about a third of temperature-sensitive pwMS experience sensitivity to both heat and cold. This finding is relevant, as it highlights a group of pwMS who may have escaped appropriate characterization. Indeed, it is commonly reported that ~85% of pwMS may experience heat sensitivity (Davis et al., 2010), whilst ~15% experience cold sensitivity (Grahm et al., 2008, Syndulko et al., 1995). However, in those few studies investigating the prevalence of temperature sensitivity in MS, whether individuals experience concurrent sensitivity to both heat and cold is rarely reported. Our findings indicate that pwMS who are both heat and cold sensitive are the second most common group of temperature-sensitive pwMS (following on heat-sensitive only), accounting for a third of all temperature-sensitive patients. This sub-group of pwMS is likely to experience a reduced operational range when compared to their heat- and cold-sensitive only counterparts, as the same patient will experience worsening of key symptoms (e.g. fatigue) with both increases and decreases in body temperature. This observation is clinically relevant and should be considered by clinicians when advising patients about thermal resilience interventions to manage their temperature sensitivity effectively. For example, whilst body cooling may be beneficial for a heat sensitive only MS patient, the same intervention may require careful consideration when administered to a heat and cold sensitive patient. Indeed, it is reasonable to hypothesise that body cooling could mitigate heat sensitivity in heat and cold sensitive pwMS; yet it could also trigger the onset of cold sensitivity if body temperature is lowered below normothermia. Future studies should therefore evaluate thermal intervention strategies that are tailored to the unique type of temperature sensitivity experienced by different groups of pwMS (i.e., heat, cold, and both heat and cold sensitive).

Our patient-centred analysis of the triggers of temperature sensitivity in heat-sensitive pwMS highlighted the primary role of environmental factors such as hot days and high humidity. We also found that pwMS who were more likely to be triggered by hot days were the ones who were older and lived at lower latitudes. Hot days and weather fluctuations have been subjectively reported to worsen MS symptoms in previous studies (Flensner et al., 2011, VM Leavitt et al., 2012, Ogawa et al., 2004, Johnson, 2002), and our results confirm such observations. Interestingly, our survey has indicated that high humidity is reported as the second most common trigger of heat sensitivity. High humidity has been previously reported to be a risk factor for general MS symptoms worsening (Norman et al., 1983, Fonseca et al., 2009, Laborde et al., 1988); yet, there has been limited evidence for its role as a trigger of heat sensitivity (Kay et al., 2001, O'Reilly and O'Reilly, 1991). From a biophysical standpoint, high humidity will reduce evaporative capacity and the amount of sweat being evaporated from the skin, which in turn will result in a greater increase in body temperature for the same heat load (Parsons, 2002). Therefore, it is not surprising that pwMS may

experience worsening of their symptoms in humid ambient conditions, given that they are more likely to become hotter in hot humid, than in hot dry, environments. From an applied standpoint, these observations have implications for pwMS who are impacted by the heat when the weather becomes warmer, especially during seasonal changes (e.g. spring to summer), and during humid heatwaves (Chacko et al., 2021). The general climate may also play a role, as pwMS who live in more tropical climates with high temperature and humidity levels throughout the year might be affected more than pwMS living in more temperate climatic zones (Elser et al., 2021). Finally, when combined with high environmental temperatures, high humidity may have implications for perceived fatigue and therefore the general wellbeing of patients (Mora et al., 2017). It is also worth noting that hot baths were reported as the third most common trigger of heat sensitivity by heat sensitive patients. This observation is in line with the early use of hot baths in diagnosis MS (Malhotra and Goren, 1981). Perhaps most importantly, this observation has implications for patients' safety. Indeed, symptoms worsening as a result of hot baths may involve fatigue and poor balance (see paragraphs below on *Symptoms worsening*), which in turn could lead to an increased risk of falls (Mollaölu and Üstün, 2009).

Our patient-centred survey also provides relevant evidence on the triggers of cold sensitivity. Indeed, pwMS reported cold days, weather changes, and lack of sunlight as primary triggers of symptoms worsening. Also, we found that pwMS who were more likely to be triggered by cold days were the ones who were older, suffered from RRMS, and experienced fatigue. These observations are in line with previous studies reporting that cold (Watson, 1959) and especially cold weather, can worsen one's MS (Ogawa et al., 2004). However, our results indicated a greater susceptibility to cold in relation to changes in weather. This effect is likely to be more pronounced as a result of changes in season (e.g. colder weather as winter sets in), and it therefore highlights that certain parts of the year may prove more critical for symptoms management in older, cold-sensitive, people with RRMS (Honan et al., 1987).

When considering the effects of temperature sensitivity on MS symptoms, our survey clearly indicated that fatigue was the primary symptom to worsen during both heat and cold exposures. Furthermore, we found that the pwMS who were more likely to experience fatigue worsening when becoming either hot or cold were the ones who already presented high levels of fatigue and motor disability. These results are in line with previous studies, which have highlighted the frequent occurrence of fatigue worsening during episodes of both heat (Flensner et al., 2011, Bergamaschi et al., 1997, Guthrie and GUTHERIE, 1951, Bol et al., 2012) and cold sensitivity (Petrilli et al., 2004). Fatigue is an important predictor for the deterioration in mental and physical health, and in quality of life in MS (Benedict et al., 2005); and motor disability is a substantial predictor for poor MS prognosis (Bergamaschi, 2007). Accordingly, future studies should consider the extent by which the experiencing temperature sensitivity as a recurrent phenomenon further deteriorates MS progression. Interestingly, poor walking appeared as a top-3 symptom for both heat and cold exposures. However, heat-sensitive pwMS also reported weakness within their top-3 symptom, whereas cold-sensitive patients reported muscle cramping in conjunction with fatigue and poor walking. This observation is relevant, as it highlights the different temperature-mediated mechanisms that are likely to be associated with a worsening of walking. On the one side, body cooling can impact muscle function and force generation, and this may have implications for fatigue onset and the reported muscle cramping in the cold sensitive group (Lloyd et al., 2015). On the other side, body heating is accompanied by peripheral vasodilation and changes in blood pressure regulation, and this may have implications for the onset of weakness and fatigue (Sawka et al., 2011, Huang et al., 2016).

The findings above provide novel evidence and insights on the experience and likely pathophysiology of heat and cold sensitivity in MS. Indeed, whilst the general clinical picture on the symptoms arising

from an episode of heat or cold sensitivity may appear similar at first (i.e. both heat and cold exposures are accompanied by fatigue and poor walking), it is likely that the underlying mechanisms of action differ substantially (e.g. peripheral vs. central effects on muscle function and blood pressure). This observation is clinically relevant, as it has implications for the development of thermal resilience strategies that target relevant temperature-mediated mechanisms (e.g. maintenance of muscle temperature in the cold vs. maintenance of central blood volume in the heat). It should also be noted that, aside from pathophysiological mechanisms, pwMS may also experience negative thoughts in relation to thermal exposures, that is a "nocebo effect", which is the experience of physiological and psychological symptoms because of the belief and anticipation of adverse outcomes resulting from changes in body temperature (Christogianni et al., 2018).

Our survey also provided some novel patient-centred evidence on the direct impact of temperature sensitivity on life quality in MS. Indeed, pwMS reported "walk" and "concentrate" as the most likely things they cannot do when becoming hot or cold, thereby highlighting the practical impact of temperature sensitivity on motor and cognitive functions in pwMS. It is of note that functions such as "concentrate" and "think" were more commonly reported as impaired as a result of heat than cold exposures. Whilst evidence indicates that (mental) fatigue is detrimental to motor performance regardless of the type of thermal stress (i.e. heat vs. cold) in healthy individuals, it remains to be established the extent by which body heating may have greater detrimental effects to cognitive function in pwMS than body cooling (Valenza et al., 2020).

When considering the primary thermal resilience strategies adopted by our survey responders, our findings indicated that when becoming hot or cold, pwMS adopted changes in clothing insulation and the use of air conditioning (i.e., via air cooling, heating, and fanning). Furthermore, we found that the pwMS who were more likely to wear light weight clothing, use air conditioning and fans when becoming hot were the ones experiencing greater levels of motor disability. Finally, we found that pwMS who were more likely to use house warming when becoming cold are the ones who experience greater stress levels. Changing clothing insulation and artificially modifying ambient temperature and ventilation are part of the repertoire of human thermoregulatory behaviours used to maintain thermal comfort (Parsons, 2002). It therefore appears that, despite a greater susceptibility to heat and cold stress, pwMS adopt adaptive behaviours in line with the expected maintenance of thermal comfort. However, it is important to note that factors other than the efficacy of those practices may be at play in determining the likelihood of adopting a specific behaviour. For example, access to air conditioning may be dependant not just on needs and efficacy for mitigation of symptoms, but also on affordability. It is interesting to note that the use of fans appeared as a common practice in heat sensitive pwMS, as this represents an effective and economic cooling solution (Ravanelli et al., 2015). To our knowledge, the information available on the strategies adopted by pwMS to mitigate heat and cold stress is mostly anecdotal. Our findings are therefore novel, as they provide a patient-centred perspective on those practices that are commonly part of self-management of symptoms in pwMS. We also believe that the information provided here could be useful to support the development of telemedicine and telemonitoring solutions which considers extreme weather events in relation to patients' individual susceptibility and resilience to thermal stress. Specifically, the real-time integration of data on individual thermal stress susceptibility, along with wearable bio-sensing and meteorological conditions, could indeed support early warning as well as telemonitoring systems that help better protecting and monitoring vulnerable neurological patients during heatwaves and cold spells.

Conclusions

We believe that the data presented here provide the most comprehensive, patient-driven account on the triggers, impact, and responses to

temperature sensitivity in pwMS to date. Our findings are novel and clinically relevant, as they shed light on a little investigated, yet commonly experienced, “invisible” symptom of MS. Temperature-sensitive pwMS appears to be a heterogeneous group, who may be impacted by either or both heat and cold; yet they all report to be primarily impacted by changes in their surrounding thermal environments. In turn, this leads to a significant worsening of their fatigue, with severe implications for their ability to walk, concentrate and think. This patient-centred knowledge could play an important role in the development of individualised healthcare plans (including telemonitoring) for temperature-sensitive pwMS. Finally, this knowledge could inform the optimization of thermal resilience planning for health protection during extreme weather events by public health bodies, which consider the unique needs and behaviours of vulnerable patient groups such as pwMS.

Declarations

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Availability of data and material

The data presented in the study are available from the corresponding author upon reasonable request.

Code availability

Not applicable.

Ethics approval

Informed consent was obtained from all respondents prior to fill in the online survey and the Ethical approval was granted by the Loughborough University Human Ethics Sub-Committee in the UK.

Credits authors

AC, JO, RB, AF, DF conceived and designed the work. AC and JO acquired the data. AC and DF analysed the data, and all authors interpreted the data. AC and DF drafted the manuscript, and all authors revised the manuscript critically for intellectual content. All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

Declaration of Competing Interest

The authors declare no conflict of interest.

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Supplementary materials

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