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Pain tolerance after stroke: The Tromsø study

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Abstract

Background: Stroke lesions might alter pain processing and modulation by affecting the widely distributed network of brain regions involved. We aimed to compare pain tolerance in stroke survivors and stroke-free persons in the general population, with and without chronic pain.

Methods: We included all participants of the sixth and seventh wave of the population-based Tromsø Study who had been tested with the cold pressor test (hand in cold water bath, 3°C, maximum time 106 s in the sixth wave and 120 s in the seventh) and who had information on previous stroke status and covariates. Data on stroke status were obtained from the Tromsø Study Cardiovascular Disease Register and the Norwegian Stroke Register. Cox regression models were fitted using stroke prior to study attendance as the independent variable, cold pressor endurance time as time variable and hand withdrawal from cold water as event. Statistical adjustments were made for age, sex, diabetes, hypertension, hyperlipidaemia, body mass index and smoking.

Results: In total 21,837 participants were included, 311 of them with previous stroke. Stroke was associated with decreased cold pain tolerance time, with 28% increased hazard of hand withdrawal (hazard ratio [HR] 1.28, 95% CI 1.10–1.50). The effect was similar in participants with (HR 1.28, 95% CI 0.99–1.66) and without chronic pain (HR 1.29, 95% CI 1.04–1.59).

Conclusions: Stroke survivors, with and without chronic pain, had lower cold pressor pain tolerance, with possible clinical implications for pain in this group.

Significance: We found lower pain tolerance in participants with previous stroke compared to stroke-free participants of a large, population-based study. The association was present both in those with and without chronic pain. The results may warrant increased awareness by health professionals towards pain experienced by stroke patients in response to injuries, diseases and procedures.

1 | INTRODUCTION

Pain is among the most common complications in the early phase after stroke (Bovim et al., 2018; Indredavik et al., 2008; Langhorne et al., 2000), and later many report presence (Klit et al., 2011) or development (Bovim et al., 2018) of chronic pain. Pain after stroke includes, but is not limited to, specified post-stroke pain syndromes. It is also reported that stroke patients experience pain considered *not* to be stroke related (Bovim et al., 2018; Indredavik et al., 2008; Lundström et al., 2009; Naess et al., 2010), such as pain in the unaffected as well as the affected side (Jönsson et al., 2006; Naess et al., 2010). Several features of chronic post-stroke nociceptive or

neuropathic pain syndromes are overlapping, and shared pathophysiology has been suggested (Zeilig et al., 2013). As pain is processed in a widespread network in the brain (Coghill, 2020; Mercer Lindsay et al., 2021), affection to any part of the network might alter pain processing, with possible implications for the occurrence and severity of acute, procedural and chronic pain in stroke patients.

Experimental pain studies allow for assessment of responses to controlled nociceptive stimuli, including pain thresholds, direct pain ratings or pain tolerance, reflecting various aspects of the individual's pain sensitivity. Such studies of stroke survivors are generally small and have often focused on the pathophysiology of specific post-stroke pain syndromes (i.e. post-stroke shoulder pain [PSSP] and central post-stroke pain [CPSP]) or the consequences of specific stroke lesion locations. Stroke participants are often recruited from rehabilitation centres (Roosink et al., 2011; Zeilig et al., 2013) or pain centres (Tuveson et al., 2009), or inclusion criteria require specified deficits (Casey et al., 2012; Krause et al., 2016; Roosink et al., 2012), post-stroke chronic pain condition (Roosink et al., 2011; Soo Hoo et al., 2013; Tuveson et al., 2009) or stroke lesion location (Ruscheweyh et al., 2014). Studies on pain sensitivity in stroke survivors without chronic pain are scarce, but increased sensitivity is reported in 30 pain-free cerebellar stroke patients (Ruscheweyh et al., 2014) and in pain-free stroke control subjects ($n < 30$) in two studies (Krause et al., 2016; Roosink et al., 2011).

We aimed to compare pain tolerance assessed by the cold pressor test (CPT) in subjects with and without prior stroke, and with and without chronic pain, in the setting of a large population-based study.

2 | METHODS

2.1 | Study design and participants

We conducted an epidemiological study using data from the Tromsø study, which is a population-based multipurpose health study that has been carried out with intervals of 6–7 years since 1974 (Jacobsen et al., 2012). Participants are recruited through an invitation letter sent to whole birth cohorts and age-stratified random samples living in the municipality of Tromsø in Northern Norway. We used data from the sixth and seventh survey, carried out in 2007–2008 and 2015–2016 respectively. In Tromsø 6, 19,762 inhabitants above 30 years of age were invited and 65.7% participated (Eggen et al., 2013), while in Tromsø 7, all 32,591 inhabitants above 40 years of age were invited and 64.7% participated (Hopstock et al., 2022) (Figure 1). Participants completed questionnaires, provided blood samples and completed a range of clinical examinations, among them tests of experimental pain tolerance. Included in this study were 9935 participants of Tromsø 6 aged 40 years and above, and 11,902 participants of Tromsø 7 who had not been included in the Tromsø 6 sample, who had completed the experimental pain examination. Thus, two independent samples from Tromsø 6 and Tromsø 7 were analysed, and subsequent combined analysis was performed by pooling the two samples. Participants for whom information on stroke status and covariates were unavailable were excluded (Figure 1).

2.2 | Ascertainment of stroke status

The Tromsø Study Cardiovascular Disease Register contains validated information on incident strokes of all subtypes in participants until 31 December 2014 (31 December 2017 for subarachnoid haemorrhage). Information on ischaemic and haemorrhagic strokes occurring after 01 January 2015, was obtained from the Norwegian Stroke Register (Varmdal et al., 2021). In both registries, strokes are defined in accordance with the WHO definition, as rapidly developed clinical signs of focal or global disturbance of cerebral function, lasting more than 24 h or until death, with no apparent cause other than vascular (WHO MONICA Project Principal Investigators, 1988). Strokes are classified as ischaemic if diagnostic imaging reveal an acute ischaemic lesion or rules out haemorrhage. Haemorrhagic strokes and subarachnoid haemorrhages are classified according to findings on diagnostic imaging. If no imaging has been performed in the acute phase, the stroke is defined as unclassifiable. The registries do not include information on stroke location or laterality. As the purpose of The Tromsø Study Cardiovascular Disease Register was to provide information on end points for study of cardiovascular risk factors, only the first of each stroke type were registered. Data collection were done by expert review of medical records and hence very resource-intensive. The Norwegian Stroke Register was established in 2012 and includes information on ischaemic, haemorrhagic and unclassifiable strokes. After a validation study confirming sufficient quality (Varmdal et al., 2021), it was decided that data from The Norwegian Stroke Register was to be used for information on stroke status in the Tromsø Study from 01 January 2015.

We included participants in the stroke group if they were registered with ischaemic, haemorrhagic or unclassifiable stroke or subarachnoid haemorrhage that had occurred prior to participation. Transient ischaemic attacks were defined as ischaemic stroke when an acute ischaemic lesion was present on diagnostic imaging.

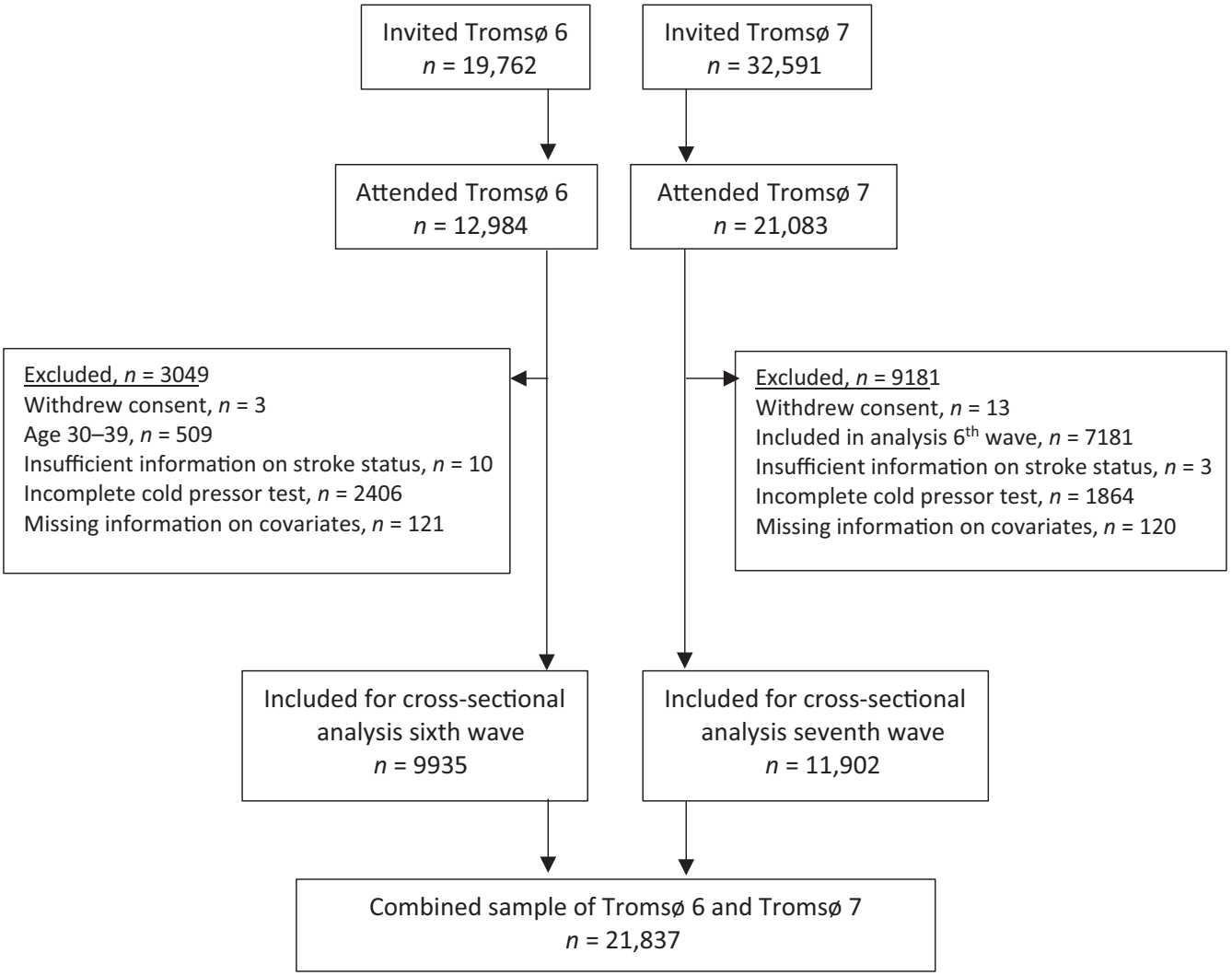

FIGURE 1 Flow chart of participants of Tromsø 6 and Tromsø 7 and this study. In Tromsø 6, 19,762 inhabitants above the age of 30 were invited, selected by random sampling, whole birth cohorts or due to participation in previous waves. Participants aged 30–39 were excluded from analyses, in order to get similar groups for comparison in the stroke versus no stroke group as well as in the Tromsø 6 and Tromsø 7 cross-sectional samples. There were no strokes in this age group. In Tromsø 7, all inhabitants above the age of 40 were invited.

2.3 | Experimental pain examination

Pain tolerance was assessed with the CPT, where the participants were asked to hold their hand and wrist in circulating cold water, 3°C, for as long as they were able to or until a maximum time limit was reached. Controlled water temperature was ensured by using a cooling circulator (FP40-HE, Julabo GmbH Germany) with continuous exchange to the vat in which the participant held their hand. Exclusion criteria for CPT included (a) participants declining to perform the test; (b) inability to comprehend and follow instructions; (c) amputation or paresis of the hand; (d) open sores on the hand; (e) medical issues that, in the participants experience, cold exposure would put them at risk of negative side effects, such as cold allergy, Raynaud's syndrome; (f) sensory or motor dysfunction if this could interfere or put the participant at risk. In Tromsø 6, the maximum time limit was 106 s, the dominant hand was submerged. In Tromsø 7, the maximum time was 120 s, the non-dominant hand was submerged. For descriptive purposes, participants were classified as pain tolerant if they kept their hand in the cold water until the maximum time, and pain sensitive if they did not.

2.4 | Covariates

To adjust for putative confounders, risk factors for stroke that could also affect pain tolerance were selected as covariates, namely age, sex, diabetes, hypertension, hyperlipidaemia, body mass index (BMI) and smoking. Diabetes was defined as self-reported diabetes, use of anti-diabetic medication or HbA1c ≥6.5%. Hypertension was defined as self-reported hypertension, use of

antihypertensive medication or blood pressure above 140 systolic or above 90 diastolic. Hyperlipidaemia was defined as use of lipid-lowering drugs or total cholesterol/HDL ratio above 5. BMI was calculated using the formula weight/height^2 (kg/m^2). Smoking status was assessed by questionnaire as current, previous or never daily smoking. If any of the above-mentioned covariates were missing, the participant was excluded from all analyses. Chronic pain was assessed by questionnaire ('do you have persistent or constantly recurring pain that has lasted for 3 months or more?') and information on this item was used for subgroup analysis in subsamples with available information on this item. C-reactive protein (CRP) was added as an additional covariate in subsamples with available information on the item, to assess potential confounding from inflammation.

2.5 | Statistical methods

Descriptive statistics are reported as counts and percentages for categorical data, means and standard deviations for continuous variables. Group differences were evaluated with *t*-tests for continuous variables and chi-squared tests for categorical variables. While participants were classified according to pain tolerance for descriptive purposes, CPT tolerance time was used as a continuous right censored variable in the analyses, and hand withdrawal as the event. Kaplan–Meier plots were created for visualization of CPT tolerance time. The effect of stroke on CPT was modelled using Cox proportional hazard methods. Censoring time was the maximum time limit of the test—106 s in Tromsø 6 and 120 s in Tromsø 7. Putative confounders were added to the model as covariates. Interaction effects were tested for age and sex by adding interaction terms to the model (stroke status multiplied with age and sex respectively). Additional adjustment was done for CRP in subsamples with available information on this item. Graphical check of the proportional hazards (PH) assumption confirmed that observed versus expected survival plots were overlapping and that log–log survival curves were parallel. Statistic test of scaled Schoenfeld residuals confirmed that the PH assumption was met for the relationship between stroke and CPT tolerance time.

Separate analyses were performed for participants in Tromsø 6 and participants in Tromsø 7, as well as for the combined sample, with additional adjustment for study wave (Tromsø 6 or Tromsø 7). In the combined sample, subgroup analyses were performed for each stroke subtype separately (ischaemic stroke, haemorrhagic stroke or subarachnoid haemorrhage). Finally, chronic pain subgroup analysis was performed on subsamples consisting of participants with or without chronic pain for participants with available information on this item ($n = 9924$ in Tromsø 6 and $n = 11{,}086$ in Tromsø 7).

Statistical analyses were performed using STATA version 16.1 for windows (StataCorp LLC). Statistical significance level was set to 0.05.

3 | RESULTS

Descriptive characteristics of the samples are presented in Table 1. Among participants included from Tromsø 6, 181 had a history of stroke prior to attendance, while there were 130 participants with prior stroke in the Tromsø 7 sample. The majority of strokes were ischaemic (83%). Time between stroke and CPT was 35 days–44 years in Tromsø 6, and 30 days–44 years in Tromsø 7. Participants with a history of stroke were older and included fewer women, a higher proportion had diabetes, hypertension, hyperlipidaemia and were smokers and mean BMI was higher. The prevalence of chronic pain was similar in the two groups.

While the overall proportion who were pain tolerant was larger in Tromsø 6 than in Tromsø 7, the proportion of pain-tolerant subjects was lower in those with previous stroke than in those without stroke in both surveys (60.2% vs 68.3% in participants with and without previous stroke, respectively, in Tromsø 6, and 26.9% vs 36.4% in Tromsø 7). Kaplan–Meier plots of CPT tolerance time by stroke status and sex are presented in Figure 2. Plot of baseline hazard of hand withdrawal according to stroke status is presented in Figure S1. In Cox proportional hazard models, participants with a history of stroke had decreased pain tolerance compared to participants without stroke in all three samples (Table 2). In the Tromsø 6 sample, previous stroke was associated with a 33% increased risk of hand withdrawal (HR 1.33, 95% CI 1.05–1.68), and the relationship remained significant when adjusting for age and sex and when adding additional covariates in the multivariable model (HR 1.42, 95% CI 1.12–1.80). In the Tromsø 7 sample, the association was similar (HR 1.30, 95% CI 1.06–1.59) and remained significant when adjusting for age and sex, but not after adjustment for additional covariates (HR = 1.22, 95% CI 0.99–1.49). In the analysis of the combined sample, HR was 1.31 (95% CI 1.13–1.53) and remained significant in all models (HR 1.28, 95% CI 1.10–1.50 in multivariable analysis). Interaction terms for age or sex were not significant and were omitted from further analyses. Additional adjustment for CRP in subsamples with available information on this item had minimal impact on the results (HR 1.27, 95% CI 1.09–1.50 in combined sample, $n = 21{,}075$).

In the combined sample, the association between stroke and pain tolerance was similar in participants

TABLE 1 Demographic and clinical characteristics of cross-sectional samples in Tromsø 6 and Tromsø 7 and combined sample of Tromsø 6 and Tromsø 7, according to stroke status.

	Tromsø 6			Tromsø 7			Combined		
	Stroke $n=181$	No stroke $n=9754$	p	Stroke $n=130$	No stroke $n=11,772$	p	Stroke $n=311$	No stroke $n=21,526$	p
Age in years, mean ± SD	66.0 ± 10.1	57.1 ± 11.5	<0.001	63.3 ± 9.6	53.0 ± 9.6	<0.001	65.0 ± 9.9	54.9 ± 10.7	<0.001
Women, *n* (%)	63 (34.8)	5027 (51.5)	<0.001	45 (34.6)	6038 (51.3)	<0.001	108 (34.7)	11,065 (51.4)	<0.001
Diabetes, *n* (%)	27 (14.9)	633 (6.5)	<0.001	20 (15.4)	629 (5.3)	<0.001	47 (15.1)	1262 (5.9)	<0.001
Hypertension, *n* (%)	150 (82.9)	4774 (48.9)	<0.001	100 (76.9)	4312 (36.6)	<0.001	250 (80.4)	9086 (42.2)	<0.001
Hyperlipidaemia, *n* (%)	119 (65.8)	3075 (31.5)	<0.001	100 (76.9)	3248 (27.6)	<0.001	219 (70.4)	6323 (29.4)	<0.001
BMI, mean ± SD	27.5 ± 4.0	26.9 ± 4.2	0.069	28.3 ± 3.8	27.4 ± 4.6	0.017	27.9 ± 3.9	27.2 ± 4.4	0.007
Daily smoking, *n* (%)			0.422			0.059			0.049
Current	34 (18.8)	1996 (20.5)		25 (19.2)	1691 (14.4)		59 (19.0)	3687 (17.1)	
Previous	87 (48.1)	4212 (43.2)		61 (46.9)	4947 (42.0)		148 (47.6)	9159 (42.6)	
Pain tolerant	109 (60.2)	6661 (68.3)	0.021	35 (26.9)	4285 (36.4)	0.027	144 (46.3)	10,946 (50.9)	
Chronic pain[a]	58 (32)	3112 (31.9)	0.976	44 (33.9)	4088 (34.8)	0.375	102 (32.8)	7200 (33.5)	0.779
Stroke subtype[b]									
Ischaemic	147			110			257		
Intracerebral haemorrhage	16			7			23		
Subarachnoid haemorrhage	12			16			28		
Unclassified	7			0			7		

Note: Participants were classified as pain tolerant if they could endure the maximum time of the cold pressor test, which was 106 s in Tromsø 6 and 120 s in Tromsø 7. *p*-value is for difference between stroke and no stroke group.

Abbreviation: BMI, body mass index.

[a]Chronic pain is presented for participants with available information on this item. In Tromsø 6, 11 participants (no strokes) had missing information on this item, while in Tromsø 7, it was 816 (24 strokes).

[b]In Tromsø 6, one participant was registered with both an ischaemic and an unclassifiable stroke. In Tromsø 7, three participants were registered with both an ischaemic stroke and an intracerebral haemorrhage.

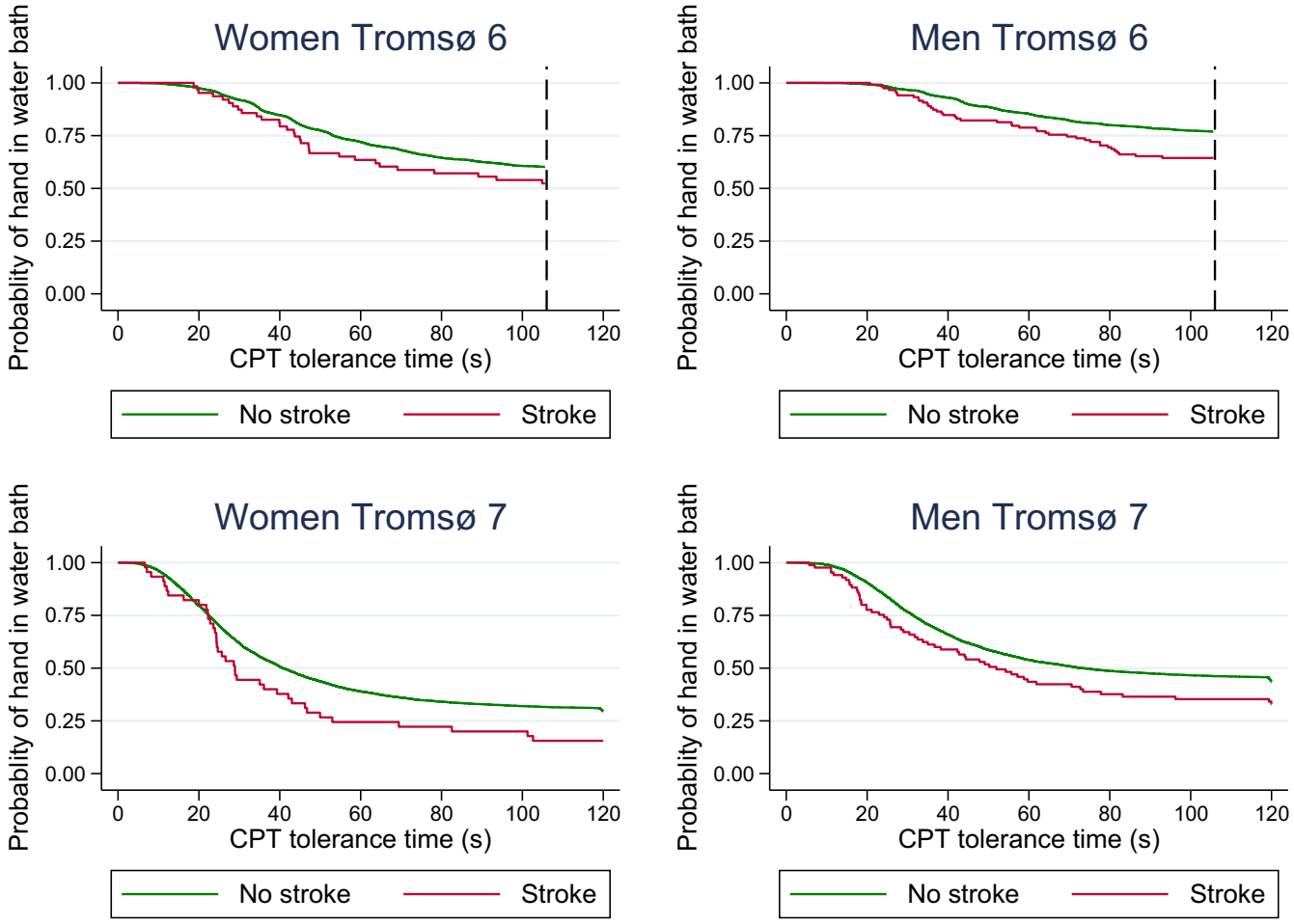

FIGURE 2 Kaplan–Meier plot of CPT tolerance time for women and men in Tromsø 6 and Tromsø 7. Probability of keeping the hand in the water bath for women and men, according to stroke status. In both study waves, participants with a history of stroke had increased rates of hand withdrawal from cold water bath. The maximum time was 106 s in Tromsø 6, indicated by reference line, while in Tromsø 7 it was 120 s. CPT, cold pressor test.

TABLE 2 Cox regression analyses of the association between stroke and pain tolerance time.

	Tromsø 6			Tromsø 7			Combined		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
Crude[a]	1.33	1.05–1.68	0.016	1.30	1.06–1.59	0.011	1.31	1.13–1.53	<0.001
Model 1[b]	1.50	1.18–1.90	0.001	1.31	1.07–1.61	0.009	1.38	1.18–1.61	<0.001
Model 2[c]	1.42	1.12–1.80	0.004	1.22	0.99–1.49	0.062	1.28	1.10–1.50	0.002

Note: Analyses are Cox proportional hazards model with time with hand in cold-water bath as outcome and stroke status as independent variable. Hazard ratios above 1 indicate higher hazard of hand withdrawal, that is, lower pain tolerance. Tromsø 6: max time 106 s, 181 strokes. Tromsø 7: max time 120 s, 130 strokes. Combined sample: 311 strokes.

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a]Crude: no adjustment in Tromsø 6 or Tromsø 7, in combined sample adjustment for study indicator (Tromsø 6 or Tromsø 7).

[b]Model 1: adjusted for age and sex. In combined sample additional adjustment for study indicator.

[c]Model 2: adjusted for age, sex, diabetes, hypertension, hyperlipidaemia, body mass index and smoking. In combined sample additional adjustment for study indicator.

with and without chronic pain (multivariable adjusted HR 1.28 [95% CI 0.99–1.66] in participants with chronic pain [$n = 7302$] and 1.29 [95% CI 1.04–1.59] in participants without chronic pain [$n = 13{,}708$] in combined sample). The association was somewhat stronger for participants with chronic pain in the Tromsø 6 sample, and weaker for participants with chronic pain in the Tromsø 7 sample, compared to participants without chronic pain (Table 3).

TABLE 3 Subgroup analysis of the association between stroke and pain tolerance time, in participants with or without self-reported chronic pain.

	Tromsø 6 ($n = 3170$)			Tromsø 7 ($n = 4132$)			Combined ($n = 7302$)		
With self-reported chronic pain	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***
Crude[a]	1.58	1.1–2.28	0.013	1.13	0.79–1.61	0.489	1.30	1.01–1.68	0.040
Model 1[b]	1.82	1.26–2.63	0.001	1.17	0.82–1.68	0.376	1.40	1.09–1.81	0.010
Model 2[c]	1.72	1.19–2.48	0.004	1.07	0.74–1.53	0.727	1.28	0.99–1.66	0.056
Without self-reported chronic pain	**Tromsø 6 ($n = 6754$)**			**Tromsø 7 ($n = 6954$)**			**Combined ($n = 13,708$)**		
	HR	**95% CI**	***p***	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***
Crude[a]	1.21	0.89–1.64	0.232	1.37	1.02–1.84	0.034	1.29	1.04–1.59	0.019
Model 1[b]	1.33	0.98–1.81	0.068	1.42	1.05–1.90	0.021	1.37	1.11–1.70	0.004
Model 2[c]	1.29	0.94–1.76	0.111	1.31	0.97–1.76	0.076	1.29	1.04–1.59	0.022

Note: Analyses are Cox proportional hazards model with time with hand in cold-water bath as outcome and stroke status as independent variable. Hazard ratios above 1 indicate higher hazard of hand withdrawal, that is, lower pain tolerance. Tromsø 6: max time 106 s, 181 strokes. Tromsø 7: max time 120 s, 130 strokes. Combined: 311 strokes.

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a]Crude: no adjustment in Tromsø 6 or Tromsø 7, in combined sample adjustment for study indicator (Tromsø 6 or Tromsø 7).

[b]Model 1: adjusted for age and sex. In combined sample additional adjustment for study indicator.

[c]Model 2: adjusted for age, sex, diabetes, hypertension, hyperlipidaemia, body mass index and smoking. In combined sample additional adjustment for study indicator.

TABLE 4 Subgroup analysis of association between stroke and pain tolerance in stroke subtypes, in combined sample of Tromsø 6 and Tromsø 7.

Stroke type	No. of strokes	HR	95% CI	*p*
Ischaemic	253	1.35	1.14–1.59	0.001
Haemorrhagic	20	0.65	0.29–1.45	0.294
Subarachnoid haemorrhage	28	1.50	0.97–2.35	0.071

Note: Analyses are Cox proportional hazards model with time with hand in cold-water bath as outcome and stroke status as independent variable, adjusted for study indicator (Tromsø 6 or Tromsø 7), age, sex, diabetes, hypertension, hyperlipidaemia, body mass index and smoking. Participants with other types of stroke were excluded from analysis (e.g. when doing analysis for ischaemic stroke, participants with haemorrhagic stroke or subarachnoid haemorrhage were excluded). Hazard ratios above 1 indicate higher hazard of hand withdrawal, that is, lower pain tolerance.

Abbreviations: CI, confidence interval; HR, hazard ratio.

In stroke type subgroup analysis in the combined sample (Table 4), the association was significant for ischaemic stroke (HR 1.35, 95% CI 1.14–1.59), but not for intracerebral (HR 0.65, 95% CI 0.29–1.45) or subarachnoid haemorrhage (HR 1.50, 95% CI 0.97–2.35). However, the number of participants with haemorrhagic stroke and subarachnoid haemorrhage was quite low, 20 and 28 participants, respectively, rendering this conclusion uncertain.

4 | DISCUSSION

Our main finding was that individuals with a history of stroke have lower pain tolerance compared to individuals without stroke, in a large, general population-based sample. The finding was similar across study samples, and in subgroups with and without chronic pain. The association was also found in subgroup analysis of participants with ischaemic stroke, which constituted 83% of all included strokes. While the overall CPT tolerance time was shorter in Tromsø 7 than in Tromsø 6 in all participants, this did not affect the results from analyses comparing participants with and without stroke. Inspection of Kaplan–Meier plots of probability of keeping the hand in the water bath also suggest that the difference did not influence the shape of the curves.

Pain is a multidimensional experience processed in an extensive network of brain regions (Mercer Lindsay et al., 2021) and pain tolerance is likely to be influenced by its sensory-discriminative, affective-motivational and cognitive-evaluative dimensions as well as modulatory mechanisms. Altered sensitivity to pain in stroke patients may be due to stroke lesions affecting the somatosensory pathway and distributed corresponding to lesion location. While key regions and corresponding contributions to other dimensions of pain processing have been identified (Apkarian et al., 2005; Mercer Lindsay et al., 2021), a core

quality of pain processing and modulation is its distributed nature and high degree of interconnectivity. This entails that it is highly resilient; the ability to experience pain is rarely extinguished despite focal or widespread injury in the brain (Coghill, 2020). However, the high degree of interconnectivity also implies that a disruption can have consequences across multiple anatomical and temporal scales (Kuner & Flor, 2016), leading to altered function and plasticity. In the light of this, it is reasonable that a stroke can affect pain in ways that do not necessarily correspond to stroke lesion location but rather reflect its impact on the pain processing network and the dynamic interplay in it.

Previous studies using experimental pain assessments in stroke patients have found altered pain sensitivity in body regions corresponding to stroke lesion location in patients with PSSP (Roosink et al., 2011, 2012; Soo Hoo et al., 2013; Zeilig et al., 2013) and CPSP (Krause et al., 2016). Evidence of higher pain sensitivity in the ipsilateral/unaffected side, suggesting widespread hypersensitivity, has been found in patients with PSSP (Roosink et al., 2011, 2012; Soo Hoo et al., 2013) and CPSP (Casey et al., 2012; Krause et al., 2016; Tuveson et al., 2009), as well as in stroke patients with sensory abnormalities, but not chronic pain (Krause et al., 2016) and pain-free cerebellar stroke patients (Ruscheweyh et al., 2014).

As previous evidence indicate that chronic pain is associated with increased pain sensitivity (Kosek & Ordeberg, 2000; Woolf, 2011), increased sensitivity (and correspondingly decreased CPT tolerance time) in stroke patients could conceivably be an effect of a post-stroke chronic pain condition such as CPSP or PSSP. However, we found similar association between stroke and pain tolerance in participants with and without chronic pain, suggesting that this was not the case. Increased pain sensitivity in stroke patients without chronic pain is previously reported by smaller studies (i.e. $n \leq 30$) (Krause et al., 2016; Ruscheweyh et al., 2014). This implies that increased pain sensitivity after stroke is not only a possible consequence of chronic post-stroke pain, but also a potential risk factor for it. This indicates that central sensitization could be a contributing factor in the pathophysiology of post-stroke pain syndromes, as previously suggested (Klit et al., 2009), and could also increase the risk and intensity of pain related to other diseases, injuries and medical procedures in stroke patients. Even though it is not yet clear how experimental pain assessments translate to clinical pain, relevance of CPT is supported by studies finding that lower CPT tolerance time is associated with increased risk of post-operative pain (Bisgaard et al., 2001) and with chronic pain (Stabell et al., 2013), while in one prospective study reduced CPT tolerance time at baseline was associated with non-recovery after whiplash (Kasch et al., 2005).

The possible clinical implications of lower pain tolerance have particular importance in stroke patients, considering the co-occurrence of aphasia and cognitive decline that render many of these patients with limited ability to communicate their pain (Edwards et al., 2020). If stroke patients are more sensitive to pain, or have more difficulty coping with it, this calls for awareness in health professionals.

4.1 | Limitations and strengths

The strengths of our study are the large representative samples which allows comparison with stroke-free participants of the general population, the inclusion of participants with and without chronic pain and consistency of findings across study samples.

The study also has several limitations, of which the lack of details on stroke location and deficits is the most substantial. This precluded analysis of whether reduced pain tolerance is more pronounced on the hand contralateral or ipsilateral to the stroke. However, hand paresis was an exclusion criterion for CPT and the participants were asked if they had sensory or motor dysfunction that could interfere with testing or put them at risk. If so, they were excluded or tested on the other hand. Due to this selection procedure, it is likely that stroke patients with severe deficits are underrepresented in our study, which would be expected to weaken our results. Whether recurrent stroke or time since stroke is a factor in the relationship could not be evaluated as we did not have sufficient information on the number of strokes in each participant. Our study is observational and consequently does not allow causal inference, nor can it be excluded that the association may be due to unmeasured confounding. Pain assessments are poorly correlated (Janal et al., 1994; Neziri et al., 2011) and inference cannot be made directly from CPT to other pain stimuli or assessments. A previous study found shorter CPT tolerance time in cases with mild to moderate Alzheimer, while supra-threshold pain ratings were lower in the same group (Jensen-Dahm et al., 2015). In our study, we cannot disentangle and explain the mechanistic underpinnings of lower CPT tolerance in stroke survivors.

5 | CONCLUSION

Participants with a history of stroke have lower pain tolerance. This association is present in stroke survivors both with and without chronic pain. This may have important clinical implications: these patients could be more sensitive to acute and procedural pain, and considering that many stroke patients have difficulty communicating

their symptoms, this calls for increased awareness among health professionals.

AUTHOR CONTRIBUTIONS

TA Melum executed the statistical analyses and drafted the article with supervision from CS Nielsen, EB Mathiesen and H Stigum. CS Nielsen, ÓA Steingrímsdóttir and A Stubhaug executed the collection of pain sensitivity data and EB Mathiesen was responsible for quality control of the stroke data from medical registries. AP Årnes assisted in the implementation of statistical models. All authors discussed the results and commented on the article. All authors have approved this article.

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CONFLICT OF INTEREST STATEMENT

None of the authors have declared any conflicts of interest.

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