Original Experimental

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Robustness of the cold pressor test: Study across geographic locations on pain perception and tolerance

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Abstract

Objectives – The cold pressor test, in which subjects immerse part of an extremity in cold water for a specified amount of time, evokes both pain and unpleasantness. As it is low cost and readily available, it is widely used in pain research. However, data on the impact of race, area of exposure, and the effects of instructions are lacking.

Methods – Cold pressure test data were recorded in a mixed Asian and European healthy population. Trial 1 was a randomised crossover trial varying the extent of hand submersion (two fingers, four fingers, and whole hand) (n = 54). Trial 2 was a randomised cross-sectional design, investigating instructed and non-instructed pain expectations, n = 40.

Results – European subjects tolerated the cold pressor test longer than Asian subjects (116 ± 14 versus 93 ± 36 s, p < 0.001), and fewer subjects withdrew their hand in less than two minutes (9% vs 43%, p = 0.007). Stimulation area influenced pain tolerance, with more subjects able to maintain two-finger immersion in cold water for 2 min compared to whole-hand immersion (p < 0.001). The instruction or no instruction did not affect the numeric rating scale when comparing instruction levels (p = 0.88). Additionally, pain tolerance was not affected either (p = 1).

Conclusion – The cold pressor test is a robust tool across genders, race, and instruction levels. Significant differences were found in pain perception and tolerance across different locations and stimulation intensities. However, instructions in expected pain did not affect the outcomes, reflecting the robustness of the test.

Keywords: pain perception, pain tolerance, cold pain, gender, cross-cultural comparison

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1 Introduction

Pain has always been a challenging aspect to investigate in clinical settings due to the subjective nature of its perception [1,2], influenced by several aspects such as culture, social environment, genetics, gender, and emotional status [3–6]. Patients suffering from pain, though having the same diagnosis, can perceive its intensity and unpleasantness very differently [3,5,7,8]. This difference in response can be difficult to measure in clinical practice. Quantitative sensory testing is a method where specific pathways in the nociceptive system can be activated by various types of stimuli, with subsequent quantification of the patient's response [9–14]. Among these various standardised stimulations, thermal stimulation (heat or cold) is a frequently used method [13,15–26]. Immersion of the hand in cold water, known as the cold pressor test, was initially developed as a trigger for cardiovascular response [27–32]. This test is now being used in clinical pain studies. Cold stimulation activates peripheral nociceptors and central pain systems and produces both acute and tonic noxious pain responses [33]. While pain is modulated by both endogenous inhibitory and facilitatory mechanisms, making it a very complex phenomenon [34], the cold pressor test is believed to be the best-known model to mimic clinical pain [35].

The cold pressor test is considered a safe, simple-to-administer test [1,27,36,37], which produces a high-intensity pain stimulus [1,38,39]. The hand is the most utilised limb for immersion [40]. During the test, pain is described as dull and aching [33,41], with a maximum intensity at 60–90 section [1,42]. The method seems reliable across the upper limit of tolerance [25], with changes as small as 2°C being significant in tolerance outcomes [25].

Although the cold pressor test is well-studied, there are still areas where there is a knowledge gap. To our knowledge, there is little investigation on the effects of the cold pressor test across areas of exposure, gender, and race. The effect of the size of the stimulation area has been investigated in the past and was found to elicit larger heart rate response, systolic arterial blood pressure, and muscle sympathetic nerve activity, but the pain experience was not investigated [43]. Westcott et al. investigated the effects of area of exposure, and gender. While they found that both a larger area of submersion, and being female resulted in a shorter endurance times they did not record pain sensation [44]. Many studies have chosen not to include women due to the gender effects on pain [45–47]. Zheng et al., however, did not find any differences in the proportion of people who were pain-sensitive or pain-insensitive between genders [48]. Previous reviews of the cold pressor test have chosen not to include ethnicity or race due to a lack of available data [6]. Ethnicity has started to be included in newer studies with mixed outcomes [49,50]. When conducting studies across different geographic locations, it is important to consider how language and cultural context may influence the delivery and interpretation of instructions. To address this, we will include a subgroup that will receive no instructions related to expected pain and compare it to a group that was instructed on what pain to expect, allowing us to assess the potential impact of instructional framing within the same cultural and linguistic context.

We hypothesise that the cold pressor test is a robust tool for evaluating pain, which can be used among different populations across genders and geographic locations. The aims of this study were to explore whether the cold pressor test is influenced by (a) race and gender, (b) area of exposure, and (c) effects of instructions.

2 Materials and methods

2.1 Study overview

Two sets of data were collected for this study. Trial 1 focused on the effects of the size of exposure (amount of hand submersion) on perceived pain across Europe and Asia, and trial 2 focused on instruction or on-instruction on perceived pain and how that affected the experience of pain and the ability to hold the hand in cold water. All trial sites obtained local ethical committee approval, Ref. CElm: P12023-093 (Alicante, Spain) N-20230054 (Aalborg, Denmark), 17787-8/2020/EÜIG (Budapest, Hungary), IECPG-670/2255.1.11.2.2002200 (New Delhi, India), AIG/IEC-BH&R08/10.2020-01 (Hyderabad, India), and Riphah/RCRS/REC/1954 (Islamabad, Pakistan). Each subject's age, gender, race, and inclusion site were documented.

2.1.1 Study design

This study obtained regulatory approvals from local ethical committees/review boards. Subjects were recruited from professional networks.

2.1.2 The cold pressor test

For both trials, the cold-pressor test was used. Water was kept at 2°C in an insulated container large enough to submerge the whole hand. Subjects were instructed to keep their non-dominant hand in the water for as long as possible but no longer than 2 min. If the subjects were able to hold their hand for the duration of the experiment, they were noted for 120 s.

A stimulus–response curve was obtained during the cold pressor test to gauge the perceived pain. This was achieved by asking the subjects to rate the pain they experienced on a numeric rating scale (NRS) from 0 to

10, with 0 being no pain, 1 being the first sensation of pain, and 10 being the worst pain imaginable.

2.2 Assessment of pain response

For all recordings, the stimulus-response curves were analysed using the area under the curve (AUC). AUC was calculated for the individual NRS responses for each subject using a trapezoidal integration over time. If the subject withdrew their hand before 120 s, multivariate imputation was used to compare AUC levels over the same period of time. Pain tolerance was measured as the total time in seconds that subjects were able to hold their hand in cold water.

2.3 Size of exposure

To gauge the effect of the area submerged trial, one was designed as a randomised crossover trial, including healthy subjects from India (Hyderabad and Delhi), Pakistan (Islamabad), and Denmark (Aalborg). Subjects were instructed to sequentially submerge either their whole hand up to the wrist, two fingers (index and middle fingers), or four fingers (index, middle, ring, and little fingers) up to the metacarpophalangeal joint. The order of stimulations was randomised with a washout period of at least 24 h.

2.4 Instructions on pain expectation

Trial 2 was a randomised cross-sectional design with data collected in Spain (Alicante) and Hungary (Budapest). Subjects were randomised into either an instructed or non-instructed group. Among instructed subjects, the progression of experienced pain was shown as an averaged graph of experienced pain obtained from trial 1, emphasising how NRS flattens after the 60-s mark and intensity does not worsen. The intention was to try to mitigate the risk of removing the hand early in anticipation of high levels of pain. The control group was not given any instructions on what to expect but only instructed in the experimental procedure. All subjects were naive to the cold pressor test.

2.5 Statistical analysis

Multivariate imputation by chained equations version 3.17.0 was used to account for missing data in the fluctuation of pain (AUC). The data were imputed using: age, gender, geographical location, and stimulation as predictors, accounting for local variations in pain response. Normality for continuous variables was assessed using histograms and *Q*–*Q* plots. Categorical variables are reported as counts (%), continuous variables as means and standard deviations when the data were normally distributed, and medians with interquartile ranges when not normally distributed. The differences in perception of pain across geographic locations were calculated using an analysis of variance to compare perceived pain (AUC) and age across locations (Alicante, Aalborg, Budapest, Delhi, Hyderabad, and Islamabad) with Tukey honestly significant difference for *post hoc* analysis. To compare the perception of pain across stimulation, a linear mixed model with the factors of pain and size of exposure (two fingers, four fingers, and whole hand) was used with subject ID as a random intercept. Lastly, for the perception of pain and instruction level, a *T*-test was used to compare pain and instructions (instruction, no instruction) and global differences (Europe and Asia). Fisher's exact test for count data was used to investigate the distribution of gender across location and pain tolerance, comparing the binary outcome completion of hand immersion (yes/no) to differences between Europe and Asia, Stimulation intensities, and levels of instruction.

All analysis was considered significant at $p < 0.05$. All data were analysed using R version 4.2.2.

Table 1: Demographic variables across inclusion sites

	Aalborg (n = 15)	Alicante (n = 20)	Budapest (n = 20)	Delhi (n = 6)	Hyderabad (n = 18)	Islamabad (n = 15)
Sex, male, n (%)	7 (46.7)	10 (50)	9 (45)[a]	6 (100)	17 (94.4)[a]	7 (46.7)
Age, years (SD)	42 (11.5)	38 (13.8)	36 (13)	35 (9.7)	39 (10.6)	30 (7)

The gender distribution differed between sites ($p < 0.01$); the *post hoc* analysis showed a difference between Hyderabad and Budapest; $p < 0.05$. There were no differences in the age distribution between sites ($p > 0.05$).
The "a" denotes significant differences between Hyderabad and Budapest.

3 Results

3.1 Study population

A total of 94 subjects were included in the analysis. No subjects were excluded, and there were no dropouts. All subjects signed informed consent before inclusion in the study. Demographic variables are summarised in Table 1. Gender varied across the enrolment sites ($p < 0.01$), as subjects in Delhi and Hyderabad were mostly men compared to Aalborg, Alicante, and Budapest. Age did not differ across enrolment sites ($p = 0.1$).

3.1.1 Recruitment

Convenient sampling was employed to recruit participants for the study. This method was chosen due to practical considerations, including time constraints and ease of access to potential participants. The study was conducted from June to August 2022.

3.2 Pain across geographic locations using the assessment of pain response

For this analysis, all instructed subjects who had a whole hand recording were included, resulting in a new total population ($n = 74$). Subjects in Europe and Asia report similar stimulus-response curves, $p = 0.34$; see Figure 1a. However, across enrolment sites, pain was perceived differently, $p < 0.001$. The *post hoc* analysis revealed that Budapest had a lower reported AUC compared to Aalborg [43], Alicante [57], Delhi [37], Hyderabad [50], and Islamabad [29], all $p < 0.01$. In addition, Islamabad had a lower average AUC compared to Alicante [28] and Hyderabad [22], $p < 0.01$; see Figure 1b.

3.3 Pain tolerance across geographic locations and gender

Subjects in Europe kept their hand in the cold water for a longer duration compared to subjects from Asia (116 ± 14.2 versus 92.9 ± 35.9 s, $p < 0.001$); see Figure 1c. Among European

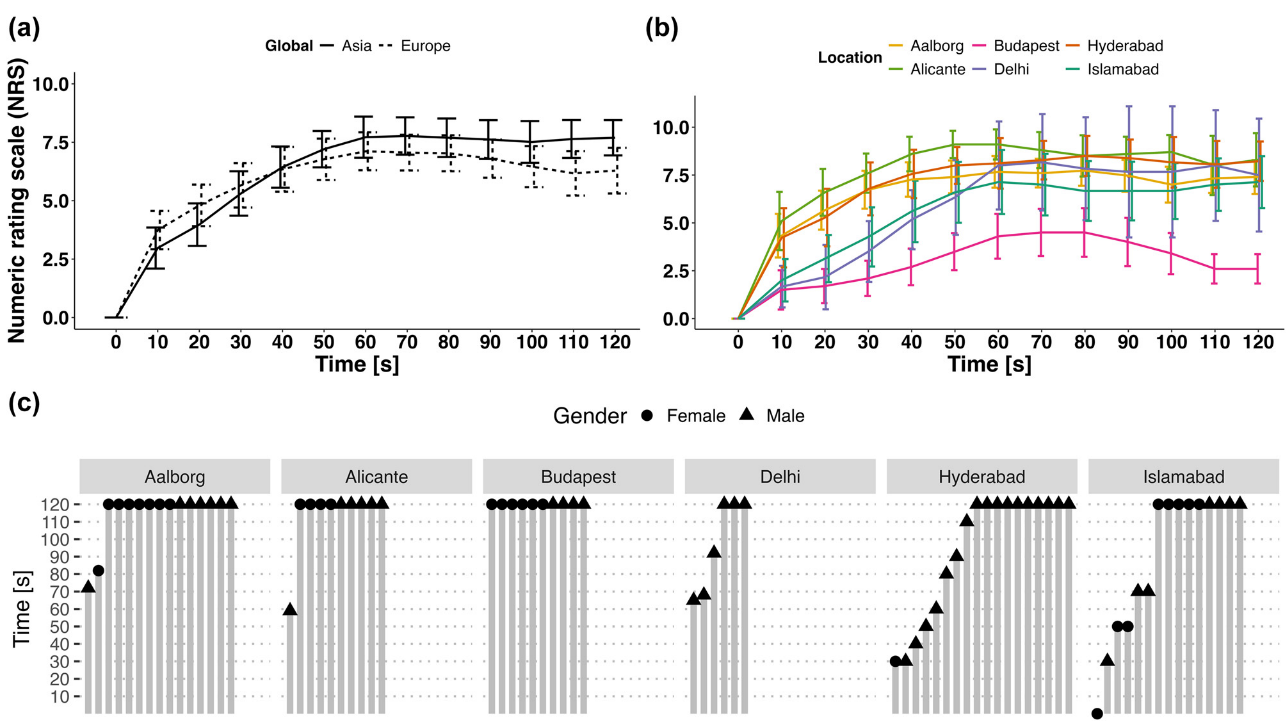

Figure 1: (a) Data on instructed subjects with their whole hand submerged. The pain response curve during the cold-pressor test in subjects from Europe and Asia showed no significant difference. (b) Pain response curves for individual sites. There was a significant difference between Budapest and Aalborg, Alicante, Delhi, Hyderabad, and Islamabad; additionally, Islamabad had a lower average AUC compared to Alicante and Hyderabad. In (c), a waterfall plot of individual pain tolerance on all subjects and their corresponding gender is shown. People from Asia withdrew their hands earlier than Europeans on average. Correcting for multiple comparison, there were no significant differences between enrolment sites. No differences were observed between genders.

subjects, 3 (8.6%) withdrew their hand in less than 2 min, in contrast to Asian subjects, where 17 (43.6%) withdrew sooner (p = 0.007); see Figure 1c. Across enrolment sites, the pain tolerance differed (p = 0.02). The *post hoc* analysis, correcting for multiple comparisons, revealed no significant differences between enrolment sites (all p above 0.4).

There was no difference in the duration of time males and females could keep their hands in water (103 ± 28 versus 105 ± 33 s, p = 0.28); see Figure 1c.

3.4 Influence of the size of exposure on the cold-pressor test response

The participants from Aalborg, Delhi, Hyderabad, and Islamabad were pooled for this analysis, giving a total of 54 subjects. When analysing the effect of spatial summation on cold-pressor test responses, using the AUC for the different stimulation areas, an overall difference was observed (p < 0.001). When comparing AUC obtained from whole-hand immersion, a reduction of 28% for two-finger immersion (p < 0.001) and 17% for four-finger immersion (p = 0.002; Figure 2a).

3.5 Pain tolerance for different stimulation areas

The pain tolerance was changed by the different stimulation areas (p < 0.001), the *post hoc* analysis revealed an increase in the number of subjects being able to maintain their hand for 2 min, comparing the whole hand and two-finger immersions (p < 0.001) and a non-significant change for two fingers (p = 0.07). The data are available in Figure 2b.

3.6 Instructions on pain expectation

The effect of instruction was analysed among the Alicante and Budapest populations, resulting in 40 subjects being analysed. The instruction or no-instruction did not affect NRS when comparing instruction levels (p = 0.88). Additionally, pain tolerance was not affected either (p = 1). The data are available in Figure 3.

4 Discussion

In this study, we determined the differences in pain perception when using the cold pressor test in a mixed-gender and European and Asian geographical location population. Comparing different geographical locations, changes in pain tolerance were found to be associated with a diminished ability of the Asian population to maintain hand immersion in cold water. The effect of spatial summation showed a significant reduction in pain tolerance when the

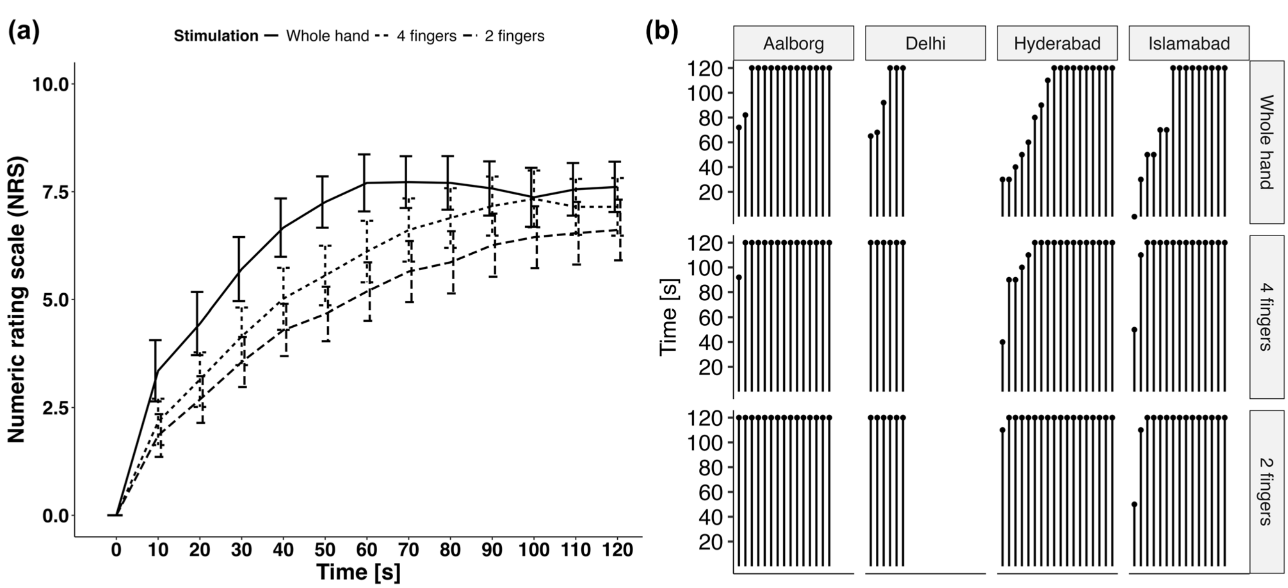

Figure 2: (a) Pain response curve reflecting pain tolerance for the three stimulation areas. Two and four fingers differed from the whole hand area. (b) The corresponding waterfall plot of individual pain tolerances for the whole hand, two fingers, and four fingers. More people were able to hold the hand for 2 min with two fingers compared to the whole hand and two fingers.

whole hand was immersed compared with four and two fingers. Instructions on the expected pain intensity and its plateau after 60 s did not influence pain intensity or tolerance.

4.1 The effect of geographic and environmental factors

Previous studies have determined the differences in pain perception when comparing healthy subjects of European and African American descent; European ancestry had greater cold pain tolerance in both male and female groups [51]. Gordon et al. [52] described the relation between race and pain by comparing the response to the cold pressor test in non-Hispanic white and African American subjects, among whom increased pain intensity was found.

In Asian populations, similar tendencies to our own were described. Ahn et al. [53] have found consistently higher pain ratings among Asian Americans between 45 and 85 years with knee osteoarthritis compared to the non-Hispanic-white population, not only in experimental settings but also in the perception of clinical pain. These findings were similar when comparing healthy non-Hispanic-white and Asian populations, both born in the United States and in Asia, where cold pain sensitivity in Asians was higher than in the non-Hispanic-white population, with no difference between those born in Asia or North America [54]. In contrast to our findings, the Indian population has previously been attributed to having higher pain tolerance to cold water stimulation when compared to patients from Western cultures, specifically from the United States [55]. This cultural discrepancy has been suggested to be attributed to a less emotional approach to pain response and catastrophising of Indian culture compared with their counterparts [55], but the cause of ethnic differences in pain perception still requires further investigation.

Environmental factors may also have a role in pain perception, as described when analysing data from the Tromsø Study (Tromsø 7), in which cold pain tolerance, defined as the time of hand withdrawal, was linked to seasonal and climate variations, determining a lower tolerance in warmer months [56]. However, this would not explain the difference found in pain perception between southern Europe and Asia.

4.2 The effect of spatial summation

The spatial summation of pain has been described before in accordance with our current findings. When comparing submersion of the index finger (to the proximal phalanges joint) to the whole hand in healthy subjects, it was found that submersion time decreased for the whole hand submersion [44]. In more recent studies, spatial summation and discrimination were determined when applying thermal stimulation, concluding that an increase in the

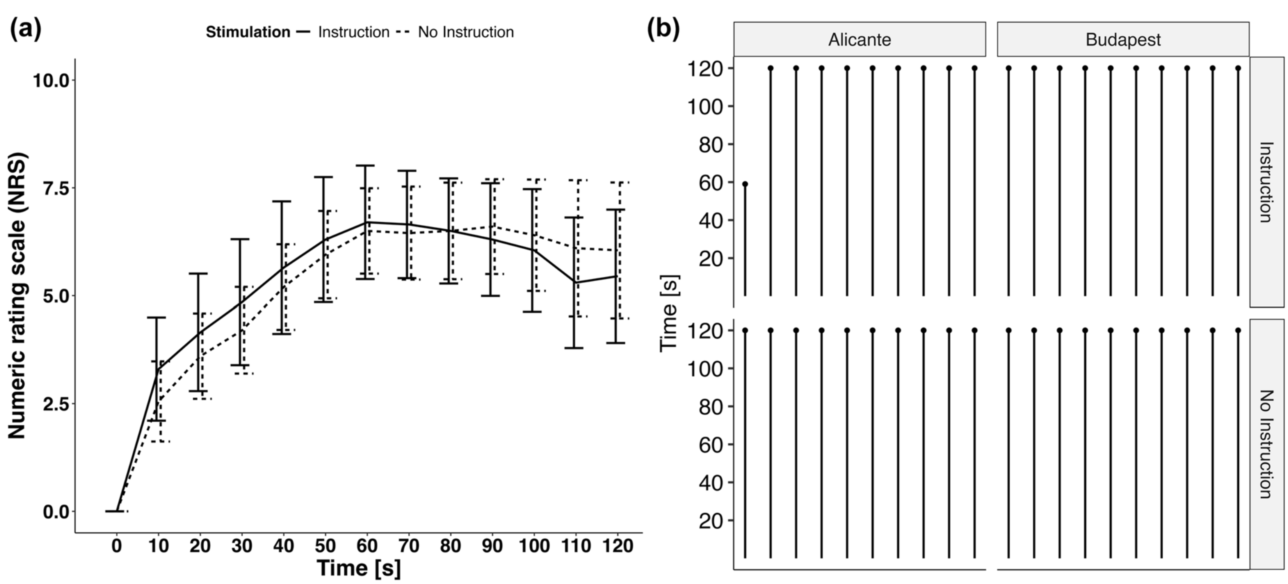

Figure 3: Pain response curves reflecting the instruction or no-instruction (a) and the corresponding waterfall plot of individual pain tolerance among spatial summation (b). No changes were observed between groups.

separation of probes of 5 cm of the stimulation area caused an increase in NRS scores of perceived pain [57,58].

4.3 The effect of instruction

Pain expectation and its correlation to perceived pain intensity have been found to have differing results. Contrary to our findings, it has previously been determined that instruction, attention to bodily sensation, or distracting factors do alter pain perception [59–62]. Among healthy subjects, Cormier et al. [63] concluded that prior expectation of high pain perception, as well as suggestion-induced expectation, can enhance or even block the analgesic effects of cold pain by applying ice packs after electrical stimuli. But when comparing self-defined high physical pain-fearing healthy women to those not fearing pain, it was found that instruction on sensation and pain expectation made subjects in the first group report greater distress after the cold pressor test than their non-instructed counterparts, with the opposite effect in the latter group [64]. While investigating instruction or no-instruction subjects, on average, did not reach pain values above 8 on the NRS, nor did they continue till pain intolerance, except for one participant in the instructed group. Thus, the subjects did not necessarily reach pain levels or durations that would make them withdraw their hands, either as naive or prepared subjects. This might be part of the reason why there was no difference in instruction or no instruction in our study.

4.4 Bias and limitations

This study includes participants from diverse backgrounds and races from different parts of the world, leading to a rich analysis of pain perception. The main limitation is in the inclusion of a small number of patients for each of the recording locations, leading to potential selection bias and type 2 errors. There is also an imbalance of gender across sites, mainly from the Indian sites. This was due to cultural considerations from their sites. The use of different types of water baths in this study was unavoidable since not all centres had the same equipment. Common for all centres was that before the hand was submerged, the temperature of the water was verified to be 2 ± 2°C, and all instructions for submerging the hand to predefined levels were identical. The cold water threshold (the first sensation of pain after immersion) was not conducted in this study. The cold water threshold is a common outcome of the cold pressor test, along with tolerance and intensity, which we recommend should be implemented in any future studies.

5 Conclusion

Cold pressor pain has proven to be a robust test across genders and levels of instruction. We recommend a whole-hand immersion in water set to 2°C.

Research ethics: This article complied with the Code of Ethics of the World Medical Association (Declaration of Helsinki). Research involving human subjects complied with all relevant national regulations and institutional policies, is in accordance with the tenets of the Helsinki Declaration (as amended in 2013), and has been approved by the author's Institutional Review Board or equivalent research ethical committee (ethical committee numbers: N-20230054, Ref. CElm: P12023-093, 17787-8/2020/EÜIG, IECPG-670/2255.1.11.2.2002200., AIG/IEC-BH&R08/10.2020-01, and Riphah/RCRS/REC/1954).

Informed consent: Before the subjects were included, they signed consent and descriptive data (Age, gender, race) were recorded prior to the cold pressor test. There are no identifications of personal information in this paper.

Author contributions: All authors have critically revised the manuscript and gave final approval for publication. The authors have agreed to be accountable for all aspects of the work.

Competing interests: Asbjørn Mohr Drewes is an editorial team member of Scandinavian Journal of Pain. The authors report no competing interests.

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Data availability: The raw data can be obtained on reasonable request from the corresponding.

***Artificial intelligence/Machine learning tools:** Not applicable.

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