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Habituation of the cold shock response: A systematic review and meta-analysis

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ABSTRACT

Cold water immersion (CWI) evokes the life-threatening reflex cold shock response (CSR), inducing hyperventilation, increasing cardiac arrhythmias, and increasing drowning risk by impairing safety behaviour. Repeated CWI induces CSR habituation (i.e., diminishing response with same stimulus magnitude) after ~4 immersions, with variation between studies. We quantified the magnitude and coefficient of variation (CoV) in the CSR in a systematic review and meta-analysis with search terms entered to Medline, SportDiscus, PsychINFO, Pubmed, and Cochrane Central Register. Random effects meta-analyses, including effect sizes (Cohen's *d*) from 17 eligible groups (k), were conducted for heart rate (HR, n = 145, k = 17), respiratory frequency (f_R, n = 73, k = 12), minute ventilation (V_e, n = 106, k = 10) and tidal volume (V_t, n = 46, k=6). All CSR variables habituated ($p < 0.001$) with large or moderate pooled effect sizes: ΔHR -14 (10) bt. min^{-1} (*d*: −1.19); Δf_R −8 (7) br. min^{-1} (*d*: −0.78); ΔV_e, −21.3 (9.8) L. min^{-1} (*d*: −1.64); ΔV_t −0.4 (0.3) L^{-1}. Variation was greatest in V_e (control *vs* comparator immersion: 32.5&24.7%) compared to V_t (11.8&12.1%). Repeated CWI induces CSR habituation potentially reducing drowning risk. We consider the neurophysiological and behavioural consequences.

1. Introduction

The World Health Organisation (WHO) estimates that drowning claimed more than 2.5 million lives between 2008 and 2018 (Meddings et al., 2021). Drowning accounts for 7% of all injury-related death and is the 3rd leading cause of unintentional injury death worldwide in adults (WHO, 2020). Moreover, drowning is also identified amongst the top ten causes of death for young people in every region of the world (WHO, 2014). The WHO provides guidance on how to implement an effective drowning prevention framework (WHO, 2017). A key step in the framework is to raise awareness of drowning risks and develop campaigns to maximise the chances of survival for those accidently immersed. It is suggested that these steps can prevent a significant number of deaths through effective behaviour change interventions for those who are accidently immersed into water (Meddings et al., 2021). The rationale for effective behaviour change in the aquatic environment extends beyond minimising the individual, societal and moral burden of drowning. It was recently estimated that the economic cost of the maritime rescue response in the United Kingdom alone was approximately £139.2 million GBP (RNLI, 2022). The onward cost of medical care associated with the morbidities resulting from fatal and non-fatal drownings are additional to this figure (Mahony et al., 2017). Clearly, it is a societal interest to develop effective pathways to efficacious behavioural interventions to maximise the chances of survival following accidental immersion.

Yet, in countries where water temperatures are transiently or permanently cold (e.g., the United Kingdom & Canada; (Brooks et al., 2005; Tipton, 1989), the potential for an effective behavioural response is impaired by the psychophysiological response to cold water (Barwood et al., 2018). Sudden skin cooling on cold water entry evokes a life-threatening cascade of responses via a reflex volley of thermoafferent input to the midbrain (pons) and the hypothalamus via spinal lamina I neurons (Abbadie et al., 1994; Todd et al., 2005). The resultant sympathetic outflow produces a cold shock response (CSR; (Tipton,

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1989) comprising an "inspiratory gasp," hyperventilation, a resultant hypocapnia, tachycardia, peripheral vasoconstriction and hypertension (Barcroft and Edholm, 1943; Burke and Mekjavić, 1991; Cooper et al., 1976; Goode et al., 1975; Keatinge and Evans, 1961; Keatinge et al., 1964; Mekjavić et al., 1987). The hyperventilatory component of the CSR can increase breathing rate by more than 110% and ventilation by more than 600% (Datta and Tipton, 2006; Hayward and French, 1989; Tipton, 1989), thus increasing the chances of involuntarily aspirating water and drowning (Hayward and French, 1989; Tipton and Vincent, 1989). The CSR peaks between first 20–90 s of CWI and has largely subsided by 3-min (Golden and Hervey, 1981; Tipton et al., 1991). However, concomitant anxiety-induced stress, as is plausible in a survival scenario, can increase the magnitude (i.e. peak in heart rate [+9–12 b.p.m^{-1}]) and duration (i.e., average heart rate [+6 b.p.m^{-1}]; minute ventilation [+5.4 [7.1] L. min^{-1}]) for at least 7-min (Barwood et al., 2013), thereby extending the period of drowning risk (Barwood et al., 2018). The respiratory component of the CSR is under greater voluntary control than the cardiac component (Barwood et al., 2006). For example a psychological intervention extended breath-hold time by ~80% with no effect on heart rate (Barwood et al., 2006). It is suggested that, possibly because of a lack of the conscious control, a greater proportion of "drowned" victims than once thought succumb to adverse cardiac responses, especially in those with predisposing conditions such as channelopathies or ischaemic heart disease (Shattock and Tipton, 2012; Tipton et al., 1999; Tipton, 2014)). Moreover, cognitive performance is also impaired in cool (Buoite Stella and Morrison, 2022) and cold water (Jones et al., 2019), making an adaptive behavioural response in the initial minutes of CWI even more difficult to achieve (Barwood, 2018). It follows that any intervention that reduces the CSR has the potential to reduce the direct risk of drowning or a cardiac problem on initial immersion, as well as improve the conscious behavioural response, thereby maximising the chance of survival.

One possibility to reduce the magnitude of the CSR, and associated risks, is to undertake repeated cold-water immersions to induce a habituation of the CSR (Barwood et al., 2007; Keatinge and Evans, 1961; Tipton et al., 1998a, 1998b, 2000). Habituation is a form of non-associative learning and is the reflex response reduction induced by repeated and constant stimuli in compliance with a specificized set of phenomenological criteria (Christoffersen, 1997; Thompson, 2009). Moreover, the response decrement does not involve sensory adaptation, sensory fatigue or motor fatigue (Rankin et al., 2009). CSR habituation can be induced by undergoing a minimum of four short whole body CWIs (Barwood et al., 2007; Tipton et al., 1998a). The within-session (response profile during the immersion) and between-session (change in response profile between the immersion) habituation of the CSR follows a classic negative exponential curve with a reduced response for each subsequent immersion (e.g., (Barwood et al., 2013; Keatinge and Evans, 1961). This relatively rapid habituation suggests "true" habituation (Christoffersen, 1997) to a naturally occurring stimulus that poses a threat to the organism and is of both practical and neurophysiological interest (Barwood et al., 2016, 2018).

Some characteristics of CSR habituation are known. For example, after 4 immersions the heart rate and respiratory frequency response in the first 30-s of CWI were observed in one study to reduce by ~18% and ~23% of that seen on first immersion (Barwood et al., 2007) but with significant variability between individuals. Moreover, after 8 immersions the extent of habituation is far greater for the respiratory component than the cardiac component with the respiratory frequency and minute ventilation responses reduced by 49% and 56% respectively compared to heart rate (34%) (Tipton et al., 2000). Collectively, this probably represents an initial short-term habitation (i.e., onset and recovery with timescales of minutes (Cooke and Ramaswami, 2020) achieved with a relatively short inter-stimulus interval and in line with a 50% reduction versus naïve response after five to fifteen stimulus exposures (Christoffersen, 1997). Nevertheless, this repeated exposure to cold water is retained for seven months (31% reduction across cardiorespiratory variables) and partially present up to 14 months later (heart rate only; 18% reduction) (Tipton et al., 2000); indicating a long-term habituation (i.e., onset and recovery with timescales of days/weeks; Cooke and Ramaswami, 2020).

From a practical perspective, it is plausible that reducing the CSR may confer some benefit to defending the airway in the emergency scenario as the hyperventilatory drive seen in unhabituated participants is significantly reduced (Tipton et al., 1998b). Whilst CSR habituation is a relatively stable experimental observation, studies have tended to observe large inter-individual variability in the extent of the CSR (e.g., (Keatinge and Nadel, 1965; Tipton, 1992) and habituation (e.g., Barwood et al., 2013a; Tipton et al., 1998a). Part of the variation in the habituated response is explained by the extent of coincidental anxiety, evidenced experimentally as a form of manipulated associative learning (Barwood et al., 2013; Glaser et al., 1959), accounting for a greater part of the resultant respiratory response (i.e., 32%; (Barwood et al., 2018) than cardiac component (~20%). Chronic anxiety has also been shown to prevent CSR habituation, highlighting the influential role of stimulus specificity and strength (Barwood et al., 2017), thereby revealing some of the basic properties of the response (Christoffersen, 1997; Rankin et al., 2009; Thompson, 2009). Hence coincidental interventions may confound and contribute to variation (Golden and Tipton, 1988). No study to date has captured the magnitude of CSR habituation across studies to inform any putative reliability; doing so would represent a novel contribution to the literature.

Whilst habituation of the CSR during whole-body human cold-water exposure is a relatively novel experimental pursuit, habituation to other stimuli has been an experimental consideration since the 19th century (Peckham and Peckham, 1887). Habituation is a widely reported property of a variety of types of reflex across the animal kingdom (Christoffersen, 1997; Thompson, 2009). Importantly, habituation enables animals and humans to filter out irrelevant stimuli and focus selectively on salient stimuli (Rankin et al., 2009). This benefit has also been suggested to be relevant from a conscious behavioural perspective in simulated cold water survival potentially improving survival chances (Barwood et al., 2006, 2011). Moreover, CSR habituation may benefit attentional focus on survival training cues when bandwidth for attentional focus is reduced due to limitations to cognitive processing (Barwood et al., 2018; Leach, 2005). The mechanisms underpinning habituation have been suggested and tested since the early 20th century (Levine, 2007; Sherrington, 1907) with synaptic depression a widely discussed plasticity mechanism for short term habituation in mammals (Christoffersen, 1997; Simons-Weidenmaier et al., 2006). Long term habituation to cold stimuli has been linked with specific intact central anatomical locations (e.g., frontal areas of the cerebral cortex (Glaser and Griffin, 1962; Griffin, 1963) and somatosensory cortex (Klingner et al., 2014) and top-down inhibitory potentiation networks at the neuron and inter-neuron level (Ramaswami, 2014; Sokolov, 1963; Thompson and Spencer, 1966). Whilst the mechanisms for CSR habituation remain a matter of some debate (Barwood et al., 2018; Yurkevicius et al., 2022) the occurrence CSR habituation has not been reviewed for 17 years (i.e., Datta and Tipton, 2006) and has never been contextualised against possible inhibitory networks; a further novel contribution to this area of study. For reasons of brevity (habituation has been reported in many hundreds of thousands of studies across species) it is not practically feasible to systematically search all underpinning mechanistic literature. Nevertheless, we offer some suggestions of mechanism in this review, including evidence from studies in animals (Chaloner and Cooke, 2022), humans (Cooke and Ramaswami, 2020) and representative models (Carnaghi and Starobin, 2019; Ramaswami, 2014).

1.1. Aims

No study has collectively considered the meta-statistical effects of CSR habituation across studies; probably because of the paucity of

comparable studies in this field. We now believe that such an analysis is possible having undertaken a number of key studies in this area across our research group over the last ~40 years, whilst the founding and recent work of other groups adds significantly to this body of literature (e.g., (Jones et al., 2017; Keatinge and Evans, 1961). Accordingly, this study will contribute new knowledge to the field by systematically reviewing studies reporting the habituation of the life-threatening CSR. We aim to i) quantify the magnitude of the cardiorespiratory components of the CSR on initial immersion across studies ii) to quantify the magnitude of habituation in the cardiorespiratory components of the CSR after a minimum of 4 repeated, standardised immersions iii) describe the variation in the CSR within and between studies with a view to commenting on the consistency of the response. iv) Consider the neural processes involved in the CSR and its habituation. The potential for confounding influences on the habituation of the CSR will be considered before CSR habituation can be recommended as a protective intervention. From a practical perspective, the results will help identify an effective protocol to achieve CSR habituation for survival training purposes.

2. Methods

We registered the protocol for a systematic review of habituation of the cardiorespiratory components of the cold shock response as an intervention to reduce drowning risk: a systematic review and meta-analysis in November 2022 [CRD42022377103] using the International Prospective Register of Systematic Reviews (PROSPERO).

2.1. Search strategy

Electronic searches were conducted in March 2021, repeated in November 2021 and updated to December 2022. The review process followed the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021). A systematic search of peer reviewed literature from five online databases was conducted (Ovid Medline, SportDiscus, PsychINFO, Pubmed, and the Cochrane Central Register of Controlled Trials) to identify potentially relevant studies up until December 2022. The search strategy began with separate searches for terms related to the CSR (i.e., “cold shock” OR “cold-shock” OR “cold shock-response” OR “cold-shock response” OR “cold-water immersion” OR “cold immersion” OR “cold water immersion” OR “cold water”) and habituation (i.e., “habituation” OR “repeated” OR “adaptation”), before combining these searches using the Boolean operator “AND”. Where relevant for a given database, subject headings related to these terms were also included in the searches.

2.2. Eligibility criteria

Studies were considered and potentially eligible for inclusion if they reported empirical data in a peer reviewed journal, the study measured or reported one of the components of the CSR over multiple CWIs (see outcomes), and the full text was available in English. A PICOT (Population, Interest Area, Comparator, Outcome, and Timeline) framework (Riva et al., 2012) was used to define eligibility criteria before searches of online databases were performed. The pre-defined eligibility criteria were then systematically applied to the records identified via the comprehensive search strategy.

2.2.1. Population

To be eligible for inclusion, an article must have reported original data from human participants between 18 and 65 years old who had no documented thermoregulatory impairment that may influence the afferent or efferent components of the CSR; (e.g., spinal injury, ventilatory disorder; (Freund et al., 1984; Macey et al., 2005). Participants must have been unhabituated to cold water at the time of the study commencing, having undergone fewer than four cold water exposures in the past year (Tipton et al., 2000). Clear statements confirming prior ethical approval and participants’ informed consent were required in eligible articles.

2.2.2. Intervention - cold water habituation

Laboratory- or field-based studies were considered where participants’ unprotected skin was repeatedly exposed to cold water (i.e., not air, water-perfused suits, etc.) on a minimum of four separate occasions inclusive of their first and final immersions. Studies using water temperature (T_w) of $\leq$26 °C were eligible; i.e., the threshold at which maximum skin blood flow reduction through vasoconstriction occurs in humans with a normal deep body temperature (Folkow and Neil, 1971). A minimum body surface area coverage of 50% was required for habituation exposures, including the front or back of the torso but excluding exposure of the face to avoid evoking a dive response (Foster and Sheel, 2005). This ensured a sufficiently large and consistent thermal receptive field was stimulated in areas of high cold receptor density respectively (Christoffersen, 1997; Hensel and Schafer, 1984; Waldman, 2009). A minimum exposure duration of 150 s (2.5 min) was required to enable the CSR to peak and subside with no more than 8 days between consecutive exposures (Tipton, 1989).

2.2.3. Comparator

Studies were eligible if participants were immersed in water for their first and final exposure. Participants must have been unclothed (i.e., swimming costume and unprotected skin), immersed up to at least the sternum during the test immersions with standardised immersion rate, depth, and T_w; in order to standardise (within comparator immersions) the rate of spatial and temporal summation of thermoreceptors in response to temperature change (Hensel and Schafer, 1984). Whilst studies with concurrent potentially confounding interventions at the time of the compared immersions (e.g., experimentally induced anxiety e.g., (Barwood et al., 2017) were excluded. Within-participant and between-group designs were both eligible. Case studies conducted in unrepresentative participants (e.g., those habitually exposed to cold) and reviews were not eligible.

2.2.4. Outcomes

Eligible records reported at least one component of the cardiorespiratory components of the CSR within 7 min of water entry, either as absolute values or changes between immersions. Established components of the CSR include: heart rate response (HR), gasp response, respiratory frequency (f_R), minute ventilation (V_e), tidal volume (V_t), end expired carbon dioxide and oxygen ($P_{ET}CO_2$ & $P_{ET}O_2$) including nadir CO_2, and mouth occlusion pressure (P0.1).

2.2.5. Timeline

Relevant outcome measures must have been measured and reported within 7 min of entering the water during the control and comparator (i.e., first and last) immersions.

2.3. Study selection

The titles and abstracts of records identified through the original search strategy were screened independently (i.e., without consultation) by two authors (SH and NJ) to remove ineligible articles. For the remaining records, full texts were sought for retrieval. The full texts were read independently by the same two authors (SH and NJ) and articles were deemed eligible or ineligible based on the pre-defined inclusion criteria. Both stages of screening (titles/abstracts and full text screening) were conducted twice by both reviewers before results were compared. In the case of a disagreement between authors, a third author (MB) was consulted for a final decision. Where a lack of clarity existed relating to a key eligibility criteria, or data were measured but not reported, the authors of the relevant publication were contacted for guidance. If no response was received, or it remained impossible to

determine whether a study conclusively meet the inclusion criteria, the record was deemed ineligible. Where multiple articles reported the results of a single study, only one record of each study was considered eligible.

To ensure a comprehensive search strategy, forwards and backwards citation searching was performed in relation to the studies identified as potentially eligible after the original search records were screened. Citation searching was performed using the 'shiny' R software package *citationchaser* (Haddaway et al., 2022) to search the Lens.org database (consisting of PubMed, PubMed Central, CrossRef, Microsoft Academic Graph and CORE; https://www.lens.org).

2.3.1. Data extraction

Mean and standard deviation (SD) data were extracted from eligible records by two authors (SH and MB) and entered into a custom-made Microsoft Excel spreadsheet. Extracted data included: 1) publication details: authors, title, year 2) study design: (i.e., within or between group 3) participant characteristics: sample size, sex, age, body mass 4) protocol characteristics: T_w, immersion depth, number and frequency of water exposures, immersion duration 5) outcome measures (see section 2.2.4). Authors of the original research articles were contacted for any missing data; however, where these were not accessible, they were imputed using the sample pooled SD from similar included studies (Furukawa et al., 2006). Where data were plotted in figures but not reported in text, data were extracted using publicly available software (WebPlotDigitizer, Version 4.5 (Rohatgi, 2021). Where a study reported habituation data (i.e., responses during first and last immersions) distinctly for multiple independent groups of eligible participants, these were extracted separately. A single study may thus contribute more than one group of participants. All comparisons were made between the first and last eligible cold-water immersion within-participant even where a between-group design was adopted.

2.3.2. Quality and risk of bias assessment

The study quality and risk of bias (RoB) of was assessed using the Downs and Black checklist (Downs and Black, 1998). The 27-item checklist was modified to only include items that were relevant to assessing the risk of bias and methodological quality of non-clinical cross-sectional or observational studies. The modified checklist included 18 items, which were scored as 'Yes' (1), 'No' (0) or 'Unable to determine' (0). The maximum possible score was 18 and a higher score indicated a higher level of quality. A binary approach was adopted to question 27 to assess sample size (O'Connor et al., 2015) where a value of '1' was allocated to studies that included a sample size sufficient to achieve an 80% power to detect a significant difference. This was considered against a theoretically clinically important difference which we based on the mean SD difference that was calculated in the HR variable across all studies (Richmond et al., 2013). Two authors (MB&NJ) conducted the quality and RoB assessment. Any conflicts were resolved by a third reviewer (SH). NJ assessed all eligible empirical studies where MB was listed as an author.

2.4. Quantitative synthesis and analytic strategy

Extracted data from the first and final immersions were used to calculate a common effect size for each study (Polanin and Snilstveit, 2016). Hedges'*g* standardised mean differences (SMD) and 95% confidence intervals (CI) were calculated and allowed comparison between different protocols and outcome measurements. Effect sizes were interpreted as trivial (SMD <0.20), small (SMD = 0.20–0.49), moderate (SMD = 0.50–0.79) or large (SMD ≥0.80) (Cohen, 1992). Meta-analyses were performed using the metaphor package in RStudio (Version 4.0.3, Vienna, Austria (RCoreTeam, 2020; Viechtbauer, 2010). Random effects models were used based on restricted maximum likelihood estimation. Heterogeneity was assessed using the I^2 statistic and interpreted as might not be important (0–40%), may represent moderate heterogeneity (30–60%), may represent substantial heterogeneity (50–90%), or considerable heterogeneity (75–100%) (Deeks et al., 2019). Findings were back transformed for presentation in text and funnel plots. Egger's test was performed for each outcome to assess the likelihood of publication bias. A significant ($p < 0.05$) Egger's test would warrant exploration of Duval and Tweedie's trim and fill correction (Duval, 2005) but no such corrections were necessary. As an indication of variation between studies, the coefficient of variance (CoV) was calculated across the raw outcome variable data for the first immersion and the final immersion (i.e., after habituation had been induced). To assess the effect of T_w on the magnitude of CSR habituation, meta regressions (moderator analyses) were conducted for the outcome variable with most eligible groups (i.e., HR). Effect sizes are presented as SMD ±95% confidence intervals (CI), raw outcome data are presented as mean ± SD and CoV data are expressed as a percentage (%).

3. Results

3.1. Study selection

Final database searches yielded 5676 records of which 2325 were removed as duplicates. Thereafter 3351 titles and abstracts were screened for relevance with a further 3248 ineligible records removed. The full texts of the remaining 103 records were sought for retrieval. One record was not accessible in English; thus 102 full-text articles were reviewed with reference to the predetermined exclusion criteria. Forward and backward citation searches yielded a further 628 unique records, which was reduced to 13 following screening of titles/abstracts. The PRISMA chart is provided in Fig. 1 and outlines the records removed at each stage along with reasons for removal based on full-text review. The number of eligible studies where submissible data were available (not just measured), including all eligible groups (k), from the outcome variables (section 2.2.4) were: heart rate response (HR; k = 17), gasp response (k = 1), respiratory frequency (f_R; k = 12), minute ventilation (V_e; k = 10), tidal volume (V_t; k = 6), end expired carbon dioxide and oxygen ($P_{ET}CO_2$ & $P_{ET}O_2$ k = 0&0), nadir CO_2 (k = 1) and mouth occlusion pressure (P0.1; k = 0). Hence, meta-analyses were only conducted for HR, f_R, V_e and V_t on the basis of feasibility.

3.2. Overview of participant characteristics

Participant demographics and study characteristics for eligible papers are presented in Table 1. All studies were published in peer reviewed journals between 1988 and 2019. A total of 13 published papers were included. Seven studies used a within participant repeated measures design (Barwood et al., 2013; Brazaitis et al., 2014; Gordon et al., 2019; Jansky et al., 1996; Jones et al., 2017; Stocks et al., 2001; Wakabayashi et al., 2012) and 6 studies used a between group design (Barwood et al., 2007; Eglin and Tipton, 2005; Golden and Tipton, 1988; Lunt et al., 2010; Tipton et al., 2013); from which the additional groups were extracted. A total of 159 participants (~8.8 ± 2.6 per group; similar across variables) were studied with 145 specific to HR, 73 for f_R, 106 for V_e and 46 for V_t. Males were predominantly considered with 10 studies exclusively recruiting males and 3 studies recruiting a minority of females (n = 13; ~8% of cohort total). The study cohorts primarily comprised of university students.

3.3. Protocols to evoke CSR (number, frequency, mode of immersion, immersion duration)

The data used to calculate the averages for the number, frequency, modes (qualitatively reported), immersion duration and water temperatures (results section 3.4 for water temperature) for the included studies are reported in Table 1. The mean number of immersions across the studies reporting habituation of CSR components was 9.1 ± 3.8 immersions and was similar for HR (8.6 ± 3.6; range 6–18), f_R (7.8 ±

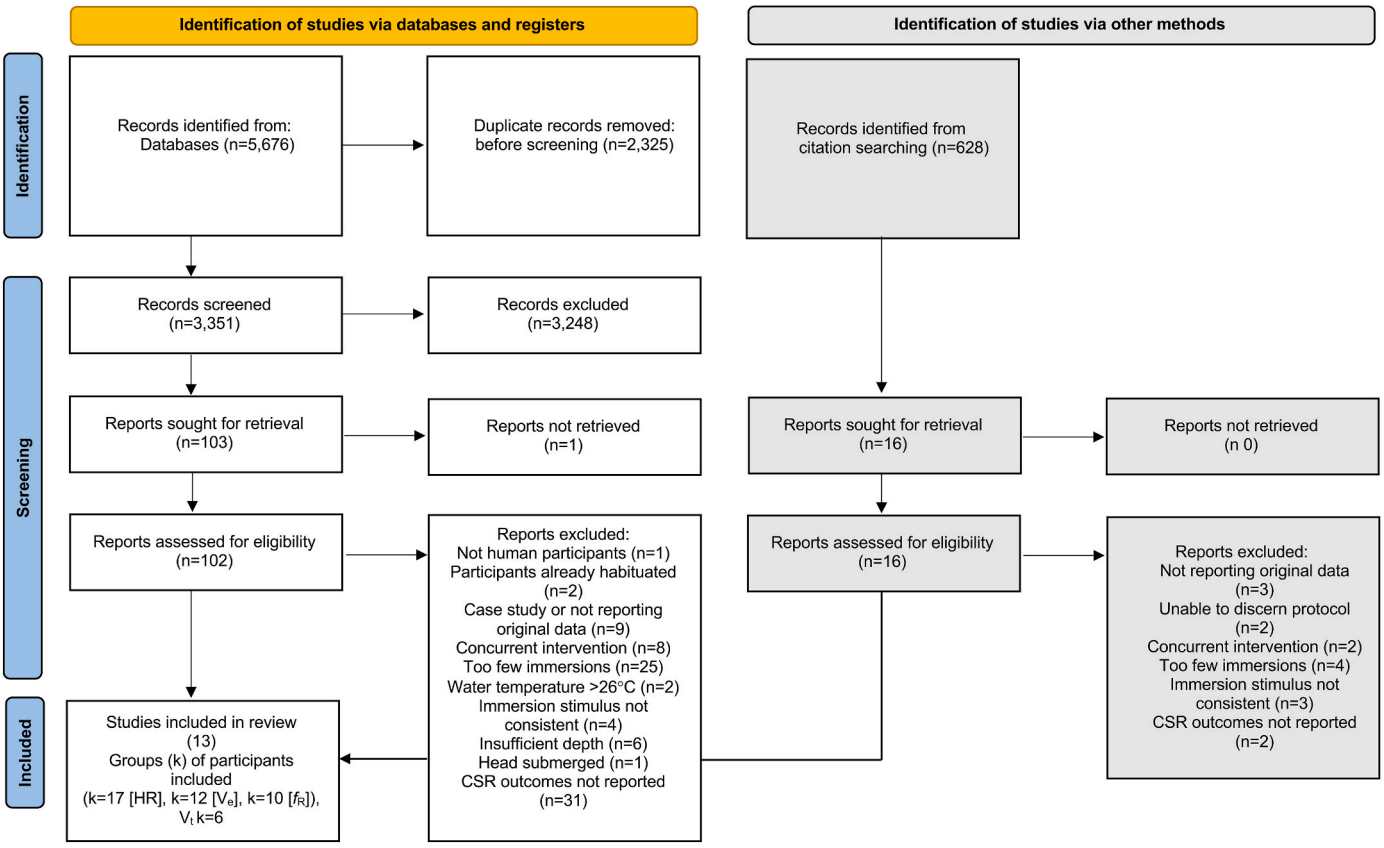

Fig. 1. Prisma flow chart of the study selection process.

1.6; range 6–12), V_e (7.8 ± 1.7; range 6–17) and V_t (7.7 ± 0.5; range 7–8) components. Eight immersions have been suggested as a critical threshold to fully habituate components of the CSR (Keatinge and Evans, 1961; Tipton, 1989) although not all included studies reported statistically significant habituation primarily in V_t (e.g., k = 4 across 4 studies (Barwood et al., 2013; Eglin and Tipton, 2005; Tipton et al., 1998b; Tipton et al., 2013). The frequency (i.e., inter-stimulus interval) of immersions was a mean of ~1.4 ± 0.5 days and never exceeded an immersion every 2.3 days (Jansky et al., 1996; Wakabayashi et al., 2012). No human studies have directly investigated the effect of varying inter-stimulus on the extent of CSR habituation or its re-establishment following ceasing CWIs. However, the control group (n = 4) of one ineligible study provides some insight (Tipton et al., 2000) – already represented by data from a preceding paper – (Tipton et al., 1998b). Tipton et al. (2000) immersed participants an average of every ~79 days across 6 occasions and saw some habituation of the CSR in the latter part (between 30 and 150 s) of repeated 3.0-min immersions. Fully habituated participants undergoing 8 immersions at a frequency of every ~1.3 days displayed CSR habituation for up to 7-months after this sequence and hence participants in the present featured studies are likely to experience long-term CSR habituation for at least this long (Tipton et al., 2000).

Most studies (7, representing k = 13 groups) used an electric winch, enabling a reproducible rate of 5.9 ± 3.1 m min^{-1}, to immerse participants. Immersion duration varied substantially between studies and averaged 43.3 ± 41.8 min (range 2.5–130 min). It was shortest for f_R (17.9 ± 30.9 min; range 2.5–90 min) and V_t (18.2 ± 35.2 min; range 3.0–90 min) with little descriptive difference between HR (38.2 ± 36.9 min; range 2.5–90), and V_e (39.7 ± 44.5 min; range 2.5–130) components. f_R is likely to be a primary variable of interest where a study is specifically focussed on investigating the CSR whereas V_t may be considered secondary (Tipton et al., 2017b) and changes in V_e more likely to be considered beyond the first ~5 min of immersion on the basis that changes in metabolic rate evoked by eventual core temperature cooling and shivering would be better reflected in this variables (e.g., (Brazaitis et al., 2014). No study to date has indicated that adaptation evoked through longer (i.e., more severe) cold exposure (e.g., those exceeding 10-min) impairs or alters habituation of the CSR evoked by shorter (i.e., up to 7-min) exposures. One study (Tipton et al., 2013) has indicated these adaptations are highly specific, complementary and temporally distinct and hence it is appropriate in the present study to pool findings that have considered cold immersions that exceed 7 min whilst initially reporting CSR related variables. Indeed the analysis epoch across all featured studies was 77 ± 82 s likely capturing the peak in all components of the CSR (Tipton, 1989).

3.4. *Water temperature (T_w)*

Whilst studies with a range of *Tw* between 0 °C and 26 °C were eligible (constant between control and comparator immersions), the mean T_w was ~13°C for test immersions and ~14 °C for the habituations; these values were similar for each component of the CSR meta-analysed variables (HR 13.4 ± 4.8 °C & 13.9 ± 4.5 °C; f_R 12.9 ± 4.9 °C & 13.9 ± 4.7 °C; V_e 13.4 ± 4.5 °C & 14.3 ± 4.2 °C; V_t 11.2 ± 2.0 °C & 12.8 ± 2.5 °C). Whilst there is no accepted definition of "cold water" it has been suggested that T_w of <15°C is "cold" on the basis that the CSR peaks between 10 °C and 15 °C (Tipton et al., 1991, 2017a); immersion below 10 °C is likely to induce pain through cold nociceptor activation (Keatinge and Nadel, 1965; Story et al., 2003). Nevertheless, a sub-maximal CSR is still evoked above 15 °C (e.g., Buoite Stella et al., 2022).

Table 1
Design, participant characteristics, protocol characteristics (including T_w and number of immersions) and main findings (including absolute values, measurement epoch and magnitude of change [%]) of eligible studies reporting one or more outcome variable.

Publication Details	Eligible Groups	Participant Characteristics	Protocol Characteristics	Outcome Variables	Main Findings
Barwood et al. (2007)	2 (between-group design)	*Group 1:* 10 ♂ Age = 21 ± 1.5 yrs, Mass = 82.4 ± 14.3 kg *Group 2:* 10 ♂ Age = 20 ± 1.6 yrs, Mass = 75.4 ± 9.5 kg	*All Groups* T_w: 12.2 ± 0.4 °C *Immersion depth:* To the clavicle *Rate:* 8 m.min^{-1} by electric winch *Number of immersions:* 7 (Control & comparator immersions 2&6) *Frequency:* 7 across 9 days (every ~0.8 days) *Immersion duration:* 2.5 min	HR, f_R, nadir CO_2	*Group 1:* P < 0.05 after 4 immersions HR (first 30s) ↓14% *Control:* 116 ± 26 b t.min^{-1} *Comparator*: 100 ± 20 b t. min^{-1} f_R (first 30s) ↓31% *Control:* 32 ± 14 br.min^{-1} *Comparator*: 22 ± 7 br.min^{-1} Nadir CO_2 (first 30s) ↑33% *Control:* 19.6 ± 7.9 mmHg *Comparator*: 26.0 ± 6.9 mmHg *Group 2:* P < 0.05 after 4 immersions HR (first 30s) ↓16% *Control:* 110 ± 15 b t.min^{-1} *Comparator*: 92 ± 10 b t. min^{-1} f_R (first 30s) ↓32% *Control:* 31 ± 14 br.min^{-1} *Comparator*: 21 ± 13 br. min^{-1} Nadir CO_2 (first 30s) ↑30% *Control:* 23.8 ± 9.7 mmHg *Comparator*: 30.9 ± 9.7 mmHg
Brazaitis et al. (2014)	1 (within-participant design)	*Group 1:* 14 ♂ Age = 22 ± 0.5 yrs, Mass = 79.3 ± 1.9 kg	*All Groups* T_w: 14.0 °C *Immersion depth:* Head-out *Rate:* Lowered, semi-recumbent position. *Number of immersions:* 17 (Control & comparator immersions 1&17) *Frequency:* 17 across 20 days (every ~1.2 days) *Immersion duration:* ?? Minutes	V_e	*Group 1:* P < 0.05 after 2 immersions V_e (first 60s) ↓35% *Control:* 37.5 ± 4.5 L min^{-1} *Comparator*: 24.3 ± 0.3 L min^{-1}
Barwood et al. (2013)	1 (within-participant design)	*Group 1:* 6 ♂, 4♀ Age = 19 ± 2.0 yrs, Mass = 77.6 ± 16.8 kg	*All Groups* T_w: 15.0 ± 0.1 °C *Immersion depth:* To the clavicle *Rate:* 8 m.min^{-1} by electric winch *Number of immersions:* 7 (Control & comparator immersions 1&CON) *Frequency:* 7 across 7 days (every ~1.0 days) *Immersion duration:* 7.0 min	HR, f_R, V_e, V_t	*Group 1:* P < 0.05, except V_t, after 4 immersions HR (first 60s) ↓22% *Control:* 101 ± 11 b t.min^{-1} *Comparator*: 79 ± 7 the ca f_R (first 60s) ↓31% *Control:* 32 ± 10 br.min^{-1} *Comparator*: 22 ± 7 br.min^{-1} V_e (first 60s) ↓41% *Control:* 46.7 ± 15.0 L min^{-1} *Comparator*: 27.6 ± 6.4 L min^{-1} V_t (first 60s) ↓19% (nsd) *Control:* 1.6 ± 0.5 L *Comparator*: 1.3 ± 0.4 L
Eglin and Tipton (2005)	3 (between-group design)	*Group 1:* 4 ♂, 2♀ Age = 25 ± 6.0 yrs, Mass = 74.3 ± 10.6 kg *Group 2:* 5 ♂, 1♀ Age = 26 ± 3.5 yrs, Mass = 80.5 ± 11.1 kg *Group 3:* 4 ♂, 2♀ Age = 26 ± 6.9 yrs, Mass = 82.5 ± 11.9 kg	*All Groups* T_w: 9.6 ± 0.2 °C *Immersion depth:* To laryngeal prominence *Rate:* 4.2 m min^{-1} by electric winch *Number of immersions:* 2, 6 cold showers (Control & comparator immersions 1&8) *Frequency:* 8 across 5 days (every ~1.6 days) *Immersion duration:* 3.0 min	HR, f_R, V_e, V_t HR, f_R, V_e, V_t HR, f_R, V_e, V_t	*Group 1:* P < 0.05, except V_t, after 8 immersions [exposures] HR (first 30s) ↓20% *Control:* 98 ± 16 b t.min^{-1} *Comparator*: 78 ± 12 b t. min^{-1} f_R (first 30s) ↓38% *Control:* 29 ± 8 br.min^{-1} *Comparator*: 18 ± 6 br.min^{-1} V_e (first 30s) ↓45% *Control:* 51.9 ± 17.9 L min^{-1} *Comparator*: 28.8 ± 16.9 L min^{-1} V_t (first 30s) ↓17% (nsd) *Control:* 1.8 ± 0.3 L *Comparator*: 1.5 ± 0.6 L *Group 2:* P < 0.05, except f_R, after 8 immersions [exposures] HR (first 30s) ↓18% *Control:* 95 ± 26 b t.min^{-1}

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Table 1 (*continued*)

Publication Details	Eligible Groups	Participant Characteristics	Protocol Characteristics	Outcome Variables	Main Findings
					Comparator: 78 ± 12 b t.min^{-1} f_R (first 30s ↓20% (nsd) *Control:* 20 ± 6 br.min^{-1} *Comparator*: 16 ± 5 br.min^{-1} V_e (first 30s) ↓54% *Control:* 34.8 ± 12.6 L min^{-1} *Comparator*: 15.9 ± 4.1 L min^{-1} V_t (first 30s) ↓37% *Control:* 1.9 ± 0.6 L *Comparator*: 1.2 ± 0.5 L *Group 3:* $P < 0.05$, except f_R, after 8 immersions [exposures] HR (first 30s) ↓13% *Control:* 98 ± 19 b t.min^{-1} *Comparator*: 85 ± 20 b t.min^{-1} f_R (first 30s ↓10% (nsd) *Control:* 20 ± 7 br.min^{-1} *Comparator*: 18 ± 4 br.min^{-1} V_e (first 30s) ↓39% *Control:* 42.8 ± 13.0 L min^{-1} *Comparator*: 26.2 ± 6.6 L min^{-1} V_t (first 30s) ↓32% *Control:* 2.2 ± 0.4 L. *Comparator*: 1.5 ± 0.5 L
Golden and Tipton (1988)	2 (between-group design)	*Group 1:* 8 ♂ Age = 22 ± 5.0 yrs, Mass = 74.3 ± 15.0 kg *Group 2:* 8 ♂ Age = 23 ± 3.0 yrs, Mass = 73.0 ± 8.0 kg	*Group 1:* T_w: 15.0 °C *Immersion depth:* To the clavicle *Rate:* Rapid, reproducible by electric winch *Number of immersions:* 8 (Control & comparator immersions 2&9. *Frequency:* 8 relevant to habituation) across 10 days (every ~1.5 days) *Immersion duration:* 40 min *Group 2:* T_w: 15.0 °C *Immersion depth:* To the clavicle *Rate:* Rapid, reproducible by electric winch *Number of immersions:* 6 (Control & comparator immersions 3&8. *Frequency:* 6 relevant to habituation) across 8 days (every ~1.3 days) *Immersion duration:* 40 min	HR, V_e HR, V_e	*Group 1:* $P < 0.05$, except V_t, after 8 immersions HR (first 60s) ↓12% *Control:* 94 ± 27 b t.min^{-1} *Comparator*: 83 ± 19 b t.min^{-1} V_e (first 60s) ↓32% *Control:* 58.3 ± 15.6 L min^{-1} *Comparator*: 39.6 ± 14.5 L min^{-1} *Group 2:* $P < 0.05$ after 6 immersions HR (first 60s) ↓28% *Control:* 116 ± 18 b t.min^{-1} *Comparator*: 84 ± 10 b t.min^{-1} V_e (first 60s) ↓55% *Control:* 65.1 ± 16.7 L *Comparator*: 29.2 ± 6.2 L min^{-1}
Gordon et al. (2019)	1 (within-participant design)	*Group 1:* 7 ♂ Age = 24 ± 4.0 yrs, Mass = 82.2 ± 12.9 kg	*All Groups:* T_w: 14.5 °C *Immersion depth:* To the clavicle *Rate:* Lowered *Number of immersions: Group 1*; 7 (Control & comparator immersions 1&7. *Frequency:* 7 relevant to habituation) across 7 days (every ~1.0 days) *Immersion duration:* 60 min	HR	*Group 1:* $P < 0.05$ after 7 immersions HR (first 300s) ↓17% *Control:* 85 ± 6 b t.min^{-1} *Comparator*: 71 ± 7 b t.min^{-1}
Jansky et al. (1996)	1 (within-participant design)	*Group 1:* 10 ♂ Age = 23 ± 2.2 yrs, Mass = 79.1 ± 7.0 kg	*All Groups:* T_w: 14.0 °C *Immersion depth:* To 5th intercostal space *Rate:* Seated, lowered *Number of immersions: Group 1*; 18 (Control & comparator immersions 1&18). *Frequency:* 18 relevant to habituation) across 42 days (every ~2.3 days) *Immersion duration:* 60 min	HR	*Group 1:* $P > 0.05$ after 18 immersions HR (first 300s) nsd *Control:* 61 ± 3 b t.min^{-1} *Comparator*: 54 ± 3 b t.min^{-1}
Jones et al. (2017)	1 (within-participant design)	*Group 1: 8* ♂, 4♀ Age = 26 ± 5.2 yrs, Mass = 75.6 ± 13.1 kg	*All Groups:* T_w: 10.0 °C *Immersion depth:* To mid sternum *Rate:* Stepped in and sat immediately *Number of immersions: Group 1*; 7 (Control & comparator immersions	HR	*Group 1:* $P > 0.05$ after 7 immersions HR (first 60s) nsd *Control:* 86 ± 17 b t.min^{-1} *Comparator*: 91 ± 13 b t.min^{-1}

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Table 1 (*continued*)

Publication Details	Eligible Groups	Participant Characteristics	Protocol Characteristics	Outcome Variables	Main Findings
			1&7). *Frequency:* 7 relevant to habituation) across 7 days (every ~1.0 days) *Immersion duration:* 90 min		
Lunt et al. (2010)	1 (between-group design)	*Group 1: 16* ♂ Age = 27 ± 7.0 yrs, Mass = 77.3 ± 8.4 kg	*All Groups:* T_w: 12.1 °C *Immersion depth:* To the axilla. *Rate:* Seated, lowered by an electric winch. *Number of immersions: Group 1*; 6 (Control & comparator immersions 1&6). *Frequency:* 6 relevant to habituation) across 3 days (every ~0.5 days) *Immersion duration:* 5 min	HR, f_R, V_e,	*Group 1:* $P < 0.05$ after 6 immersions HR (first 60s) ↓16% *Control:* 101 ± 22 b t.min^{-1} *Comparator*: 85 ± 18 b t. min^{-1} f_R (first 60s ↓19% *Control:* 27 ± 6 br.min^{-1} *Comparator*: 22 ± 5 br.min^{-1} V_e (first 60s) ↓36% *Control:* 66.6 ± 29.0 L *Comparator*: 42.7 ± 23.9 L
Stocks et al. (2001)	1 (within-participant design)	*Group 1: 7* ♂ Age = 25 ± 4.7 yrs, Mass = 74.4 ± 6.4 kg	*All Groups:* T_w: 18.4 °C *Immersion depth:* To the 4th intercostal space. *Rate:* Seated, lowered. *Number of immersions: Group 1*; 15 (Control & comparator immersions 1&15). *Frequency:* 15 relevant to habituation) across 15 days (every ~1.0 days) *Immersion duration:* 90 min	HR	*Group 1:* $P < 0.05$ after 6 immersions HR (first 60s) ↓11% *Control:* 76 ± 2 b t.min^{-1} *Comparator*: 68 ± 2 b t.min^{-1}
(Tipton et al., 1998)	1 (between-group design)	*Group 1: 8* ♂ Age = 22 ± 0.5 yrs, Mass = 78.9 ± 8.0 kg	*All Groups:* T_w: 9.8 °C *Immersion depth:* To the laryngeal prominence. *Rate:* 12 m min^{-1} by electric winch in a supine position. *Number of immersions: Group 1*; 8 (Control & comparator immersions 1&8). *Frequency:* 8 relevant to habituation) across 6 days (every ~1.3 days) *Immersion duration:* 3 min	HR, f_R, V_e, V_t,	*Group 1:* $P < 0.05$, except V_t, after 7 immersions HR (first 30s) ↓15% *Control:* 128 ± 13 b t.min^{-1} *Comparator*: 109 ± 20 b t. min^{-1} f_R (first 30s) ↓49% *Control:* 47 ± 18 br.min^{-1} *Comparator*: 24 ± 10 br. min^{-1} V_e (first 30s) ↓57% *Control:* 72.2 ± 12.5 L min^{-1} *Comparator*: 31.3 ± 11.4 L min^{-1} V_t (first 30s) (nsd) *Control:* 1.7 ± 0.5 L *Comparator*: 1.45 ± 0.4 L
Tipton et al. (2013)	2 (between-group design)	*Group 1:* 7 ♂ Age = 21 ± 1.4 yrs, Mass = 81.3 ± 9.9 kg *Group 2:* 7 ♂ Age = 21 ± 2.1 yrs, Mass = 85.0 ± 11.5 kg	*All Groups:* T_w: 12.0 °C *Immersion depth:* To the supra-sternal notch. *Rate:* 4.8 m min^{-1} by electric winch in a supine position. *Number of immersions: Group 1*; 7 (Control & comparator immersions 1&7). *Frequency:* 7 relevant to habituation) across 14 days (every ~2.0 days). *Immersion duration:* 45 min	HR, V_e, HR, f_R V_e, V_t	*Group 1:* $P < 0.05$ after 7 immersions HR (first 60s) ↓24% *Control:* 123 ± 15 b t.min^{-1} *Comparator*: 93 ± 12 b t. min^{-1} V_e (first 60s) ↓54% *Control:* 73.1 ± 25.2 L min^{-1} *Comparator*: 48.6 ± 18.2 L min^{-1} *Group 2:* $P < 0.05$, except V_t, after 7 immersions HR (first 60s) ↓6% *Control:* 105 ± 6 b t.min^{-1} *Comparator*: 99 ± 7 b t.min^{-1} f_R (first 60s) ↓19% *Control:* 43 ± 12 br.min^{-1} *Comparator*: 35 ± 11 br. min^{-1} V_e (first 60s) ↓20% *Control:* 86.5 ± 33.5 L min^{-1} *Comparator*: 69.6 ± 29.3 L min^{-1} V_t (first 30s) (nsd) *Control:* 1.7 ± 0.3 L *Comparator*: 1.7 ± 0.4 L
Wakabayashi et al. (2012)	1 (within-participant design)	*Group 1:* 7 ♂ Age = 22 ± 2.1 yrs, Mass = 61.4 ± 8.0 kg	*All Groups:* T_w: 26.0 °C *Immersion depth:* To chest. *Rate:* 1.0 m min^{-1} by electric winch. *Number of immersions: Group 1*; 12	HR, f_R, V_e	*Group 1:* $P > 0.05$ after 12 immersions HR (first 60s) (nsd) *Control:* 60 ± 9 b t.min^{-1} *Comparator*: 61 ± 11 b t.

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Table 1 (*continued*)

Publication Details	Eligible Groups	Participant Characteristics	Protocol Characteristics	Outcome Variables	Main Findings
			(Control & comparator immersions 1&12). *Frequency:* 12 relevant to habituation) across 28 days (every ~2.3 days). *Immersion duration:* 60 min		min^{-1} f_R (first 60s) (nsd) *Control:* 17 ± 3 br.min^{-1} *Comparator*: 18 ± 3 br.min^{-1} V_e (first 60s) (nsd) *Control:* 16.0 ± 4.9 L min^{-1} *Comparator*: 12.5 ± 2.6 L min^{-1}
		Total: 159, 146 ♂, 13♀	Mean ± SD T_w: 13.4 ± 4.0 °C *Rate:* 5.9 ± 3.1 m min^{-1} (where reported as m.min^{-1} or derivative; k = 13) *Number of immersions:* 9.1 ± 3.8 immersions. *Frequency:* every ~1.4 ± 0.5 days. *Immersion duration:* 43.4 ± 42.1 min.	CSR Variables HR = 12 studies, k = 17 groups f_R = 6 studies, k = 10 groups V_e = 8 studies, k = 12 groups V_t = 3 studies, k = 6 groups $P_{ET}CO_2$ = 0 studies $P_{ET}O_2$ = 0 studies nadir CO_2 = 1 study, 1 P0.1 = 0 studies	Mean ± SD Measurement epoch: 77 ± 82 s

3.5. Quality and risk of bias assessment

The average quality score was 13 ± 1 out of 18 equating to a 74 ± 5% rating overall. Quality scores ranged from 61% to 83% (Table 2). The included studies scored poorly on external validity (questions 11–13). None of the studies included enough detail to determine whether the individuals asked to participate were representative of the entire population from which they were recruited, or whether the participants prepared to participate represented the entire population most likely due to non-random, snowball sampling. However, studies involving repeated cold-water immersions are unpleasant for most participants to complete and are difficult to recruit to which also explains a lack of any reported *a-priori* power estimations. Lastly, none of the studies actually took place outside of the lab scenario (i.e., in the applied scenario where the effect of CSR habituation on drowning risk could be discerned) most likely on the basis of safety. It has been suggested that the magnitude of the CSR is greater in those immersed in open water (Cooper et al., 1976; Tipton, 1989) possibly because of the anxiety inducing effect of the field environment (see (Barwood et al., 2013). The remaining criteria were largely met by the included studies.

3.6. Quantitative synthesis of results – HR meta-analysis

Table 1 and Fig. 2 summarise the extracted data and resultant effect sizes from the HR meta-analysis. The random effects-model meta-analysis contained 17 effect sizes from 13 studies. The pooled effect was statistically significant indicating repeated cold-water exposure significantly reduced the HR component of the CSR ($p < 0.001$), with a large effect size (SMD: −0.98, 95% CI: −1.43 to −0.53). There was substantial heterogeneity ($I^2 = 62.4\%$). The mean ± SD HR response for the first immersion (i.e., the control) was 97 ± 19 b t. min^{-1} and had reduced to 83 ± 14 b t. min^{-1} after habituation in the comparator condition (-Δ14%). CoV remained relatively stable between the control (19.9%) and the comparator immersion (17.1%).

3.6.1. Quantitative synthesis of results - f_R meta-analysis

Table 1 and Fig. 3 summarise the extracted data and resultant effect sizes from the f_R meta-analysis. The random effects-model meta-analysis contained 10 effect sizes from 6 studies. The pooled effect was statistically significant indicating repeated cold-water exposure significantly reduced the f_R component of the CSR ($p < 0.001$), with a moderate effect size (SMD: −0.66, 95% CI: −0.97 to −0.35). And low heterogeneity ($I^2 = 0.0\%$). The mean ± SD f_R response for the first immersion (i.e., the control) was 30 ± 10 br. min^{-1} and had reduced to 22 ± 5 br. min^{-1} in the comparator immersion after habituation (-Δ27%). CoV reduced between the control (32.5%) and the comparator immersion (24.7%).

3.6.2. Quantitative synthesis of results - V_e meta-analysis

Table 1 and Fig. 4 summarise the extracted data and resultant effect sizes from the V_e meta-analysis. The random effects-model meta-analysis contained 12 effect sizes from 8 studies. The pooled effect was statistically significant indicating repeated cold-water exposure significantly reduced the V_e component of the CSR ($p < 0.001$), with a large effect size (SMD: −1.27, 95% CI: −1.95 to −0.58) but with substantial heterogeneity ($I^2 = 67.6\%$). The mean ± SD V_e response for the first immersion (i.e., the control) was 54.3 ± 19.8 L min^{-1} and had reduced to 33.0 ± 15.4 L min^{-1} in the comparator immersion after habituation (-Δ39%). CoV increased between the control (36.5%) and the

Table 2
Results of quality and risk of bias assessment; 13 studies, k = 17.

Reference	Downs and Black (1998) Question																		Total	Total (%)
	1	2	3	4	6	7	10	11	12	13	16	17	18	20	21	22	23	27		
Barwood et al. (2007)	1	1	1	1	1	1	1	0	0	0	1	1	1	1	1	1	0	0	13	72
Brazaitis et al. (2014)	1	1	1	1	1	1	0	0	0	0	1	1	1	1	1	1	0	1	13	72
Barwood et al. (2013)	1	1	1	1	1	1	1	0	0	0	1	1	1	1	1	1	0	0	13	72
Eglin and Tipton (2005)	1	1	1	1	1	1	0	0	0	0	1	1	1	1	1	1	1	0	13	72
Golden and Tipton (1988)	1	1	1	1	1	1	0	0	0	0	1	1	1	1	1	1	0	0	12	67
Gordon et al. (2019)	1	1	1	1	1	1	1	0	0	0	1	1	1	1	1	1	0	0	13	72
Jansky et al. (1996)	0	1	1	1	1	1	0	0	0	0	1	1	1	1	1	1	0	0	11	61
Lunt et al. (2010)	1	1	1	1	1	1	1	0	0	0	1	1	1	1	1	1	1	1	15	83
Jones et al. (2017)	1	1	1	1	1	1	1	0	0	0	1	1	1	1	1	1	0	0	13	72
Stocks et al. (2001)	1	1	1	1	1	1	0	0	0	0	1	1	1	1	1	1	0	0	12	67
Tipton et al. (1998a, 1998b)	1	1	1	1	1	1	0	0	0	0	1	1	1	1	1	1	0	0	12	67
Tipton et al. (2013)	1	1	1	1	1	1	1	0	0	0	1	1	1	1	1	1	0	0	13	72
Wakabayashi et al. (2012)	1	1	1	1	1	1	0	0	0	0	1	1	1	1	1	1	0	0	12	67

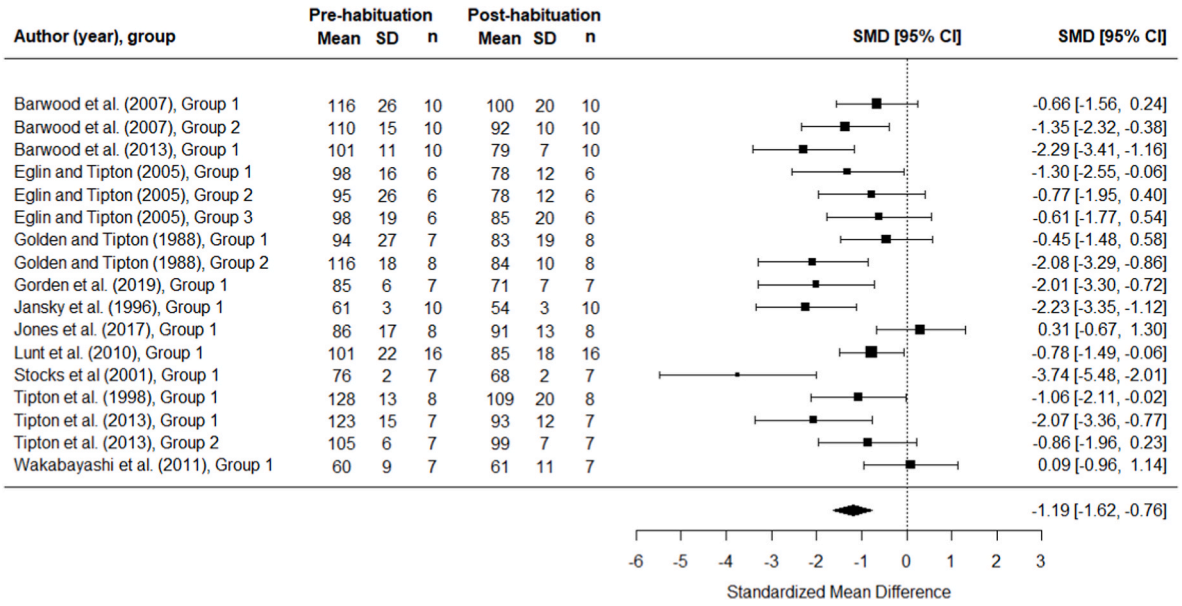

Fig. 2. Forest plot of the effect mean ± SD HR response from control and comparator immersions and the resultant effect size (SMD; 95% CI); k = 17.

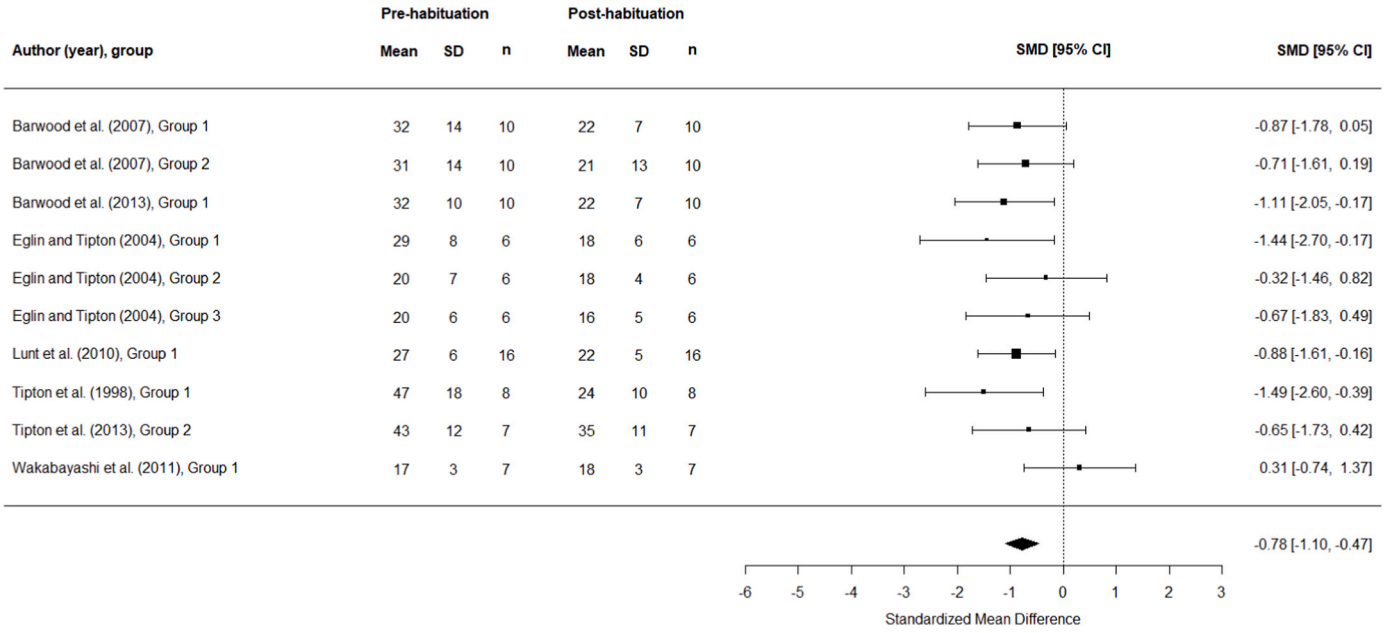

Fig. 3. Forest plot of the mean ± SD f_R response from control and comparator immersions and the resultant effect size (SMD; 95% CI); k = 10.

comparator immersion (46.7%).

3.6.3. *Quantitative synthesis of results - V_t meta-analysis*

Table 1 and Fig. 5 summarise the extracted data and resultant effect sizes from the V_t meta-analysis. The random effects-model meta-analysis contained 6 effect sizes from 4 studies. The pooled effect was statistically significant indicating repeated cold-water exposure significantly reduced the V_t component of the CSR ($p < 0.001$), with a moderate effect size (SMD: −0.63, 95% CI: −1.07 to −0.19) and with low heterogeneity ($I^2 = 0.0\%$). The mean ± SD V_t response for the first immersion (i.e., the control) was 1.8 ± 0.2 L min^{-1} and had reduced to 1.4 ± 0.2 L min^{-1} in the comparator immersion after habituation (-Δ22%). CoV was low and remained relatively stable between the control (11.8%) and the comparator immersion (12.1%).

3.7. *Quantitative synthesis of results – HR meta-regression*

Meta-regression analysis did not show any significant influence of T_w on the magnitude of the HR component of the CSR ($r^2 = 0.01$, 95% CI: −0.12 to 0.12, $p = 0.99$) indicating a relatively consistent magnitude of change between studies irrespective of T_w.

4. Discussion

We undertook a systematic review, including a meta and meta-regression analysis, i) to quantify the magnitude of the cardiorespiratory components of the CSR on initial immersion across studies (i.e., the control immersion; see Table 1), ii) to quantify the magnitude of habituation in the cardiorespiratory components of the CSR after a minimum of 4 repeated, standardised immersions and iii) describe the

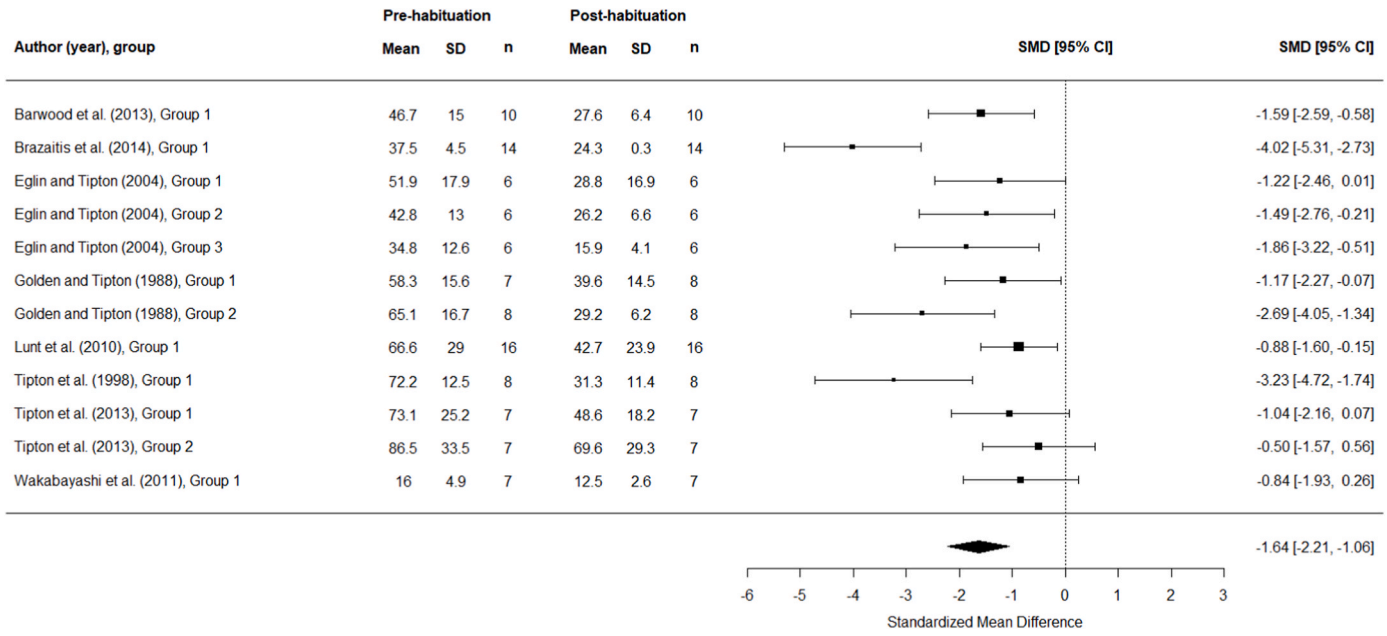

Fig. 4. Forest plot of the mean ± SD V_e response from control and comparator immersions and the resultant effect size (SMD; 95% CI); k = 12.

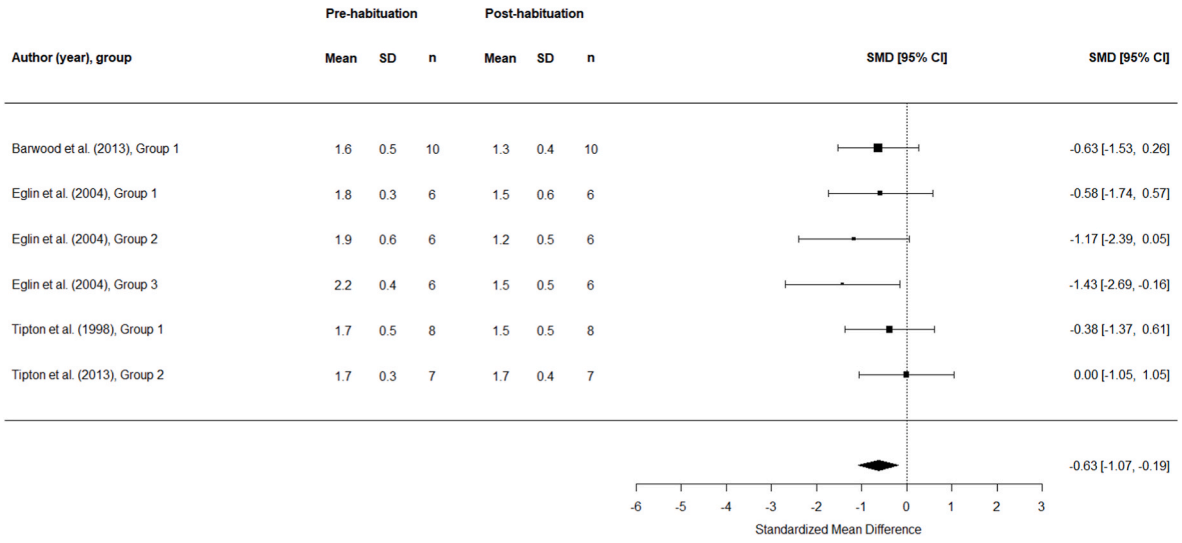

Fig. 5. Forest plot of the mean ± SD V_t response from control and comparator immersions and the resultant effect size (SMD; 95% CI); k = 6.

variation in the CSR within and between studies with a view to commenting on the stability of the response. The measurement epoch we used produced an average of the period where the peak in the CSR was likely to occur concurrent with the greatest threat of drowning (Tipton, 1989). Below we consider the implications of these data for the behavioural response in the applied scenario of accidental cold-water immersion with a view to minimising the threat to health. The potential for confounding influences on the habituation of the CSR is considered. Inferences on probable mechanisms are drawn from animal and human studies describing components of the CSR, the stress response and its habituation. There are no definitive studies that have fully elucidated this pathway and hence we explicate it here.

In the context of our first aim (i.e., to i) quantify the magnitude of the cardiorespiratory components of the CSR on initial immersion across studies), the extent of the cardiorespiratory CSR seen on average in the control immersion (i.e., the first immersion) was relatively modest in the context of the reported peak of the CSR (Golden et al., 1997; Hayward and Eckerson, 1984; Keatinge and Evans, 1961; Tipton, 1989). For example, representative (T_w: 15 °C, 8 m.min^{-1}, to the clavicle) *peak* HR and f_R of 129 b t. min^{-1} (range: 102 to 146) and 61 (range: 30 to 118) br. min^{-1} have been reported (Barwood et al., 2013). Taking f_R data from the present study as a representative example of the increased risk of drowning associated with the loss of respiratory control, we saw *mean* values within this range (min-max range between featured groups 17 to 47 br. min^{-1}) with the calculated mean and maximum reported values we report still representing an approximate 250% and 390% increase against textbook resting f_R values (~12 br. min^{-1} in healthy participants (Marieb, 2004). Despite our attempts to standardise the protocols of the included studies, the mean f_R data we report (see Table 1) are likely mitigated by the marginally different water temperatures, immersion rates and measurement epochs. This contextualises the risk posed by cold water immersion even when considering the *average* initial CSR over 60–90 s in T_w between 26 and 10 °C. The response profile of the averaged data across studies probably represents a best-case scenario for someone accidently immersed in cool/cold water. The response characteristics of the thermally activated thermoreceptors (Hensel et al.,

1951; Ivanov et al., 1982) and spinal lamina 1 cool neurons (Craig et al., 2001) indicate a transient overshoot in their discharge followed by an adjustment to a higher static firing frequency in accordance with the cooler thermal input from the skin (adapting temperature). This dynamic-static peripheral and central discharge profile initiates the CSR but is latent (i.e., discharge declines first) to the measured skin temperature cooling profile seen across a range of T_w (5, 10, 15 °C; (Tipton et al., 1991). This CSR initiation is a physiological reflex with some top-down voluntary control over respiratory responses only with psychological training (Barwood et al., 2006). Whilst the influence of the cardiovascular responses on drowning risk cannot be ruled out, they probably contribute more substantially to sudden death on immersion. To precipitate sudden death on immersion, the conditions of prior breath-holding (i.e., to produce autonomic conflict induced arrhythmia; Shattock and Tipton, 2012) or an underlying cardiovascular condition might need to be met (e.g., channelopathies or ischaemic heart disease) to be lethal (Shattock and Tipton, 2012) whereas the hyperventilatory components of the CSR would probably afflict all unhabituated persons and increase drowning risk. During these initial minutes of immersion the intuitive behavioural response of swimming to safety is severely impaired (Golden et al., 1986). Hence the time to minimise the CSR is critical in determining survival chances, evoking a behavioural response and is subject to a number of modifying influences falling under increasing voluntary control over time (Barwood et al., 2018).

The precise afferent pathways that result in the data reported for aim i) which are responsible for the cardiorespiratory responses to human, whole-body cold-water immersion remain to be elucidated and are largely inferred from animal studies. The speed of the response suggests an uncomplicated neural pathway (Datta and Tipton, 2006). Measurements in monkeys, cats and rats indicate the activation of monosynaptic connections specific to spinal lamina I neurons following cutaneous thermoreceptor activation in response to non-noxious (i.e., innocuous) and noxious (i.e., discomfort/pain inducing) cooling (Andrew, 2010; Andrew and Craig, 2001; Craig et al., 2001). Lamina I neurons receive modality-selective input from A-delta (δ) and C primary afferent thermoreceptors and nociceptors at the superficial dorsal horn of the spinal cord (Christensen and Perl, 1970). The CSR is likely to share a similar pathway stimulated by activation of thermoreceptors responsive to both noxious and non-noxious cooling. Studies in cats indicate that cool and polymodal nociceptive (HPC) activated neurons on this pathway have activation (Cool: 34 °C & HPC: 24 °C) and saturation (Cool: 15 °C & HPC: 9 °C) thresholds that cover the activated thermal range in the present analysis (Craig et al., 2001). In humans, TRPM8 and TRP1A thermoreceptors (McKemy et al., 2002; Story et al., 2003) are plausible candidates for the cutaneous initiation of the CSR and also share overlapping activation ranges (TRPM8: 28 to 25 °C & TRPA1: <17 °C (Bharate and Bharate, 2012; Tominaga and Caterina, 2004) with the T_w considered in the present review although the role of TRPA1 in response to noxious cooling is equivocal (Dunham et al., 2010). The response characteristics of two subpopulations of cool specific spinothalamic lamina I neurons have also been identified (Craig et al., 2001). These share similar response characteristics to the two distinct sub-populations that innervate the epidermal and dermal layers of the skin (Craig, 2018; Hensel and Schafer, 1984; Hensel et al., 1951; Ivanov et al., 1982) that have been linked to initiating the CSR (Tipton, 1989). This represents the probable immediate sensory pathway from receptor to spinal cord responsible for initiating the CSR; this requires experimental confirmation. The central integration following the activation of the cool and noxious cold thermoreceptors is a summation of the individual burst characteristics from the receptive fields activated through skin cooling (Craig, 2018); in accordance with body region, body surface area stimulated and rate of exposure - all standardised within the present review. This results in a centrally aggregated response profile that increases monotonically above threshold eventually saturating at the upper limit of the cold/noxious range (Craig et al., 2001). The central and terminal locations for the lamina 1 neurons allow for a direct afferent pathway, through parallel cell columns linked to the autonomic nervous system, for brainstem stimulation (Altman and Bayer, 1984; Craig, 2003).

The central structures that evoke the CSR and the resultant data specific to aim i) are also inferred from animal studies. Using c-fos immunohistochemistry, Tipton and Harris showed c-fos positive cold (8 °C immersion of rats to the diaphragm) activation of the caudal parts of the brainstem specific to the medulla structures of the nucleus tractus solitarius, area postrema and dorsal motor nucleus (i.e., areas of the medulla known to process cardiovascular and respiratory afferents (cited by (Datta and Tipton, 2006). Part Of the respiratory response is specific to cold stimulation of the alpha motorneurones innervating the intercoastal muscles of the diaphragm (Keatinge and Nadel, 1965) which were fully immersed (i.e., stimulated) in all of the studies included in the present review. Also in rodents and rostral to the medulla, Hinckel and SchrÖder-Rosenstock (1981) showed cold-responsive subcoeruleus units in the brainstem pons, which is a key site for noradrenaline release, in response to abdominal and leg-cooling in the range of 22–29 °C in Guinea pigs (Hinckel and Schröder-Rosenstock, 1981). Further along the ascending pathway, Kelly et al. (2011) showed increased c-fos activation in the dorsal raphe nucleus and the ventrolateral periaqueductal grey (PAG) in rats exposed to stress and cool water swimming (19 °C), when contrasted to a thermoneutral swim (35 °C) and hypothesised a role for midbrain serotonergic neurons integrating the physiologic and behavioural cues to internal and external stressors. The parabrachial nucleus (PB; in the dorsolateral pons), is intimately linked to the PAG (Krout et al., 1998), and also receives inputs from spinal lamina I neurons (Craig et al., 2001). Whilst we believe that the CSR pathway is under limited initial conscious influence in the first few seconds of cold-water immersion, terminal entry to the PAG and PB is one initial site for lamina 1 neurons to sensitise the resultant response. PAG and PB have the potential to magnify or extend the CSR by triggering aversive behaviour and additive cardiorespiratory arousal following initial and then repeated exposure to a cold water stimulus if this is perceived as noxious (Barwood et al., 2018; Kelly et al., 2011). Lastly, conscious sensory awareness of strong thermal stimuli, possibly as a result of thermal discomfort (i.e., those worthy of allocation of attentional resource), results from thermal integration of the spinal lamina 1 pathway to the primary somatosensory cortex with specific roles for the anterior cingulate cortex, insula cortex and orbitofrontal cortex in the resultant response (Craig, 2003, 2004, 2018; Fechir et al., 2010).

In the context of our second aim (ii) to quantify the magnitude of habituation in the cardiorespiratory components of the CSR), following ~8 repeated cold-water immersions across eligible groups and variables, we saw significant reductions in all featured CSR variables with moderate (f_R & V_t; Figs. 3 and 5) or large effect sizes (HR & V_e; Figs. 2 and 4). This translated to reductions between the control and comparator immersions of 14 ± 10 b t. min^{-1} (change Δ14%), 8 ± 7 br. min^{-1} (Δ27%), 21.3 ± 9.8 L min^{-1}(Δ39%), and 0.4 ± 0.3 L (Δ22%) for HR, f_R, V_e and V_t respectively. In theory this reduction would improve the chances of surviving CWI in the real-life scenario by reducing respiratory drive (drowning risk) and cardiovascular strain thereby enabling a conscious behavioural strategy to be deployed sooner (e.g., floating or swimming to safety; (Barwood et al., 2011; Bowes et al., 2016). The mechanisms and time course to achieve short-term and long-term CSR habituation have not been studied extensively and are not well understood although, similar to other habituation research, are probably distinct (Chaloner and Cooke, 2022; Christoffersen, 1997). Short-term CSR habituation (i.e., onset and recovery within minutes; i.e., within-session habituation) is consistently evident within the first one or two CWI exposures highlighted by a decline in the CSR after an initial peak (e.g., Keatinge and Evans, 1961). This is probably a result of an adjustment to the level of sympathetic nervous system response in accordance with the change in skin cold receptor discharge, after an initial overshoot, to a higher steady static discharge (Hensel and Schafer, 1984). The time course of

this adjustment suggests it is centrally mediated theoretically ruling out initial adaptation at thermoreceptor level (Tipton et al., 1998a). This adjustment could be achieved at the spinal level by lamina I spinal para-brachial neurons (SPNs) allowing for gated afferent relay response to supraspinal centres (Agashkov et al., 2019). Whilst short-term habituation at the receptor level seems unlikely, there is evidence of receptor level adaptation in high-frequency cold receptors of chronically cold (air) exposed rats which have been shown to have reduced dynamic and static firing frequencies, and the proportion of low-frequency cold receptors most sensitive to the low-temperature range decreased (Kozyreva, 2007). Shifts towards lower dynamic maxima and burst characteristics have also been recorded in cold (air) adapted cats potentially modifying the extent of thermal afferent input following repeated cold exposure (Hensel and Schäfer, 1982). Whether a similar response is evoked after acute cold-water exposure is not known. Whatever the mechanism, studies are required that focus on the evoked plasticity response after acute high-intensity cooling (i.e., that evoked by cold water) if the mechanism specific to the CSR is to be established.

There are a greater number of cold studies aimed at establishing the central structures responsible for the habituation responses seen specific to aim ii) and that probably result in long-term habituation. It has been suggested the frontal areas of the cerebral cortex are involved in the response (Glaser and Griffin, 1962). Glaser and Griffin (1962) showed that rats who underwent lesions of the occipital-parietal cortex produced tachycardic responses that were indistinguishable from control rats (i.e., no habituation) after 10-days of repeated short-term (10 min) cold water (4 °C) immersion. It was subsequently hypothesised this central structure was part of a top-down inhibitory network from higher centres to the brain stem (sub-cortical level) that could control cardiovascular responses to acute cold exposure (Griffin, 1963). Subsequently, Klosterhalfen and Klosterhalfen (1985) confirmed the importance of the cortex in establishing long-term habituation (over 24hr period) which did not occur in functionally decorticate rats (Klosterhalfen and Klosterhalfen, 1985). They also suggested the neuronal substrates required for short term and long-term habituation are different; a view that is widely supported (Ramaswami, 2014). More recently Fechir et al. (2010) confirmed the critical role the cerebral cortex plays in top-down inhibitory control on autonomic centres located in the brainstem during innocuous whole body (30-min cooling; water-perfused suit 7 °C) cooling (Fechir et al., 2010). They showed increased infrapontine brainstem and cerebellar activation during cooling with an inverse relationship between activation and right mid-insular cortex activation indicative of an absence of thermal discomfort. The CSR protocols described in the present paper probably do evoke thermal discomfort based on subjective reports collected after an initial immersion (e.g., staged immersion at 11 °C (Barwood et al., 2006). Consequently, it is likely that the insular cortex contributes to the conscious interpretation of whole-body cooling, possibly evoking feelings of discomfort similar to that reported in previous whole body cooling protocols of greater strength (10-min cooling; water-perfused suit 4 °C) with concomitant brain imaging (Craig, 2018; Egan et al., 2005).

In the context of our third aim (iii to describe the variation in the CSR within and between studies with a view to commenting on the consistency of the response), with the exception of V_t, the variation between studies in the CSR response was large (range 21.8–44.5%) but diminished by undergoing habituation (range 22.7–31.1%); highlighting one potential benefit of CSR habituation in the survival scenario. Part of this variation can be accounted for by different T_w used across studies with temperatures above 15 °C likely evoking sub-maximal CSR responses (Tipton et al., 1991). Yet, our meta-regression analysis shows that the magnitude of CSR habituation was not different as a result of the different T_w used highlighting the generalisability of CSR habituation. Moreover, when the within-study variation is considered it is similarly large (e.g., HR 18.6 & 16.3%; f_R 45.2 & 45.0%) for control and comparator immersions; from habituation immersions of (Barwood et al., 2007) groups combined n = 20). It has also been shown that there is cross-transfer of the CSR habituation between T_w (Tipton et al., 1998b) and other stressors (Lunt et al., 2010); a further benefit of CSR habituation. Lunt et al. (2010) showed short-term cold habituated participants who completed six, whole-body cold-water immersions (12.1 °C; every ~0.5 days; i.e., two immersions per day) had a reduced noradrenergic and adrenergic response to autonomic stress evoked by a different environmental stressor (i.e., hypoxia). This suggests a generic cross adaptation and that repeated cold-water immersions evokes reduced autonomic and HPA axis stimulation. Animal studies (rats) have suggested the sensitivity of the HPA axis to stress (emotional and physical; restraint) and cold contributes to variation (Benini et al., 2019; LeBlanc et al., 1971).

In the present review, on the basis of relatively homogenous study cohorts, the contribution to this variation of thermally influential variables of sex and age (e.g., (Castellani and Young, 2016) are likely minimal; although both warrant further study. However, it is likely that inter-personal differences and regional variations in thermal sensitivity (e.g., number of cold sensitive spots) do make a contribution (Yang et al., 2017). Moreover, it has been suggested that high levels of aerobic fitness help reduce the CSR through enhanced inhibitory influence of parasympathetic branch of the autonomic nervous system on the cardiorespiratory responses that are evoked (Golden and Tipton, 1988; Hull et al., 1984). By contrast, enhancing the activity of the sympathetic nervous system by increasing pre-immersion anxiety magnifies the CSR (Barwood et al., 2013) and a greater CSR is often seen as a consequence of anxiety associated with staged immersion after the first immersion (Golden and Tipton, 1988). Acute anxiety also reverses (Barwood et al., 2013) and prevents (Barwood et al., 2017) CSR habituation; observations also verified in animals using a stress paradigm (Benini et al., 2020). We know anxiety accounts for significant proportions of the resultant cardiorespiratory response (Barwood et al., 2018), and has the potential to confound any habituation. This may extend to impairing the selected survival behaviour in the real-life scenario unless careful steps are taken in the preparatory behavioural training to avoid this possibility. Maximising relaxation on cold water immersion and ensuring the (stimulus) strength and specificity (e.g., representative T_w, rate of entry, skin surface area coverage) of preparatory (survival) training would maximise the chances of CSR habituation proving effective. From an evolutionary perspective, the purpose of habituation is to filter out irrelevant, innocuous, naturally occurring stimuli in the environment and attend to those that are salient to survival (Rankin et al., 2009). It is therefore possible that a habituated response induced in the lab to an innocuous stimulus becomes a strong, life-threatening stimulus in the real-life scenario evoking a different response especially in those who are anxious (Barwood et al., 2017). We do know that perception of the environment partially mediates the CSR (Barwood et al., 2014).

In the context of our fourth aim (iv) consider the neural processes involved in the CSR and its habituation), we have previously used the interoceptive model of Craig et al. (2001) to explain the possible conscious interpretation of the sensations evoked by repeated CWI and the sensitising effect of acute anxiety on the CSR before and after habituation (Barwood et al., 2018). In the context of habituation, interoception would rely on changes to predictive coding through repeated exposure to the cold water stimulus between the expected sensory state encoded by the dorsolateral prefrontal cortex (through corollary discharge to the insula) and the actual state summated by afferent feedback from the spinal lamina I pathway (e.g., skin cooling, cardiorespiratory response) encoded by the orbitofrontal cortex (Kringelbach, 2005). Discrepancy between the coding represents an error and sensitises the response potentially stimulating the limbic system; which has been shown to be activated by thermal discomfort and anxiety (Barwood et al., 2018; Felix-Ortiz et al., 2016; Kanosue et al., 2002).

In the present study we contend that repeated exposure to CWI culminates in agreement between prediction and sensation and a lesser resultant response with each subsequent stimulus (immersion). Interestingly habituation of the CSR has been shown to result in habituation

of thermal discomfort (Golden and Tipton, 1988; Keatinge and Evans, 1961) which would result in graded deactivation of the mid-insular cortex. Continued cold exposure may eventually result in sub-conscious (less or no higher cortical activation) corticobulbar inhibitory control of autonomic output (Craig, 2018) as was reported using whole body innocuous cooling (Fechir et al., 2010), thereby enabling a consciously evoked survival strategy to be deployed. The interoception model is analogous to the 'negative-image' model of habituation learning which contends that inhibitory potentiation at the inter-neuron level provides a blueprint for a cortical image that selectively filters and attenuates the transmission of this percept to downstream brain regions (Ramaswami, 2014). This blueprint may also be the foundation for long-term habituation (Ramaswami, 2014). The PAG and PB are plausible relay sites to mediate this inhibitory control on the basis that they widely project to thalamus, hypothalamus and amygdala and show evidence of thermoreceptive-specific activation (Craig and Dostrovsky, 2001) and strong antinociceptive inhibition when stimulated (Mokha et al., 1987). Both are sensitive to top-down inhibitory influence by serotonin (Kelly et al., 2011; Poon, 2009) which has shown to mediate responses to cold compared to thermoneutral swim stress through modifying afferent input to the dorsal raphe nucleus (Kelly et al., 2011).

5. Conclusions

Our systematic review and meta-analysis quantified the cardiorespiratory components of the CSR and its habituation. We also described the variation in the CSR with a view to commenting on the potential for stability of the response in the real-life scenario. In theory, habituating the CSR would enable a coordinated behavioural response, possibly guided by survival or public safety training, to be deployed with greater success or more swiftly. From a practical perspective the results of our study help clearly identify the protocol components required to induce CSR habituation at whole body level and how this might be administered to maximise the cross-transfer of these benefits to the real life-scenario. If we accept that CSR habituation can reduce or eliminate the conscious awareness of acute skin cooling ensuring that top-down inhibitory control of the brainstem manages the resultant response, immersed victims may have more attentional resource to deploy their behavioural survival strategy. Consequently, drowning risk may be reduced although we note this habituation might be confounded by anxiety. Our findings are of neurophysiological interest and have enabled us to outline in greater detail the neurophysiological pathways potentially responsible for evoking the CSR and the inhibitory influences evoked through habituation. Animal studies have largely informed the pathways we believe to be responsible. Despite meeting the threshold for undertaking a meta-analysis with these data, there is a significant shortage of studies examining the acute responses to whole-body cold-water immersion especially in females and older participants.

Data availability

Mean ± SD data reported in Table 1 represent the data extracted and entered into the meta-analyses. The resultant effect sizes reported in Figs. 2–5 represent those used for the meta regression analyses with water temperatures used as the independent predictive variable reported in Table 1. Consequently, all data used for this paper are openly available.

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CRediT authorship contribution statement

Martin J. Barwood: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing. **Clare Eglin:** Conceptualization, Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Samuel P. Hills:** Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Nicola Johnston:** Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Heather Massey:** Conceptualization, Data curation, Investigation, Methodology, Resources, Writing – original draft, Writing – review & editing. **Terry McMorris:** Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Michael J. Tipton:** Conceptualization, Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Hitoshi Wakabayashi:** Conceptualization, Data curation, Investigation, Methodology, Resources, Writing – original draft, Writing – review & editing. **Lisa Webster:** Funding acquisition, Investigation, Resources, Writing – original draft, Writing – review & editing.

Declaration of competing interest

None of the authors have a conflict of interest.

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Appendix A. Supplementary data

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References

Abbadie, C., Honoré, P., Besson, J.M., 1994. Intense cold noxious stimulation of the rat hindpaw induces c-fos expression in lumbar spinal cord neurons. Neuroscience 59, 457–468.

Agashkov, K., Krotov, V., Krasniakova, M., Shevchuk, D., Andrianov, Y., Zabenko, Y., Safronov, B.V., Voitenko, N., Belan, P., 2019. Distinct mechanisms of signal processing by lamina I spino-parabrachial neurons. Sci. Rep. 9, 19231.

Altman, J., Bayer, S.A., 1984. The development of the rat spinal cord. Adv. Anat. Embryol. Cell Biol. 85, 1–164.

Andrew, D., 2010. Quantitative characterization of low-threshold mechanoreceptor inputs to lamina I spinoparabrachial neurons in the rat. J. Physiol. 588, 117–124.

Andrew, D., Craig, A.D., 2001. Spinothalamic lamina I neurones selectively responsive to cutaneous warming in cats. J. Physiol. 537, 489–495.

Barcroft, H., Edholm, O.G., 1943. The effect of temperature on blood flow and deep temperature in the human forearm. J. Physiol. 102, 5–20.

Barwood, M., Corbett, J., Green, R., Smith, T., Tomlin, P., Weir-Blankenstein, L., Tipton, M., 2013. Acute anxiety increases the magnitude of the cold shock response before and after habituation. Eur. J. Appl. Physiol. 113, 681–689.

Barwood, M.J., 2018. Predicting the magnitude and duration of the life-threatening cold shock response on accidental immersion: Estimating the risk of drowning. Int. J. Aquat. Res. Educ. 11, 1–2.

Barwood, M.J., Bates, V., Long, G., Tipton, M.J., 2011. "Float first": Trapped air between clothing layers significantly improves Buoyancy after immersion. Int. J. Aquat. Res. Educ. 5, 147–163.

Barwood, M.J., Burrows, H., Cessford, J., Goodall, S., 2016. 'Float first and kick for your life': psychophysiological basis for safety behaviour on accidental short-term cold water immersion. Physiol. Behav. 154, 83–89.

Barwood, M.J., Corbett, J., Massey, H., McMorris, T., Tipton, M., Wagstaff, C.R.D., 2018. Acute anxiety predicts components of the cold shock response on cold water immersion: toward an integrated psychophysiological model of acute cold water survival. Front. Psychol. 9.

Barwood, M.J., Corbett, J., Tipton, M., Wagstaff, C., Massey, H., 2017. Habituation of the cold shock response is inhibited by repeated anxiety: implications for safety behaviour on accidental cold water immersions. Physiol. Behav. 174, 10–17.

Barwood, M.J., Corbett, J., Wagstaff, C.R., 2014. Habituation of the cold shock response may include a significant perceptual component. Aviat Space Environ. Med. 85, 167–171.
Barwood, M.J., Dalzell, J., Datta, A.K., Thelwell, R.C., Tipton, M.J., 2006. Breath-hold performance during cold water immersion: effects of psychological skills training. Aviat Space Environ. Med. 77, 1136–1142.
Barwood, M.J., Datta, A.K., Thelwell, R.C., Tipton, M.J., 2007. Breath-hold time during cold water immersion: effects of habituation with psychological training. Aviat Space Environ. Med. 78, 1029–1034.
Benini, R., Oliveira, L.A., Gomes-de-Souza, L., Crestani, C.C., 2019. Habituation of the cardiovascular responses to restraint stress in male rats: influence of length, frequency and number of aversive sessions. Stress 22, 151–161.
Benini, R., Oliveira, L.A., Gomes-de-Souza, L., Rodrigues, B., Crestani, C.C., 2020. Habituation of the cardiovascular response to restraint stress is inhibited by exposure to other stressor stimuli and exercise training. J. Exp. Biol. 223.
Bharate, S.S., Bharate, S.B., 2012. Modulation of thermoreceptor TRPM8 by cooling compounds. ACS Chem. Neurosci. 3, 248–267.
Bowes, H., Eglin, C.M., Tipton, M.J., Barwood, M.J., 2016. Swim performance and thermoregulatory effects of wearing clothing in a simulated cold-water survival situation. Eur. J. Appl. Physiol. 116, 759–767.
Brazaitis, M., Eimantas, N., Daniuseviciute, L., Baranauskiene, N., Skrodeniene, E., Skurvydas, A., 2014. Time course of physiological and psychological responses in humans during a 20-day severe-cold-acclimation programme. PLoS One 9, e94698.
Brooks, C.J., Howard, K.A., Neifer, S.K., 2005. How much did cold shock and swimming failure contribute to drowning deaths in the fishing industry in British Columbia 1976-2002? Occup. Med. (Lond.) 55, 459–462.
Buoite Stella, A., Morrison, S.A., 2022. Marine survival in the mediterranean: a pilot study on the cognitive and cardiorespiratory response to sudden cool water immersion. Int. J. Environ. Res. Publ. Health 19.
Burke, W.E., Mekjavić, I.B., 1991. Estimation of regional cutaneous cold sensitivity by analysis of the gasping response. J. Appl. Physiol. 71, 1933–1940, 1985.
Carnaghi, M.M., Starobin, J.M., 2019. Reaction-diffusion memory unit: modeling of sensitization, habituation and dishabituation in the brain. PLoS One 14, e0225169.
Castellani, J.W., Young, A.J., 2016. Human physiological responses to cold exposure: acute responses and acclimatization to prolonged exposure. Auton. Neurosci. 196, 63–74.
Chaloner, F.A., Cooke, S.F., 2022. Multiple mechanistically distinct timescales of neocortical plasticity occur during habituation. Front. Cell. Neurosci. 16, 840057.
Christensen, B.N., Perl, E.R., 1970. Spinal neurons specifically excited by noxious or thermal stimuli: marginal zone of the dorsal horn. J. Neurophysiol. 33, 293–307.
Christoffersen, G.R., 1997. Habituation: events in the history of its characterization and linkage to synaptic depression. A new proposed kinetic criterion for its identification. Prog. Neurobiol. 53, 45–66.
Cohen, J., 1992. A power primer. Psychol. Bull. 112, 155–159.
Cooke, S., Ramaswami, M., 2020. Ignoring the innocuous: the neural mechanisms of habituation. In: Poeppel, D., Mangun, G., Gazzaniga, M. (Eds.), The Cognitive Neurosciences. MIT Press, Cambridge, Massachusetts, USA, p. 197.
Cooper, K.E., Martin, S., Riben, P., 1976. Respiratory and other responses in subjects immersed in cold water. J. Appl. Physiol. 40, 903–910.
Craig, A.D., 2003. Interoception: the sense of the physiological condition of the body. Curr. Opin. Neurobiol. 13, 500–505.
Craig, A.D., 2004. Distribution of trigeminothalamic and spinothalamic lamina I terminations in the macaque monkey. J. Comp. Neurol. 477, 119–148.
Craig, A.D., 2018. Central neural substrates involved in temperature discrimination, thermal pain, thermal comfort, and thermoregulatory behavior. Handb. Clin. Neurol. 156, 317–338.
Craig, A.D., Dostrovsky, J.O., 2001. Differential projections of thermoreceptive and nociceptive lamina I trigeminothalamic and spinothalamic neurons in the cat. J. Neurophysiol. 86, 856–870.
Craig, A.D., Krout, K., Andrew, D., 2001. Quantitative response characteristics of thermoreceptive and nociceptive lamina I spinothalamic neurons in the cat. J. Neurophysiol. 86, 1459–1480.
Datta, A., Tipton, M., 2006. Respiratory responses to cold water immersion: neural pathways, interactions, and clinical consequences awake and asleep. J. Appl. Physiol. 100, 2057–2064.
Deeks, J.J., Higgins, J.P., Altman, D.G., 2019. Analysing data and undertaking meta-analyses. Cochrane Handbook for Systematic Reviews of Interventions 241–284.
Downs, S.H., Black, N., 1998. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J. Epidemiol. Community Health 52, 377–384.
Dunham, J.P., Leith, J.L., Lumb, B.M., Donaldson, L.F., 2010. Transient receptor potential channel A1 and noxious cold responses in rat cutaneous nociceptors. Neuroscience 165, 1412–1419.
Duval, S., 2005. The Trim and Fill Method, Publication Bias in Meta-Analysis, pp. 127–144.
Egan, G.F., Johnson, J., Farrell, M., McAllen, R., Zamarripa, F., McKinley, M.J., Lancaster, J., Denton, D., Fox, P.T., 2005. Cortical, thalamic, and hypothalamic responses to cooling and warming the skin in awake humans: a positron-emission tomography study. Proc. Natl. Acad. Sci. U. S. A. 102, 5262–5267.
Eglin, C.M., Tipton, M.J., 2005. Repeated cold showers as a method of habituating humans to the initial responses to cold water immersion. Eur. J. Appl. Physiol. 93, 624–629.
Fechir, M., Klega, A., Buchholz, H.G., Pfeifer, N., Balon, S., Schlereth, T., Geber, C., Breimhorst, M., Maihöfner, C., Birklein, F., Schreckenberger, M., 2010. Cortical control of thermoregulatory sympathetic activation. Eur. J. Neurosci. 31, 2101–2111.
Felix-Ortiz, A.C., Burgos-Robles, A., Bhagat, N.D., Leppla, C.A., Tye, K.M., 2016. Bidirectional modulation of anxiety-related and social behaviors by amygdala projections to the medial prefrontal cortex. Neuroscience 321, 197–209.
Folkow, B., Neil, E., 1971. Circulation. Oxford University Press, Oxford.
Foster, G.E., Sheel, A.W., 2005. The human diving response, its function, and its control. Scand. J. Med. Sci. Sports 15, 3–12.
Freund, P.R., Brengelmann, G.L., Rowell, L.B., Halar, E., 1984. Attenuated skin blood flow response to hyperthermia in paraplegic men. J. Appl. Physiol. Respir. Environ. Exerc. Physiol. 56, 1104–1109.
Furukawa, T.A., Barbui, C., Cipriani, A., Brambilla, P., Watanabe, N., 2006. Imputing missing standard deviations in meta-analyses can provide accurate results. J. Clin. Epidemiol. 59, 7–10.
Glaser, E.M., Griffin, J.P., 1962. Influence of the cerebral cortex on habituation. J. Physiol. 160, 429–445.
Glaser, E.M., Hall, M.S., Whittow, G.C., 1959. Habituation to heating and cooling of the same hand. J. Physiol. 146, 152–164.
Golden, F., Hardcastle, P.T., Pollard, C.E., Tipton, M.J., 1986. Hyperventilation and swim failure in man in cold water. J. Physiol. 378, 94.
Golden, F., Tipton, M., 1988. Human adaptation to repeated cold immersions. J. Physiol. 396, 349–363.
Golden, F.S., Tipton, M.J., Scott, R.C., 1997. Immersion, near-drowning and drowning. Br. J. Anaesth. 79, 214–225.
Golden, F.S.C., Hervey, G.R., 1981. The 'after-drop' and death after rescue from immersion in cold water. In: Adam, J.A. (Ed.), Hypothjermia Ashore and Afloat. Aberdeen University Press, Aberdeen, pp. 37–56.
Goode, R.C., Duffin, J., Miller, R., Romet, T.T., Chant, W., Ackles, K., 1975. Sudden cold water immersion. Respir. Physiol. 23, 301–310.
Gordon, K., Blondin, D.P., Friesen, B.J., Tingelstad, H.C., Kenny, G.P., Haman, F., 2019. Seven days of cold acclimation substantially reduces shivering intensity and increases nonshivering thermogenesis in adult humans. J. Appl. Physiol. 126, 1598–1606, 1985.
Griffin, J.P., 1963. The role of the frontal areas of the cortex upon habituation in man. Clin. Sci. 24, 127–134.
Haddaway, N.R., Grainger, M.J., Gray, C.T., 2022. Citationchaser: a tool for transparent and efficient forward and backward citation chasing in systematic searching. Res. Synth. Methods 13, 533–545.
Hayward, J.S., Eckerson, J.D., 1984. Physiological responses and survival time prediction for humans in ice-water. Aviat Space Environ. Med. 55, 206–211.
Hayward, J.S., French, C.D., 1989. Hyperventilation response to cold water immersion: reduction by staged entry. Aviat Space Environ. Med. 60, 1163–1165.
Hensel, H., Schafer, K., 1984. Thermoreception and temperature regulation in man. In: Ring, E.F.J., Phillips, B. (Eds.), Recent Advances in Medical Thermology. Springer New York, Boston, MA, pp. 51–64.
Hensel, H., Schäfer, K., 1982. Static an dynamic activity of cold receptors in cats after long-term exposure to various temperatures. Pflügers Archiv 392, 291–294.
Hensel, H., Strom, L., Zotterman, Y., 1951. Electrophysiological measurements of depth of thermoreceptors. J. Neurophysiol. 14, 423–429.
Hinckel, P., Schröder-Rosenstock, K., 1981. Responses of pontine units to skin-temperature changes in the Guinea-pig. J. Physiol. 314, 189–194.
Hull, E.M., Young, S.H., Ziegler, M.G., 1984. Aerobic fitness affects cardiovascular and catecholamine responses to stressors. Psychophysiology 21, 353–360.
Ivanov, K., Konstantinov, V., Danilova, N., 1982. Thermoreceptor localization in the deep and surface skin layers. J. Therm. Biol. 7, 75–78.
Jansky, L., Janakova, H., Ulicny, B., Sramek, P., Hosek, V., Heller, J., Parizkova, J., 1996. Changes in thermal homeostasis in humans due to repeated cold water immersions. Pflügers Archiv 432, 368–372.
Jones, D.M., Bailey, S.P., De Pauw, K., Folger, S., Roelands, B., Buono, M.J., Meeusen, R., 2019. Evaluation of cognitive performance and neurophysiological function during repeated immersion in cold water. Brain Res. 1718, 1–9.
Jones, D.M., Bailey, S.P., Roelands, B., Buono, M.J., Meeusen, R., 2017. Cold acclimation and cognitive performance: a review. Auton. Neurosci. 208, 36–42.
Kanosue, K., Sadato, N., Okada, T., Yoda, T., Nakai, S., Yoshida, K., Hosono, T., Nagashima, K., Yagishita, T., Inoue, O., Kobayashi, K., Yonekura, Y., 2002. Brain activation during whole body cooling in humans studied with functional magnetic resonance imaging. Neurosci. Lett. 329, 157–160.
Keatinge, W.R., Evans, M., 1961. The respiratory and cardiovascular response to immersion in cold and warm water. Q. J. Exp. Physiol. Cogn. Med. Sci. 46, 83–94.
Keatinge, W.R., McIlroy, M.B., Goldfien, A., 1964. Cardiovascular responses to ice cold showers. J. Appl. Physiol. 19, 1145–1150.
Keatinge, W.R., Nadel, J.A., 1965. Immediate respiratory response to sudden cooling of the skin. J. Appl. Physiol. 20, 65–69.
Kelly, K.J., Donner, N.C., Hale, M.W., Lowry, C.A., 2011. Swim stress activates serotonergic and nonserotonergic neurons in specific subdivisions of the rat dorsal raphe nucleus in a temperature-dependent manner. Neuroscience 197, 251–268.
Klingner, C.M., Hasler, C., Brodoehl, S., Witte, O.W., 2014. Excitatory and inhibitory mechanisms underlying somatosensory habituation. Hum. Brain Mapp. 35, 152–160.
Klosterhalfen, W., Klosterhalfen, S., 1985. Habituation of heart rate in functionally decorticate rats. Behav. Neurosci. 99, 555–563.
Kozyreva, T.V., 2007. Central and peripheral thermoreceptors. Comparative analysis of the effects of prolonged adaptation to cold and noradrenaline. Neurosci. Behav. Physiol. 37, 191–198.
Kringelbach, M.L., 2005. The human orbitofrontal cortex: linking reward to hedonic experience. Nat. Rev. Neurosci. 6, 691–702.
Krout, K.E., Jansen, A.S., Loewy, A.D., 1998. Periaqueductal gray matter projection to the parabrachial nucleus in rat. J. Comp. Neurol. 401, 437–454.

Leach, J., 2005. Cognitive paralysis in an emergency: the role of the supervisory attentional system. Aviat Space Environ. Med. 76, 134–136.
LeBlanc, J., Roberge, C., Vallière, J., Oakson, G., 1971. The sympathetic nervous system in short-term adaptation to cold. Can. J. Physiol. Pharmacol. 49, 96–101.
Levine, D.N., 2007. Sherrington's "The Integrative action of the nervous system": a centennial appraisal. J. Neurol. Sci. 253, 1–6.
Lunt, H.C., Barwood, M.J., Corbett, J., Tipton, M.J., 2010. 'Cross-adaptation': habituation to short repeated cold-water immersions affects the response to acute hypoxia in humans. J. Physiol. 588, 3605–3613.
Macey, P.M., Macey, K.E., Woo, M.A., Keens, T.G., Harper, R.M., 2005. Aberrant neural responses to cold pressor challenges in congenital central hypoventilation syndrome. Pediatr. Res. 57, 500–509.
Mahony, A., Barnslet, P., Peden, A.E., Scarr, J., 2017. In: Society, R.L.S. (Ed.), A 13 Year Study of Non-fatal Drowning in Australia: Data Challenges, Hidden Impacts and Social Costs. Australia, Sydney, pp. 1–42.
Marieb, E.N., 2004. The respiratory system. In: Marieb, E.N. (Ed.), Human Anatomy and Physiology, sixth ed. Pearson Education Inc San Francisco, CA 94111, pp. 828–874.
McKemy, D.D., Neuhausser, W.M., Julius, D., 2002. Identification of a cold receptor reveals a general role for TRP channels in thermosensation. Nature 416, 52–58.
Meddings, D.R., Scarr, J.P., Larson, K., Vaughan, J., Krug, E.G., 2021. Drowning prevention: turning the tide on a leading killer. Lancet Public Health 6, e692–e695.
Mekjavić, I.B., La Prairie, A., Burke, W., Lindborg, B., 1987. Respiratory drive during sudden cold water immersion. Respir. Physiol. 70, 121–130.
Mokha, S.S., Goldsmith, G.E., Hellon, R.F., Puri, R., 1987. Hypothalamic control of nocireceptive and other neurons in the marginal layer of the dorsal horn of the medulla (trigeminal nucleus caudalis) in the rat. Exp. Brain Res. 65, 427–436.
O'Connor, S.R., Tully, M.A., Ryan, B., Bradley, J.M., Baxter, G.D., McDonough, S.M., 2015. Failure of a numerical quality assessment scale to identify potential risk of bias in a systematic review: a comparison study. BMC Res. Notes 8, 224.
Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., Shamseer, L., Tetzlaff, J.M., Akl, E.A., Brennan, S.E., Chou, R., Glanville, J., Grimshaw, J.M., Hróbjartsson, A., Lalu, M.M., Li, T., Loder, E.W., Mayo-Wilson, E., McDonald, S., McGuinness, L.A., Stewart, L.A., Thomas, J., Tricco, A.C., Welch, V.A., Whiting, P., Moher, D., 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 372, n71.
Peckham, G.W., Peckham, E.G., 1887. Some observations on the mental powers of spiders. J. Morphol. 1, 383–419.
Polanin, J.R., Snilstveit, B., 2016. Converting between effect sizes. Campbell Systematic Reviews 12, 1–13.
Poon, C.S., 2009. Optimal interaction of respiratory and thermal regulation at rest and during exercise: role of a serotonin-gated spinoparabrachial thermoafferent pathway. Respir. Physiol. Neurobiol. 169, 234–242.
Ramaswami, M., 2014. Network plasticity in adaptive filtering and behavioral habituation. Neuron 82, 1216–1229.
Rankin, C.H., Abrams, T., Barry, R.J., Bhatnagar, S., Clayton, D.F., Colombo, J., Coppola, G., Geyer, M.A., Glanzman, D.L., Marsland, S., McSweeney, F.K., Wilson, D. A., Wu, C.F., Thompson, R.F., 2009. Habituation revisited: an updated and revised description of the behavioral characteristics of habituation. Neurobiol. Learn. Mem. 92, 135–138.
RCoreTeam, 2020. R: A Language and Environment for Statistical Computing, 4.0.3 ed. R Foundation for Statistical Computing, Vienna, Austria.
Richmond, S.A., Fukuchi, R.K., Ezzat, A., Schneider, K., Schneider, G., Emery, C.A., 2013. Are joint injury, sport activity, physical activity, obesity, or occupational activities predictors for osteoarthritis? A systematic review. J. Orthop. Sports Phys. Ther. 43, 515–b519.
Riva, J.J., Malik, K.M., Burnie, S.J., Endicott, A.R., Busse, J.W., 2012. What is your research question? An introduction to the PICOT format for clinicians. J. Can. Chiropr. Assoc. 56, 167–171.
RNLI, 2022. Running costs - it cost £139.2M (€157.3M). In: 2020 to Run Our Lifesaving Service – All Funded by Our Generous Supporters. Royal National Lifeboat Institution rnli.org.
Rohatgi, A., 2021. WebPlotDigitizer, 4.5 ed. Pacifica, California, USA.
Shattock, M.J., Tipton, M.J., 2012. 'Autonomic conflict': a different way to die during cold water immersion? J. Physiol. 590, 3219–3230.
Sherrington, C.S., 1907. The integrative action of the nervous system. Nature 76, 122, 122.
Simons-Weidenmaier, N.S., Weber, M., Plappert, C.F., Pilz, P.K.D., Schmid, S., 2006. Synaptic depression and short-term habituation are located in the sensory part of the mammalian startle pathway. BMC Neurosci. 7, 38.
Sokolov, E.N., 1963. Higher nervous functions; the orienting reflex. Annu. Rev. Physiol. 25, 545–580.
Stocks, J.M., Patterson, M.J., Hyde, D.E., Mittleman, K.D., Taylor, N.A., 2001. Metabolic habituation following repeated resting cold-water immersion is not apparent during low-intensity cold-water exercise. J. Physiol. Anthropol. Appl. Hum. Sci. 20, 263–267.
Story, G.M., Peier, A.M., Reeve, A.J., Eid, S.R., Mosbacher, J., Hricik, T.R., Earley, T.J., Hergarden, A.C., Andersson, D.A., Hwang, S.W., McIntyre, P., Jegla, T., Bevan, S., Patapoutian, A., 2003. ANKTM1, a TRP-like channel expressed in nociceptive neurons, is activated by cold temperatures. Cell 112, 819–829.
Thompson, R.F., 2009. Habituation: a history. Neurobiol. Learn. Mem. 92, 127–134.
Thompson, R.F., Spencer, W.A., 1966. Habituation: a model phenomenon for the study of neuronal substrates of behavior. Psychol. Rev. 73, 16–43.
Tipton, M., Eglin, C., Gennser, M., Golden, F., 1999. Immersion deaths and deterioration in swimming performance in cold water. Lancet (London, England) 354, 626–629.
Tipton, M.J., 1989. The initial responses to cold-water immersion in man. Clin. Sci. (Lond.) 77, 581–588.
Tipton, M.J., 1992. The relationship between maximum breath hold time in air and the ventilatory responses to immersion in cold water. Eur. J. Appl. Physiol. Occup. Physiol. 64, 426–429.
Tipton, M.J., 2014. Sudden cardiac death during open water swimming. Br. J. Sports Med. 48, 1134–1135.
Tipton, M.J., Collier, N., Massey, H., Corbett, J., Harper, M., 2017a. Cold water immersion: kill or cure? Exp. Physiol. 102, 1335–1355.
Tipton, M.J., Eglin, C.M., Golden, F.C., 1998a. Habituation of the initial responses to cold water immersion in humans: a central or peripheral mechanism? J. Physiol. 512, 621–628.
Tipton, M.J., Golden, F.S., Higenbottam, C., Mekjavic, I.B., Eglin, C.M., 1998b. Temperature dependence of habituation of the initial responses to cold-water immersion. Eur. J. Appl. Physiol. Occup. Physiol. 78, 253–257.
Tipton, M.J., Harper, A., Paton, J.F.R., Costello, J.T., 2017b. The human ventilatory response to stress: rate or depth? J. Physiol. 595, 5729–5752.
Tipton, M.J., Mekjavic, I.B., Eglin, C.M., 2000. Permanence of the habituation of the initial responses to cold-water immersion in humans. Eur. J. Appl. Physiol. 83, 17–21.
Tipton, M.J., Stubbs, D.A., Elliott, D.H., 1991. Human initial responses to immersion in cold water at three temperatures and after hyperventilation. J. Appl. Physiol. 70, 317–322, 1985.
Tipton, M.J., Vincent, M.J., 1989. Protection provided against the initial responses to cold immersion by a partial coverage wet suit. Aviat Space Environ. Med. 60, 769–773.
Tipton, M.J., Wakabayashi, H., Barwood, M.J., Eglin, C.M., Mekjavic, I.B., Taylor, N.A., 2013. Habituation of the metabolic and ventilatory responses to cold-water immersion in humans. J. Therm. Biol. 38, 24–31.
Todd, A.J., Spike, R.C., Young, S., Puskár, Z., 2005. Fos induction in lamina I projection neurons in response to noxious thermal stimuli. Neuroscience 131, 209–217.
Tominaga, M., Caterina, M.J., 2004. Thermosensation and pain. J. Neurobiol. 61, 3–12.
Viechtbauer, W., 2010. Conducting meta-analyses in R with the metafor package. J. Stat. Software 36, 1–48.
Wakabayashi, H., Wijayanto, T., Kuroki, H., Lee, J.-Y., Tochihara, Y., 2012. The effect of repeated mild cold water immersions on the adaptation of the vasomotor responses. Int. J. Biometeorol. 56, 631–637.
Waldman, S.D., 2009. In: Waldman, S.D. (Ed.), Functional Anatomy of the Thermoreceptors, Pain Review. W.B. Saunders, Philadelphia, p. 190.
WHO, 2014. Global report on drowning: preventing a leading killer. In: Organization, W. H. (Ed.), Social Determinants of Health. Switzerland, p. 59.
WHO, 2017. Preventing Drowning: an Implementation Guide, Geneva, Switzerland.
WHO, 2020. Global Health Estimates 2019: Disease Burden by Cause, Age, Sex, Country, and Region, pp. 2000–2019.
Yang, F., Chen, G., Zhou, S., Han, D., Xu, J., Xu, S., 2017. Mapping sensory spots for moderate temperatures on the back of hand. Sensors 17.
Yurkevicius, B.R., Alba, B.K., Seeley, A.D., Castellani, J.W., 2022. Human cold habituation: physiology, timeline, and modifiers. Temperature (Austin) 9, 122–157.