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REVIEW PAPER

Exercise Core Body Temperature is Adequately Regulated Following Spinal Cord Injury: A Meta-Analysis

Yang Zhang[1], Stevo Popovic[1], Dusko Bjelica[1]

[1]University of Montenegro, Faculty for Sport and Physical Education, Podgorica, Montenegro

Abstract

Damage to the spinal cord results in malfunction of sympathetic pathways, which consequently influences thermoregulation during exercise. A consensus view is that athletes with spinal cord injury (SCI) are at a heightened thermal strain than the able-bodied athletes. However, a number of studies have reported similar increases in core body temperature in both populations. This study presented an up-to-date review of core body temperature response to exercise, from a meta-analytic point of view. Inclusion criteria were persons with SCI and control population (either healthy persons or wheelchair athletes without SCI) completed an exercise trial and their core body temperature responses were recorded under the same environmental conditions. Effect of SCI on thermoregulatory capabilities was quantified as raw mean core body temperature difference. Twelve studies examining 100 persons with SCI (Cervical (C2) to Lumbar (L5)) and 97 persons without SCI were meta-analyzed. The exercise interventions were submaximal exercise and the unweighted means ± standard deviations heat index and exercise duration were 31.5±11.9°C and 57±20 min, respectively. Regardless of injury, core body temperature was not different: raw mean difference, 0.048°C; 95% confidence interval, -0.12°C to 0.22°C. In conclusion, under SCI sport-specific exercise and environmental conditions, SCI does not produce outsized thermoregulatory impact, though the influence could be variable as a result of different lesion levels.

Key words: *Paraplegia, Tetraplegia, Rectal Temperature, Heat Stress*

Introduction

Prolonged exercise in the heat elevates core body temperature, which impairs endurance performance and poses increased risks of heat illness (American College of Sports Medicine et al., 2007). Like the able-bodied athletes, athletes with spinal cord injury (SCI) not only face similar heat strain when exercise training and competition occur in hot and humid environments, but also their thermoregulatory capabilities are uniquely challenged. Traumatic damage to the spinal cord, especially with resultant tetraplegia or high paraplegia is associated with a significant malfunction of the sympathetic pathways (Walter & Krassioukov, 2018). Following SCI, the afferent pathways from the periphery to the thermoregulatory effectors in the hypothalamus are disrupted, accounting for the abnormal physiological control during physical activities and exercise (Walter & Krassioukov, 2018). During continuous submaximal exercise in temperate and warm conditions (20-30°C), athletes with SCI show elevated core body temperature, and this increase in core body temperature is more evident in athletes with high level lesion when traumatic damage occurs above T6 (Price, 2016; Price & Trbovich, 2018). This alteration of sympathetic nervous system activity below the lesion level also impairs sweating, increasing susceptibility of heat illness (Price, 2016). Athletes with SCI are therefore considered to be under a greater risk of hyperthermia when compared to the able-bodied athletes (Lepretre, Goosey-Tolfrey, Janssen, & Perret, 2016).

A growing number of studies however reported that thermoregulation in persons with SCI during exercise was more dynamic than traditionally believed. Evidence for this possibility has been revisited by Price and Trbovich (2018). Briefly, persons with paraplegia appear to show similar exercise core body temperature responses compared to the able-bodied in temperate and warm environments, while persons with tetraplegia appear to show gre-

Correspondence:

Y. Zhang

University of Montenegro, Faculty for Sport and Physical Education, Narodne omladine bb, 81400, Niksic, Montenegro

E-mail: dr.zhang.yang@qq.com

ater heat imbalance due to greater loss of sympathetic nervous system control (Price & Trbovich, 2018). Despite our growing knowledge of thermoregulatory capabilities in various populations, there remains a paucity of information related to athletes with SCI. Therefore, the aim of the present review was to examine the thermoregulatory capabilities following SCI. Thermoregulation is usually described as a mechanism to maintain body temperature homeostasis in the cold/heat and characterized by a core internal temperature point. In this meta-analysis, the thermoregulatory capabilities are quantified by auditory canal, esophageal, gastrointestinal, oral, or rectal temperature as proxy measures of core body temperature response to exercise.

Methods

Literature search

An electronic literature search (EndNote, ver. X9, Clarivate Analytics, USA) was performed in the PubMed and Web of Science Core Collection databases from their earliest available date up to January 2019. A variety of search terms were explored to capture maximal relevant literature. The combination of final search terms and Boolean connectors used was: (spinal cord injur* OR paralympic OR wheelchair athlete* OR wheelchair player* OR paraplegia OR tetraplegia) AND (thermoregulation OR heat stress OR core body temperature (aural canal temperature, esophageal temperature, rectal temperature) OR skin temperature OR sweat OR sweating).

Two steps of records filtering were applied. The first step was based on screening of titles and abstracts, and those that did not meet the general inclusion criteria were eliminated based on this alone: English-language, full-length, experimental studies of persons with SCI that involved with an exercise protocol. The second step focused on the specific inclusion criteria: experimental protocol must have included a control group without SCI and the outcomes must have included measures of core body temperature. Following these records filtering, a forward citation map based on the references of eligible studies was yielded to identify any other relevant literature that potentially missed from the key words search. After these screening processes, thirteen studies met the inclusion criteria but one study was later excluded due to insufficient duration and environment to test the thermoregulatory capabilities. As a result, a total of twelve studies were included in this meta-analysis (Boot, Binkhorst, & Hopman, 2006; Castellani et al., 2001; Dawson, Bridle, & Lockwood, 1994; Fitzgerald, Sedlock, & Knowlton, 1990; Goosey-Tolfrey, Swainson, Boyd, Atkinson, & Tolfrey, 2008; Griggs, Havenith, Price, Mason, & Goosey-Tolfrey, 2017; Price & Campbell, 1997, 1999; Theisen, Vanlandewijck, Sturbois, & Francaux, 2001; Trbovich, Ortega, Schroeder, & Fredrickson, 2014; Veltmeijer, Pluim, Thijssen, Hopman, & Eijsvogels, 2014; Zacharakis, Kounalakis, Nassis, & Geladas, 2013). A flow diagram of the screening process is presented in Figure 1.

Data extraction

Participants' demographics, exercise protocols, and core body temperature profiles during exercise were extracted. Studies (Boot et al., 2006; Theisen et al., 2001; Trbovich et al., 2014) that included different lesion levels and reported the outcomes separately were extracted as independent data in the meta-analysis; otherwise, data (Goosey-Tolfrey et al., 2008) were extracted as a single composite score (Higgins & Green, 2008). As a result, a total of 16 independent data sets from the 12 included studies were meta-analyzed. Core body temperatures originally reported in the graphical form were digitally reconstructed to numeric values (Photoshop, ver. CC2018, Adobe, USA). When standard deviations of core body temperatures were not reported directly, these values were calculated from standard errors and sample sizes presented in studies. The risk of bias derived from each study was evaluated using established procedures, with scores from 0 to 11 possible (Physiotherapy Evidence-Based Database Scale (Moseley, Herbert, Sherrington, & Maher, 2002).

Meta-analysis

Effect size in this meta-analysis was calculated as the raw mean difference of core body temperature during exercise between persons with and without SCI. Among the included studies, two studies reported final measurement (cessation of exercise) core body temperature (Boot et al., 2006; Castellani et al., 2001); four studies reported change-from-baseline core body temperature (Dawson et al., 1994; Fitzgerald et al., 1990; Theisen et al., 2001; Zacharakis et al., 2013); three studies reported both final measurement and change-from-baseline core body temperature (Goosey-Tolfrey et al., 2008; Griggs et al., 2017; Trbovich et al., 2014); and three studies reported change-from-baseline core body temperature directly and presented figures of core body temperature responses, allowing indirect data extraction of final measurement core body temperature and correlation coefficients of change-from-baseline core body temperature to be calculated (see below) (Price & Campbell, 1997, 1999; Veltmeijer et al., 2014). Considering baseline core body temperatures showed difference between experimental groups, the calculation of raw mean difference in this meta-analysis was based on change-from-baseline, when both final measurement and change-from-baseline data are available.

Correlation coefficients of change-from-baseline standard deviations were computed (Fu et al., 2013) for included studies in the meta-analysis and the results are inconsistent: mean 0.2978, 95% confidence interval (CI) 0.0384 to 0.5572 (range: -1 to 0.98). Correlations of three studies (Fitzgerald et al., 1990; Theisen et al., 2001; Zacharakis et al., 2013) cannot be calculated by retrospective method and therefore these values were imputed based on the mean correlation (0.2978) in the meta-analysis.

Two sets of sensitivity analysis were performed. First, the imputed correlation coefficient was replaced by 0.0384 and 0.5572 to evaluate the impact of data imputation. Second, although the difference in core body temperature at the commencement of exercise favored reporting change-from-baseline core body temperature in several studies, the correlation coefficients are inconsistent among the included studies and the overall mean is less than 0.5, suggesting final measurement may offer more precision. Therefore, studies reporting both final measurement and change-from-baseline core body temperature or allowing indirect data extraction of final measurement core body temperature were meta-analyzed, utilizing final measurement core body temperature instead this time.

All statistical analyses were carried out using the Comprehensive Meta-Analysis (ver. 3.3.070, Biostat, USA). The meta-analysis was based on a random-effects model, accounting for the differences in the participants and exercise protocols among studies. Non-overlapping 95% CI was considered a statistical significance. Heterogeneity was assessed using Q statistic but no subgroup or meta-regression analysis could be performed. The publication bias of included studies was assessed using the Egger's test (Egger, Davey Smith, Schneider, & Minder, 1997).

Table 1. Subject Characteristics from 12 Included Studies

Citation	n, sex*		Age (yr)		Body mass (kg)		Height (cm)		SCI level	SCI training background
	SCI	CON	SCI	CON	SCI	CON	SCI	CON		
Goosey-Tolfrey et al., 2008	7M/1F	7M	27.2±6.9	25.4±4.2	68.3±17.9	75.3±10.0	N/A	N/A	C2-L2a	Trained, tennis
Griggs et al., 2017	10	7	30.0±5.0	23.0±5.0	68.4±10.5	65.3±14.8	N/A	N/A	C5/6-C7	National level, rugby
Trbovich et al., 2014	6M	19M	34.5	30.8	N/A	N/A	N/A	N/A	C5-C7	Trained, basketball/rugby
Zacharakis et al., 2013	8M	9M	31.4±8.4	20.1±0.8	72.1±11.5	73.9±5.5	180.0±7.0	179.0±5.0	C7-T6	National level, basketball
Boot et al., 2006	4M	10M	31.0±4.0	33.0±5.0	77.0±7.0	80.0±14.0	183.0±9.0	180.0±8.0	T1-T6	N/A
Trbovich et al., 2014	5M	19M	27.6	30.8	N/A	N/A	N/A	N/A	T3-T5	Trained, basketball/rugby
Price & Campbell, 1999	9	11	28.5±4.5	30.3±7.4	67.9±14.0	78.3±7.2	N/A	N/A	T3/4-L1	National level, various sports
Price & Campbell, 1997	10	9	30.1±6.4	30.6±7.9	62.9±12.7	77.7±9.5	N/A	N/A	T3/4-L4	National level
Theisen et al., 2001	6	6	32.2±7.0	28.3±5.6	82.0±10.7	78.7±10.1	181.0±7.0	180.0±8.0	T5-T9	Recreational level
Veltmeijer et al., 2014	2	4	N/A	N/A	N/A	N/A	N/A	N/A	T6/L2b	International level, tennis
Castellani et al., 2001	4M	5M	36.0±14.0	33.0±9.0	66.9±11.8	72.5±13.2	171.0±8.0	171.0±4.0	T7/8-T11c	Highly trained, track/road race
Boot et al., 2006	6M	10M	29.0±6.0	33.0±5.0	68.0±13.0	80.0±14.0	181.0±6.0	180.0±8.0	T7-T12	N/A
Trbovich et al., 2014	6M	19M	37.3	30.8	N/A	N/A	N/A	N/A	T7-T12	Trained, basketball/rugby
Fitzgerald et al., 1990	5F	5F	27.0±3.8	24.6±2.7	59.0±6.9	64.6±7.2	N/A	N/A	T9-L5	No training history
Theisen et al., 2001	6	6	31.3±8.3	28.3±5.6	60.2±11.2	78.7±10.1	174.0±10.0	180.0±8.0	T10-T12	Recreational level
Dawson et al., 1994	5M	5M	24.8±3.7	26.0±3.2	71.9±7.5	86.8±5.8	179.0±4.7	183.3±5.4	T12-L3	Recreational level
Unweighted mean	**6.3**	**8.1**	**30.5**	**27.7**	**68.7**	**75.3**	**178.4**	**178.7**		

Note: Sixteen independent data set from a total of 12 included studies (see also methods). Data are expressed as mean ± standard deviation. CON, controls; F, female; M, male; N/A, data not available; SCI, spinal cord injury. *when the reporting of sex of the subjects is not available, the overall sample size is included. a included brittle bones (n=1), spina bifida (n=1), nerve damage (n=1). b included brain stem infarction (n=1). c including post-polio individual (n=1).

Table 2. Exercise Characteristics from 12 Included Studies

Citation (lesion level)	Ambient environment (Temperature, rH)	Heat index (°C)	CBT	Exercise regime	Modality	Exercise loading	
						SCI	CON
Goosey-Tolfrey et al., 2008	30.8°C, 60.6%	35	TAC	60 min, 50% PO_{peak}	WERG/CYCLE	43±21 W	129±25 W
Griggs et al., 2017	18.4-20.9°C, 31.1-45.1%	17-20	TGI	32 min, game play	WCR	158±44 W	200±74 W
Trbovich et al., 2014	21.1-23.9°C	N/A	TGI	60 min, ISP	WCB, WCR	N/A	N/A
Zacharakis et al., 2013	23°C, 40-55%	22-23	TOR	60 min, 55% VO_{2max}	WERG	37.1±2.6 W	48.6±1.1 W
Boot et al., 2006 (T1-T6)	35°C, 70%	50	TRE	45 min, 40% PO_{peak}	ACE	38±3.5 W	61±2.5 W
Price & Campbell, 1999	21.5°C, 47%	21	TAC	60 min, 60% VO_{2max}	ACE	1.22 $L \cdot min^{-1}$	2.07 $L \cdot min^{-1}$
Price & Campbell, 1997	21.5°C, 47%	21	TAC	90 min, 80% HR_{peak}	ACE	1.34 $L \cdot min^{-1}$	1.92 $L \cdot min^{-1}$
Theisen et al., 2001 (T5-T9)	23°C, 53%	23	TES	60 min, 50% PO_{peak}	ACE	50.0±11.0 W	56.7±2.6 W
Veltmeijer et al., 2014	21.2-24.8°C, 51.8-61.4%	21-25	TGI	45 min, game play (singles)	WCT	N/A	N/A
Castellani et al., 2001	25°C, 58.9% & 32.2°C, 66%	25, 40	TRE	20 min, 0.03 kg resistance$\cdot kg^{-1}$ BM	WERG	N/A	N/A
Boot et al., 2006 (T7-T12)	35°C, 70%	50	TRE	45 min, 40% PO_{peak}	ACE	53±2.4 W	61±2.5 W
Fitzgerald et al., 1990	24-25°C, 38-52%	23-25	TOR	90 min, 50-55% VO_{2max}	WERG	221±44.9 W	255±20.3 W
Theisen et al., 2001 (T10-T12)	23°C, 53%	23	TES	60 min, 50% PO_{peak}	ACE	55.8±11.1 W	56.7±2.6 W
Dawson et al., 1994	37.4°C, 33%	39	TRE	60 min, 55-60% VO_{2max}	ACE	N/A	N/A

Note: ACE, arm-crank exercise; BM, body mass; CBT, core body temperature; CYCLE, cycle ergometer; CON, controls; ISP, intermittent sprint exercise; N/A, data not available; POpeak, peak power output; rH, relative humidity; SCI, spinal cord injury; TAC, auditory canal temperature; TES, esophageal temperature; TGI, gastrointestinal temperature; TOR, oral temperature; TRE, rectal temperature; W, watts; WCB, wheelchair basketball; WCR, wheelchair rugby; WCT, wheelchair tennis; WERG, wheelchair ergometer.

Results

Table 1 presents the participants' characteristics. A total of 100 persons with SCI and 97 persons without SCI were included in the meta-analysis. Three studies reported wheelchair athletes without SCI as control (Boot et al., 2006; Griggs et al., 2017; Veltmeijer et al., 2014), and the rest reported healthy persons as control. Eight studies recruited highly trained athletes with SCI. Table 2 summarizes the exercise protocol. Most experiments were conducted in thermoneutral and warm environments with the unweighted means ± standard deviations ambient temperature and heat index being 26.1±5.7°C and 31.5±11.9°C, respectively. Seven studies utilized wheelchair specific submaximal exercise and five studies utilized upper-body arm ergometer to simulate wheelchair exercise. The exercise intensity was prescribed based on relative maximal exercise capacity or wheelchair gameplay. The unweighted exercise duration was 57±20 min. The quality scores for these studies ranged from 9 to 11, qualifying as high quality of design.

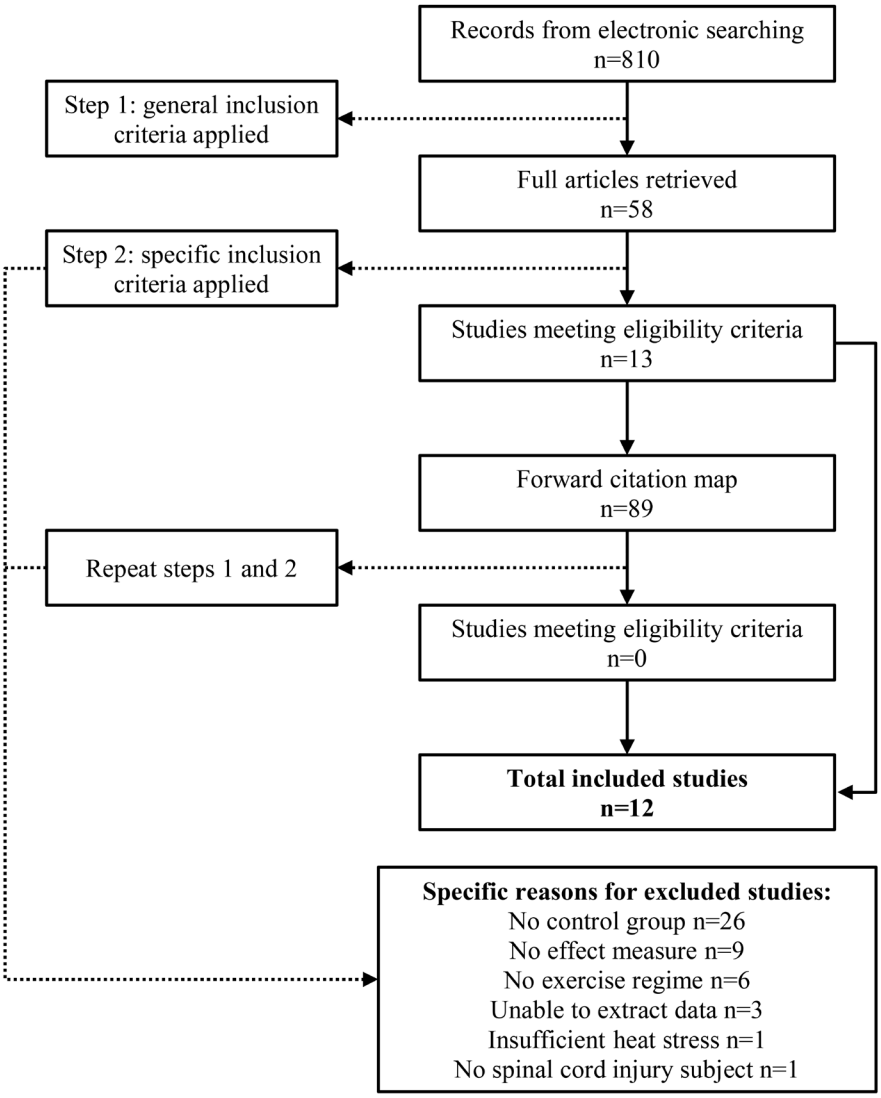

Figure1. Flow diagram of the study selection process

Overall, there was no statistical or biological meaningful difference in the core body temperature response to exercise between persons with SCI and without SCI: raw mean difference 0.048°C (95% CI: -0.12°C to 0.22°C) (Figure 2). A sensitivity test based on final measurement core body temperature shifted the overall mean difference to 0.002°C (95% CI: -0.18°C to 0.19°C) (Figure 2), thus ruled out the possibility of selective reporting and analysis on the effect size. By assuming two different correlation coefficients, the overall meta-analysis did not shift, confirming minimal impact of data imputation on the result. Significant heterogeneity was expected as a result of variable sample and experimental design. Due to the variance in sample population (i.e., mixed lesion levels within and between studies), no subgroup analysis however can be performed. The Egger's test, P = 0.42 (1-tailed), suggested low risk of publication bias.

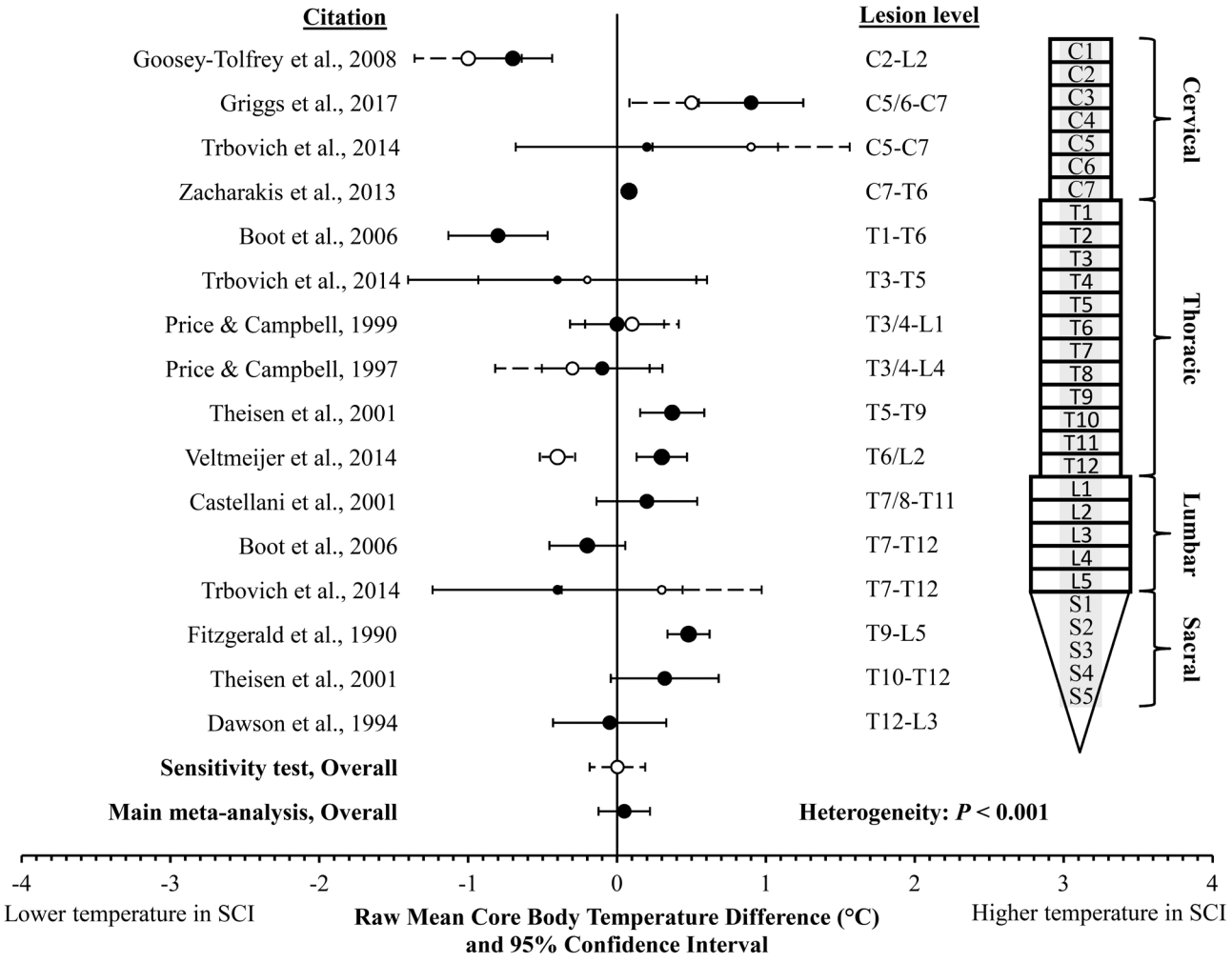

Figure2. Forest plot of core body temperature response to exercise between persons with spinal cord injury and without injury. Filled circle represents the main meta-analysis and open circle represents sensitivity analysis utilizing final measurement core body temperature when available (see also Table 1). The solid horizontal line depicts the 95% confidence interval of the main meta-analysis and the dashed horizontal line depicts the 95% confidence interval of the sensitivity analysis. The circle size was proportional to the weight of each study in the main random-effects meta-analysis.

Discussion

This is the first meta-analysis investigating the effect of SCI on thermoregulatory capabilities, quantified by the core body temperature responses during exercise. Notably, contrary to the common belief that impaired thermoregulatory mechanisms due to disrupted neural thermoregulatory pathways would increase risks of hyperthermia for athletes with SCI, current meta-analysis of core body temperature responses found that the thermoregulatory capabilities during sport-specific experiments do not show synchronized decline. Therefore, this population is not at higher risk of experiencing heat illness simply on the basis of partial disruption of thermoregulatory capabilities from SCI.

Heat illness occurrences, or life-threatening exertional heat stroke in sports, can be attributed to exercise duration and climatic conditions. In able-bodied athletes, heat illness occurs most often in marathon and ultra-distance races held in hot and humid conditions (American College of Sports Medicine et al., 2007). Considering these factors, athletes with SCI participating in marathon (T54 classification) or open field sports such as tennis lasting over 60 min in hot weather, are more likely to experience heat illness. To the best of knowledge to date, however, there is an apparent rarity of occurrence of heat illness in this population. A recent study reporting illness at the 2015 Para Athletic World Championships (venue ambient temperature 24.6-36.0°C) found only one incident of heat illness as a direct result of pathological elevation of the core body temperature (T52 classification, 39.5°C at the cessation of competition) (Grobler, Derman, Racinais, Ngai, & van de Vliet, 2019). In a field study exploring the physiological responses of elite wheelchair athletes, it has been shown that core body temperature following a 25-km race was 38.7°C (Edwards et al., 2018), which is well below the threshold temperature of 40.5°C that could trigger thermoregulatory collapse (Casa et al., 2015). In view of the available epidemiologic profiles, claims that athletes with SCI are more susceptible to heat stress than the able-bodied athletes are unwarranted.

A traditional concept regarding the thermoregulatory pathways following SCI is based on disrupted ascending peripheral afferent input to the hypothalamus, which could be activated

by the rising temperature of viscera and skin (Price & Trbovich, 2018; Walter & Krassioukov, 2018). When the peripheral temperature sensing below the lesion level is malfunctioning, this could cause delayed activation of thermoregulatory center and consequently leads to reduced heat loss response when overheated (Price & Trbovich, 2018). However, the organization of the temperature sensing underlying afferent thermal pathways involves a complex interaction of multiple sites from the peripheral and central origins. The functional contribution of central temperature sensing to the thermoregulatory mechanisms has been reported in a variety of animal species. Classic experiments have identified that artificial heating of the hypothalamus could directly elicit cutaneous vasodilation (Folkow, Strom, & Uvnas, 1949), and artificial increase in hypothalamic temperature triggered comparable heat loss response to spinal cord temperature (Jessen & Ludwig, 1971). More recent studies provided additional evidences, showing that the brain temperature could trigger signaling of neural sensors in the hypothalamus, which strongly influences the core body temperature (Conti et al., 2006; Song et al., 2016). During exercise, the brain temperature mimics temperature response of the core in animals and humans (Fuller, Carter, & Mitchell, 1998; Nybo, Secher, & Nielsen, 2002; Walters, Ryan, Tate, & Mason, 2000). Considering hypothalamic neurons are sensitive to brain temperature and the set-point thermoregulation is around 37°C (Boulant, 2006), thermal sensors residing in this region provide direct and efficient input regarding the state of body temperature homeostasis to the thermoregulatory center. It is clear, from the animal model at least, central temperature sensing plays a significant role in initiating thermoregulatory mechanisms. It has been suggested that central temperature sensing could even override lower-priority peripheral temperature sensing from the skin (Fusco, Hardy, & Hammel, 1961; Shafton, Kitchener, McKinley, & McAllen, 2014). It is possible that, despite of malfunctioning of peripheral temperature sensing from the spinal cord, viscera, and skin following SCI, the afferent thermal pathways to the hypothalamus could still function properly during exercise. The complex organization and coordination of the ascending thermoregulatory pathways following SCI await further clarification.

Rising body temperature constitutes an immediate stimulus for the activation of the heat loss mechanism through dilation of blood vessels (cutaneous vasodilation) and water evaporation (sweating) in humans. Human lesion studies suggest impaired reflex cutaneous vasodilation responses to temperature rise (Theisen et al., 2001; Van Duijnhoven et al., 2009). However, current result suggests the functional consequences to global thermoregulation during exercise seems less than expected. It remains to be determined the threshold exercise duration and environmental conditions that may lead to excessive body temperature rise (above 40°C) following partial or complete loss of spinal reflex below the lesion level.

A limitation to the present meta-analysis should be noted. Most of the included studies prescribed sport-specific exercise intensity; as a result, the absolute exercise loading eliciting heat production was not accounted for the consequent change in core body temperature. However, it should be noted that these experimental protocols attempted to mimic SCI sport-specific physical demands hence their results should be considered to be ecologically valid.

In conclusion, the present analysis of core body temperature responses under SCI sport-specific exercise and environmental conditions identified that thermoregulatory mechanisms can be adequately modulated in the presence of SCI, although special attention is still needed when adaptive endurance competitions are scheduled in hot and humid environments. Advancing our understanding of the precise physiological and neural mechanisms of thermoregulation has broad implications for this population to participate in physical activity and exercise, which could have enormous health and social benefits.

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Conflict of Interest
The authors declare that there are no conflicts of interest.

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