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Persistent post-surgical pain

Prevalence, risk factors and pain mechanisms

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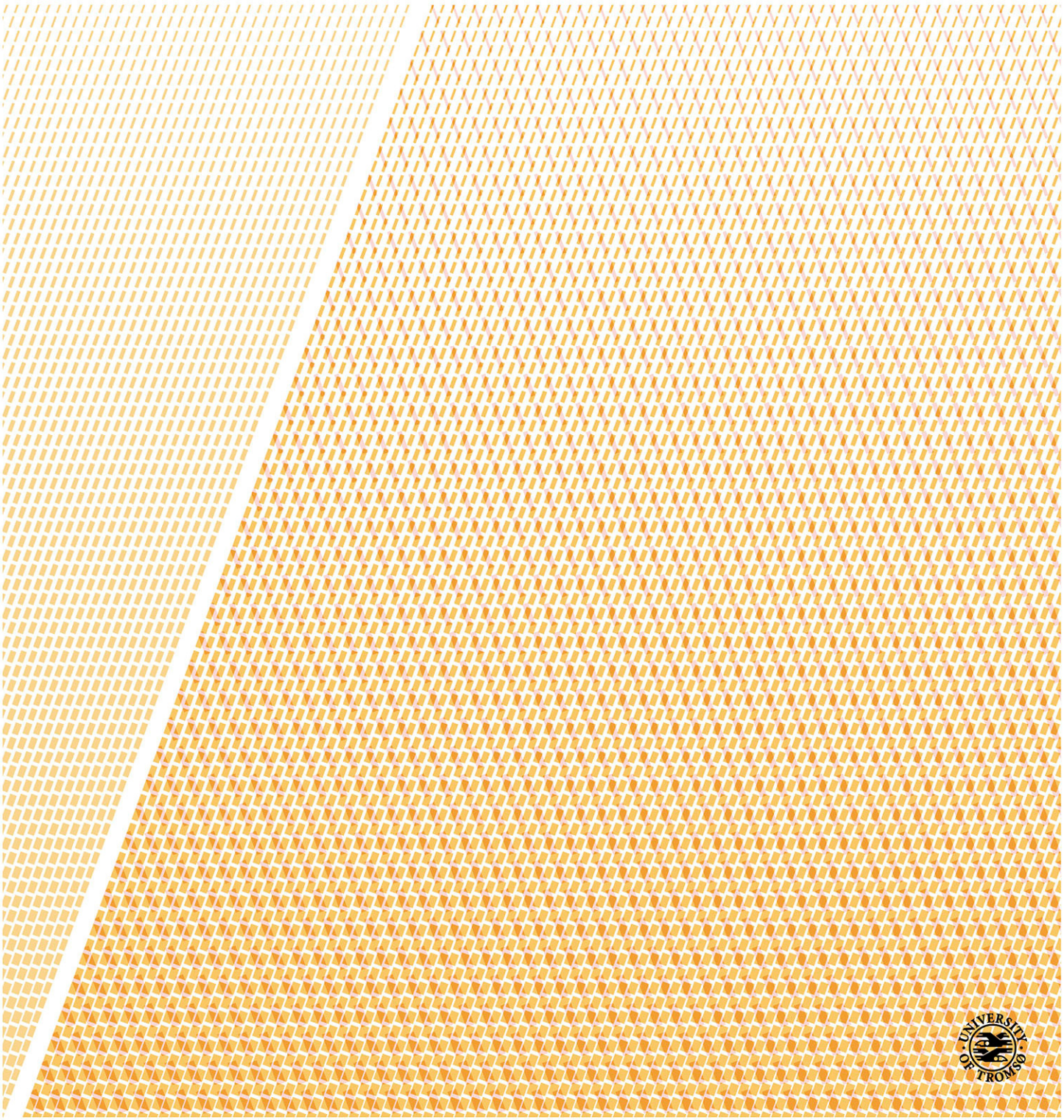

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NORSK POPULÆRVITENSKAPELIG SAMMENDRAG

(NORWEGIAN SUMMARY)

I den 6. Tromsøundersøkelsen, en folkehelseundersøkelse i Tromsø kommune 2007-2008, svarte nesten 13,000 deltakere på spørsmål om langvarig smerte og kirurgi, og deres følsomhet for smerte ble undersøkt eksperimentelt. Et utvalg av deltakerne som hadde vært operert, ble fulgt opp 15-32 måneder senere med spørreskjema og undersøkelse av følsomhet for nøytrale og smertefulle stimuli.

Vi fant at 18,3 % rapporterte moderat til alvorlig smerte i operasjonsområdet 3-36 måneder etter kirurgi. Av disse hadde de fleste samtidig langvarig smerte av andre årsaker. Da vi justerte statistisk for bidraget fra annen langvarig smerte, fant vi ingen sammenheng mellom smerte etter kirurgi og smerteføl somhet.

Vi påviste en sterk statistisk sammenheng mellom langvarig smerte etter kirurgi og selvrapporterte forstyrrelser i følsomhet i operasjonsområdet. Dette kan indikere nerveskade som mulig bidragende årsak til smerten.

Med eksperimentelle metoder påviste vi imidlertid lokale endringer i følsomhet like hyppig hos individer med og uten langvarig smerte etter kirurgi. Nerveskade alene synes altså ikke å være tilstrekkelig som årsaksforklaring.

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Finally, warm and loving thanks to my family for their unconditional and enduring support throughout a process which proved to be more time-consuming than we anticipated.

LIST OF PAPERS

1. Johansen A, Romundstad L, Nielsen CN, Schirmer H, Stubhaug A. Persistent postsurgical pain in a general population: Prevalence and predictors in the Tromsø study.
   Pain 2012;153:1390-6.

2. Johansen A, Schirmer H, Stubhaug A, Nielsen CS. Persistent post-surgical pain and experimental pain sensitivity in the Tromsø study: Comorbid pain matters.
   Pain 2014;155:341-8.

3. Johansen A, Schirmer H, Nielsen CS, Stubhaug A. Persistent post-surgical pain and signs of nerve injury. The Tromsø Study.
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NOMENCLATURE AND ABBREVIATIONS

BPI	Brief pain inventory
^{o}C	Degrees celcius (centigrade)
CI	Confidence interval
CPT	Cold pressor test
DFNS	Deutscher Forschungsverbund Neuropatischer Schmerz (German Research Network on Neuropathic Pain)
Gr	Greek
HSCL-10	Hopkins Symptom Checklist – 10 item version
HR	Cox proportional hazard ratio
IASP	International Association for the Study of Pain
IQR	Interquartile range
kPa	Pressure: Kilopascal. 1 kPa = 1000 Pascal
mm Hg	Pressure: Millimeter of mercury
mN	Millinewton. 1 mN = 1/1000 Newton
NOK	Norwegian kroner
NPSI	Neuropathic pain symptom inventory
NRS	Numeric rating scale
OR	Odds ratio
PCS	Pain catastrophizing scale
PPSP	Persistent post-surgical pain
QST	Quantitative sensory testing
sec.	Second(s)
VAS	Visual analogue scale

SUMMARY

Persistent pain is reported to be a frequent complication from surgery. Among the proposed risk factors are perioperative nerve injury and individual differences in pain sensitivity.

The 6th Tromsø Study, a cross-sectional survey and medical examination, provided questionnaire data on persistent pain in general and persistent pain following surgery in particular. Participants performed tests of sensitivity to experimental pain stimuli. A sample of participants who had performed surgery 3-36 months before the survey, were re-assessed with questionnaires and quantitative assessments of sensory function 15-32 months after Tromsø 6.

In accordance with previous research, we found that persistent pain after surgery was common. Moderate or severe pain in the area of surgery 3-36 months after the procedure was reported by 18.3 %. Most cases were coexistent with other chronic pain. Only in a small minority of cases did the patients themselves attribute persistent pain to surgery alone.

In a general surgical sample, we could not identify specific associations between persistent post-surgical pain and sensitivity to experimental pain stimuli when comorbid pain was adjusted for.

Persistent post-surgical pain was strongly associated with self-reported sensory disturbances, indicating possible nerve injury as a contributing factor. Sensory aberrations were confirmed with sensory testing in a majority of individuals with persistent pain in the surgical area. However, nerve injury does not appear sufficient for development of such pain, as signs of nerve injury, confirmed with quantitative sensory testing, were just as common among individuals without persistent post-surgical pain.

1 INTRODUCTION

1.1 About the thesis

During the last two decades, there has been a growing scientific interest in persistent pain following surgery. October 25th 2014, a search on PubMed with the terms "persistent-" or "chronic-" "postsurgical-" or "postoperative-" pain revealed 9,177 hits. Due to the large volume of surgical procedures performed every year, even conservative incidence estimates imply large numbers of individuals inflicted by pain following common surgical procedures[1]. According to Bruce et al., 39.3 % of sternotomies[2] and 63 % of surgeries for breast cancer[3] are followed by persistent pain. Kehlet states that persistent pain adversely affects daily activities in 5-10 % following groin hernia repair[4]. Translated into my local context at the University Hospital of North Norway in Tromsø, where 485 sternotomies[5], 155 primary surgical procedures for breast cancer[6], and 173 hernia repairs[7] were performed in 2013, a potential 300 individuals with persistent pain could be expected from these procedures alone.

Still, most individuals who are subject to surgery do not develop persistent pain. A growing literature is devoted to possible risk factors. Individual differences in pain sensitivity and nerve damage as a consequence of surgery are among the potential risk factors which have received most attention. Most data are based on clinical studies. Less is known about the prevalence of persistent post-surgical pain (PPSP) in the general population. This thesis is based on data from Tromsø 6, a cross-sectional population-based survey and medical examination in the urban and rural municipality of Tromsø in 2007-2008. We estimated the prevalence of PPSP from questionnaire data, and the association between PPSP and pain sensitivity was studied with experimental pain testing of the participants. In order to determine the association between possible nerve injury and pain, a sample of the participants, who had gone through surgery during the last three years preceding the survey, were re-examined in a follow-up study with repeated questionnaires and examination of sensory function in the anatomical area affected by surgery.

The thesis starts with an introduction to nociception, different pain dimensions and pain categories, before presenting fundamentals of experimental pain testing and available evidence of PPSP at the time Tromsø 6 was performed. Next, aims of the thesis, material, methods and results are presented. Methodological aspects are discussed, with emphasis on interpretation of experimental pain data and the application of epidemiological methods in the evaluation of outcome of surgery. In the discussion of results, the role of comorbid persistent pain, the possible interplay between pain and pain sensitivity, and challenges in identification of sensory disturbances and neuropathic pain is covered. Finally, conclusions with implications for clinic and research are presented.

1.2 Pain and nociception

Pain: Lat. p*oena,* punishment.

Nociception: Lat. *nocere,* to damage.

The concept of pain is intuitively understood, yet difficult to define. The ability to feel acute pain serves a vital purpose in man's adaptation to internal stimuli and the environment. The International association for the study of pain (IASP) defines pain as *"an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"*, and nociception as *"the neural process of encoding noxious stimuli"*, not necessarily accompanied by pain sensation[8] . These definitions delineate the subjective experience of pain, associated with threat to the individual's integrity, from nociception, the process of sensory transduction in nerves by aversive stimuli activating specialized nerve endings, upon which the experience of pain evolves. It is argued that pain may not necessarily involve nociceptive input[9,10].

Pain is a self-experience that depends on the circumstances under which it appears. It cannot be separated from emotions like fear or misery. Tests can neither verify nor reject the presence of pain. Only the person in pain can evaluate the severity of his or her pain[11].

By presenting the gate-control theory of pain in 1965, Melzack and Wall promoted a change in the understanding of pain as an interplay between lower (peripheral) and higher (spinal and supraspinal) neural processes[12]. With special focus on the dorsal horn of the spinal cord, the theory

proposed central inhibitory mechanisms modulating incoming (afferent) nociceptive signals from peripheral nerves. Although the proposed physiological mechanisms have been challenged, the model has served as an appropriate and fertile basis for research as well as a useful model for patient education.

1.2.1 Pain dimensions

Recognizing that pain is more than purely a sensory experience, Melzack and Casey in 1968 proposed three distinct pain dimensions[13]: the *sensory-discriminative dimension* , influenced primarily by the rapidly conducting spinal systems; the *motivational-affective dimension* engaging the reticular and limbic structures of the brain and influenced primarily by the slowly conducting spinal systems; and the *cognitive-evaluative dimension* which is processed in neocortical or higher nervous systems. They assumed that the three categories of nervous activity interact, providing the experience of pain, eventually influencing the motor activities characterizing pain behavior[14].

1.2.2 Nociceptive pain

Pain initiated by potentially harmful mechanical, thermal or chemical stimuli, transduced to electrical signals by specialized nerve endings, nociceptors, is denoted *nociceptive pain*[8].

Cell bodies of nociceptive fibers are located in dorsal root ganglions and the trigeminal ganglia. They synthesize several neuropeptides and inflammatory mediators. Upon prolonged activation of the nociceptors, the neuropeptides may be transported along the axon and released at the nerve terminals. Following tissue injury, other pain-inducing chemicals are released from surrounding tissues and may either directly activate the nociceptors or, by propagating inflammation, sensitize nociceptors, further accelerating nervous firing (Flor and Turk, pp. 25-44)[15]. The term *peripheral sensitization* refers to the phenomenon of increased nervous firing and/or engagement of adjacent nerves not directly affected by the primary injury, appearing as a result of such processes following injury or prolonged noxious stimulation (Møller, pp. 134-136)[11].

In the dorsal horn of the spinal medulla, peripheral nerve fibers synapse with second order neurons, projecting cranial to the brain stem and thalamus. Peripheral fibers also synapse with

interneurons connected to other spinal neurons. There is extensive evidence that prolonged nociceptive input is associated to plastic changes in the dorsal horn, either in the form of increased excitability of neurons, decreased inhibitory inputs, "phenotypic switch" in which normally innocuous input may initiate nociceptive signaling, or combinations of the three[16] resulting in *central sensitization.* In central sensitization, an amplification of signaling that elicits pain hypersensitivity takes part within the central nervous system [17].

Nociceptive signals ascend the spinothalamic and other designated spinal tracts to the brain stem and thalamus. From the thalamus, third order neurons project to the primary and secondary somatosensory cortex. Painful stimulation also elicits activity in other brain areas, among them the anterior cingulate cortex, insular cortex, and prefrontal cortex[15]. The dynamic interaction of multiple cortical and subcortical areas, engaging sensory-discriminative functions, arousal, attention, emotions, memory and expectancy, are believed to process the conscious experience of pain[18].

As described above, the somatosensory system transmits nociceptive input through peripheral and spinal fibers to the brain where signals are processed in cognitive, emotional and motivational ways. In addition, the healthy nervous system conveys potent pain inhibitory functions. Electrical stimulation of specific brain areas has been demonstrated to induce analgesia. Spinal descending inhibitory activity may also be activated by endogenous and exogenous opioids, endocannabinoids, and the neuropeptides serotonin and norepinephrine[15].

To conclude, the normal perception of nociceptive pain is a subjective experience which is the product of complex dynamic, interactive processing of nociceptive signals, constantly modified by active mechanisms at the peripheral, spinal, and cerebral subcortical and cortical levels.

Pain may be classified according to mechanism or cause (inflammatory pain, postherpetic neuralgia) or the anatomical structures believed to initiate the painful stimulus (radiculopathia, visceral pain). When no cause for pain can be found, it is commonly denoted idiopathic pain.

Inflammatory pain

The term *inflammatory pain* is applied when tissue injury, burns, or infections elicit acute pain and varying degrees of hypersensitivity to noxious and innocuous stimuli ("tenderness") as a result of release of inflammatory substances[19].

Visceral pain

Visceral pain refers to pain from internal organs. Several features distinguish visceral pain from other sorts of nociceptive pain. Among those are a more diffuse sense of localization, in part due to the nociceptive innervation served predominantly by C-fibers which carry less precise spatial information compared to Aδ-fibres. In addition, spinal segmental overlap with somatosensory innervation from non-visceral organs is thought to be responsible for the phenomenon of "referred pain"[20].

1.2.3 Neuropathic pain

According to the IASP task force on taxonomy, the definition of nociceptive pain (above), is intended to contrast from *neuropathic pain*, defined as *"pain caused by a lesion or disease of the somatosensory nervous system"*[8]. Neuropathic pain is commonly accompanied by sensory abnormalities such as *hypoesthesia* (decreased sensitivity to stimulation, or "sensory loss"), *hyperalgesia* (increased pain response to stimuli that normally elicits pain) or *allodynia* (pain due to a normally innocuous stimulus). The term *hyperesthesia* conveys both hyperalgesia and allodynia, two manifestations of "sensory gain"[8].

Diagnosing of neuropathic pain is difficult. Firstly, all injuring of tissue will encompass some traumatizing of nervous tissue as well, although the subsequent pain may be no different from normal nociceptive-inflammatory pain. Secondly, pain mechanisms may be mixed. Inflammatory processes may involve nerves, either directly, as in postherpetic neuralgia, or indirectly, as inflammation of surrounding tissue engages nerves. Thirdly, neuropathic pain (e.g. from compression of a nerve root) may be coexistent with, for instance, local muscular pain and referred pain in the same body region.

Questionnaire-tools for diagnosing-[21-23], or scoring the severity of-[24], neuropathic pain emphasize pain descriptors typical for neuropathic pain, like "burning", "lancinating", "electrical

shocks" etc. No descriptors are, however, pathognomonic for neuropathic pain, and the use of questionnaire-based diagnostic tools have been criticized for having too low specificity, resulting in overdiagnosis of neuropathic pain[25].

In most cases, neuropathic pain is accompanied by sensory aberrations. Intuitively, one would expect a disease or lesion to a sensory nerve to cause sensory loss. The paradoxical coexistence of sensory gain and loss is a typical, but not mandatory, feature of neuropathic pain[19,26]. Sensory aberrations may either be reported as symptoms by the individual with pain or detected by a clinical examination. The distribution of pain and sensory disturbances within a well-defined neuroanatomically territory would increase the likelihood for neuropathic pain, but partial nerve lesions, which are the most common, might give rise to sensory aberrations only in parts of the nerve's innervation territory. Pronounced temporal delays from injury to onset of symptoms may also complicate diagnosis[25]. Moreover, only a minority of individuals with nerve injuries do eventually develop neuropathic pain[27-29].

As the definition implies, correctly identifying neuropathic pain involves establishing a cause for the pain. A grading system, classifying pain as "possible", "probable" and "definite" neuropathic pain was proposed by Treede et al. in 2008[30]: Pain may be of *possible* neuropathic origin if pain distribution is neuroanatomically plausible and the history suggests a relevant lesion or disease. Symptoms of sensory loss (hypoesthesia or hypoalgesia) or -gain (spontaneous pain, hyperalgesia or allodynia) may increase susceptibility of neuropathic pain while, according to Treede et al., a positive test confirming such loss or gain of sensory function may classify pain as *probably* neuropathic. Classification as *definite* neuropathic pain requires confirmation of a relevant lesion or disease explaining the pain. In other words, "probable" neuropathic pain may be diagnosed based on a test confirming functional disturbance, while "definite" requires a confirmation of the anatomical substrate, and both must prove neuroanatomically relevant to the symptoms.

The category "probable neuropathic pain" may contain a wide spectrum of likelihood for a neuropathic cause, as nerve lesions do not necessarily result in neuropathic pain, nociceptive pain may

have qualities similar to neuropathic pain[31,32], sensory loss due to lesions of nervous tissue are not necessarily accompanied by pain[33], and sensory disturbances associated to well-defined nerve lesions may present in very different and unpredictable ways[34]. At the same time, access to diagnostic resources like magnetic resonance imaging or neurography, to verify "definite" neuropathic pain is limited.

1.2.4 Acute vs. chronic pain

With reference to duration, pain is often classified as either acute or chronic. Possibly because the term "chronic" has connotations of permanency and incurability, the designation "persistent" is frequently preferred. There is no agreement on the duration necessary to classify pain as chronic. Arbitrary definitions of three or six months are common, while some have defined acute pain as pain lasting less than 30 days[11]. With reference to the evolutionary adaptive function of pain, some authors have defined chronic pain as pain outlasting the anticipated healing period, but this definition does not take into account pain that is not elicited by trauma or acute disease.

A reason for differentiating between short- and long standing pain, is the function of the pain. While acute pain may serve as a powerful distractor, drawing attention to a potential threatening stimulus and motivate protection, chronic pain may serve no apparent function. Rather, it may undermine recovery by motivating maladaptive passivity, inducing depressed mood and promoting social isolation. Moreover, chronic pain is not necessarily preceded by an acute episode of pain with obvious cause, and a prevalent feature of chronic pain is lack of proportionality between pain and detectable somatic pathology (Flor and Turk, pp. 177-198)[15]. Following this line of reasoning, some authors have suggested classifying pain into physiologic vs. pathologic pain[11] or even eudynia (nociceptive pain, Gr.: "good pain") vs. maldynia (maladaptive pain, Gr.: "bad pain")[35].

1.2.5 Idiopathic pain

When no cause for pain can be found, it is traditionally denoted idiopathic pain (Møller, p. 13)[11]. The term "idiopathic" may attenuate therapeutic enthusiasm, and even allude to malingering or psychopathology, which may be inappropriate. Given the amounting evidence of long term

alterations in pain processing in persistent pain conditions, other terms are often available to categorize pain conditions without obvious somatic findings. This said, our improved understanding of pain mechanisms will still frequently fall short when trying to explain the specific pain problem for the individual patient in question.

1.3 Experimental pain

Experimentally induced pain allows observations of pain behavior as a response to controlled specific sensory stimuli with predefined qualities, intensities and temporal and spatial distributions. The stimulus may be of thermal, mechanical, chemical, or electrical quality.

1.3.1 Pain rating

The intensity of pain elicited by the stimuli is usually reported with the help of a visual analogue or numeric rating scale (VAS, NRS), most frequently scales with 0 and 10, or 0 and 100, as the anchors, where 0 denotes "no pain" and the maximum value "worst pain imaginable". Such scales have the obvious limitation of only assessing one dimension of the pain experience (intensity) unless scales are used repeatedly for different, specific dimensions (e.g. pain intensity and unpleasantness)[36].

1.3.2 Experimental pain vs. clinical pain

One important feature of experimental pain, distinguishing it from clinical pain, is that pain experiments, given proper ethical conduct, renders the test subject the option to abort the stimulus or even the whole test, while clinical pain is imposed on the subject with more limited or no power to modify the pain. The ability to control or modify pain may greatly influence the motivational-affective and cognitive-evaluative dimensions of pain. Escapable and inescapable pain may even be mediated in different supra-spinal neuronal networks[37].

1.3.3 Pain sensitivity

Another feature of experimental pain is the specificity of stimuli. Pain stimuli are commonly delivered as (the list is not exhaustive): local heat or cold (e.g. a hot or cold thermode applied to the skin surface), cold pressor (immersion of a body part in cold water), electrical stimuli, chemical stimuli (e.g. topical or injected capsaicine), static tactile stimuli (calibrated vonFrey filament), deep

pressure (pressure algometer) or dynamic tactile stimuli (allodynia assessed with brush or cotton). Sensitivity to different experimental pain stimuli have little within-individual correlation[38]. Consequently, the assessment of an individual's sensitivity to one experimental pain quality cannot be generalized to reflect a global pain sensitivity for that particular individual.

According to IASP, *pain threshold* is commonly explained as "the minimum intensity of a stimulus that is perceived as painful". IASP underlines that "the level at which 50% of stimuli are recognized (as painful)" is a more precise definition. This however, is not pain, but rather a limit for the sensation of pain[8]. The sensitivity to stimuli intensities exceeding the pain threshold of the individual may either be assessed as direct pain scaling or *pain tolerance*, the latter representing the maximum stimulus intensity tolerated[8]. Strictly speaking, stimulus assessments are here used as proxy for pain assessments. The expression "pain tolerance" is also frequently applied in relation to time endured under a standardized noxious stimulus, like cold water immersion[39]. More elaborate models for assessing dynamic properties of pain processing, like temporal and spatial summation of pain, conditioned pain modulation (descending inhibitory control), and offset analgesia have become more common in recent years[40].

Clinical experience as well as research indicates extreme individual variations in clinical pain from apparently comparable clinical conditions[39]. There is an abundance of evidence for sex differences in both experimental and clinical pain, with most reports indicating higher prevalence of chronic pain conditions and higher sensitivity for experimental pain among women[41]. Ethnical differences are also documented[42]. Even when these factors are accounted for, individual differences in sensitivity to experimental pain stimuli persist, and heritability of pain sensitivity to specific pain modalities have been quantified[43].

1.3.4 Quantitative sensory testing (QST)

Quantitative sensory testing (QST) is a method for evaluation of sensory thresholds, perceived pain intensity and tolerance to a variety of sensory stimuli[44,45]. Testing may be applied as measures of general sensitivity or as assessments in specific anatomical areas affected by injury or disease, to

detect signs of local sensory aberrations. The aim of sensory testing is to explore mechanisms involved in sensory transduction, transmission and perception under normal and pathophysiological circumstances[44]. In research on neuropathic pain in particular, QST is applied as a tool for assessing alterations in sensory functions in relation to known or suspected pathologic conditions.

Modalities

Stimulus modalities are selected for detecting abnormalities in specific nerve fibers. Most often mechanical and thermal stimuli are applied (Table 1). Stimulation of skin receptors is the most widely used application of QST, but other applications are feasible, e.g. in assessments of visceral pain[46].

Sensory thresholds are most commonly assessed with the method of limits or the method of levels. In the method of limits, gradual increased intensities are applied until the stimulus is detected (detection threshold) or until the perception of pain (pain threshold). This method may be prone to inaccuracy due to psychomotor skills and reaction time, and bias due to expectancy, as stimulus increase is a function of time. The method of levels does not inherit the same limitations, as the subject is forced to respond "yes" or "no" to predefined stimuli as they are presented. The intensities presented are increased or decreased on the basis of the subject's response. The method of levels is more time-consuming however, and the method of limits is usually preferred. Thresholds are commonly calculated as the mean of a series of repeated, typically 3 or 5, assessments[44,47].

Thermal thresholds are typically assessed with a thermotest device, in which quick and precise alterations in surface temperature of a thermode is induced. The thermode is applied to the skin of the subject, and the subject is instructed to press a button when either detection threshold, pain threshold or a specific pain intensity is reached. On pressing the button, the temperature returns to baseline. The thermotests are programmed with stimulus sequences, and results are automatically recorded.

Table 1. Assessment of different peripheral somatosensory channels

Stimulus	Peripheral sensory channel	QST
Thermal		
Cold	Aδ	Computer controlled thermal testing device
Warmth	C	
Heat pain	C, Aδ	
Cold pain	C, Aδ	Computer controlled thermal testing device; Cold pressor test
Mechanical		
Static light touch	Aβ	Calibrated vonFrey hairs
Vibration	Aβ	Vibrameter
Brushing	Aβ	Brush
Pinprick	Aδ, C	Calibrated pins
Blunt pressure	Aδ, C	Algometer

Adapted, with permission, from: Hansson, P, et al. Usefulness and limitations of quantitative sensory testing: Clinical and research application in neuropathic pain states. Pain 2007;129:256-259.

Following nerve lesions, sensory thresholds may be altered without change in pain thresholds and vice versa. Consequently, all four modalities - warm detection-, heat pain-, cold detection-, and cold pain thresholds - should be assessed[44]. Sensory and pain thresholds for *static light touch* are assessed with calibrated vonFrey filaments. The filaments are calibrated according to the force required to make them bend. vonFrey filaments may also be used for detecting secondary hyperalgesia to punctate touch due to central sensitization. *Allodynia to dynamic touch*, due to peripheral or central sensitization, are typically assessed with a stroke with cotton swab or brush[48].

Sensitivity to *blunt pressure* is assessed with a pressure algometer, either hand-held or automated. Gradually increasing pressure is applied, either directly towards bony or muscular tissue or by squeezing. Similar to thermal thresholds, the subject presses a button, initiating an automated recording of pressure, when the pre-defined pain intensity is achieved[49]. Deep pressure may also be applied with a cuff[50]

Repeated stimulation of C-fibers at low frequencies (0.5-2 Hz) leads to a progressive increase in firing rate by dorsal horn neurons, first demonstrated on animals in 1966 and denoted "wind-up"[51]. This is a normal feature of the nervous system, but may become pathologically accentuated in clinical conditions characterized by central sensitization, with a sudden increase in pain, often perceived as abnormal, radiating, and with aftersensations[44,52], probably mediated via NMDA (N-methyl-D-aspartate) receptors[53]. The summation-effect of repetitive stimuli may be generated from both thermal, electrical, and pinprick stimuli, and this increased response to repetitive stimulation is often referred to as *temporal summation*[54].

The cold pressor test represents an experimental pain modality with unique features. The trial participant immerses a part of the body in cold water. Dependent on water temperature, most individuals will, following a short delay, experience a sharply rising, deep aching pain, mediated by pain receptors in veins[55,56] and often accompanied by a substantial autonomic response[57]. Assessments of threshold (time to pain), perceived pain intensity and tolerance (endurance time) can be made.

1.4 Post-surgical pain

Post-surgical pain may be of both inflammatory, visceral and neuropathic origin, or combinations of those etiologies. The entity post-surgical pain is defined by the etiology – surgery - not the mechanisms involved.

Post-surgical pain is predictable in the sense that procedures involving skin incisions inevitably will be followed by pain, unless effective post-surgical analgesic treatment is provided. Efforts to prevent, evaluate and treat post-surgical pain are made not only on humanitarian grounds. Pain delays mobilization, counteracts recovery, and represents a significant risk factor for postoperative complications like delirium, respiratory failure, myocardial ischemia, thromboembolic events, and – to be elaborated on later – persistent pain[58].

1.4.1 Persistent post-surgical pain (PPSP)

For some individuals, post-surgical pain persists beyond the expected healing time. As long as other complications do not initiate re-admissions to the surgical department, the problem may pass unrecognized by the clinicians. The potential scale of the problem was first indicated by Davies et al. in 1992, reporting that 20 % of individuals referred to pain clinics in North Britain had pain from surgery[59]. The report sparked a scientific interest in persistent post-surgical pain, not only because of the clinical impact of the problem, but because pain after surgery might serve as a model for investigating chronification of acute pain. In contrast to other painful conditions, the trauma of surgery is often standardized, planned and timed in advance, and potentially open for close investigation of the postoperative course.

1.4.2 Definition

Macrae has proposed this delineation of the term chronic post-surgical pain: 1) the pain developed after a surgical procedure; 2) the pain is of at least two months duration; 3) other causes for the pain should have been excluded; and 3) the possibility that pain is continuing from a preexisting problem must be explored and exclusion attempted[60].

The definition is not straightforward, though. Firstly, what is, and what is not a surgical procedure? Patients undergoing an endovascular procedure with recanalization of coronary arteries

may refer to the procedure as surgery, while most physicians will, according to medical tradition, organization, and the rather minor physical trauma, consider this procedure as a medical, not surgical, procedure. In cases of major endovascular procedures, like inserting an aortic graft, most physicians would probably consider the procedures as "surgery". Secondly: The limit of two months duration may appear somewhat arbitrary. Macrae argues that two months is "well past the point when acute postoperative pain would be expected to have resolved, and pain that is present at 2 months seldom resolves over the next month"[60]. Thirdly: Exclusion of other causes for the pain may be difficult, even in prospective studies. Furthermore, the definition does not include preoperative pain that may have become intensified or changed in quality by the surgery.

Several reviews indicate that 10-50% of common surgical procedures are followed by persistent pain[1,4,61-64]. Among the types of surgery most often investigated, incidences vary significantly between different procedures, with limb amputations (30-85 %) and thoracotomies (5-67 %) at the higher end of the scale and dental surgery (5-13 %) and cesarean section (12 %) at the lower[62]. As shown, within each surgical procedure, reported incidences are strikingly divergent. Obvious explanations are differences in methodology, reporting, and, not least important, definition of pain.

1.4.3 Incidence, prevalence

When reviewing the literature on PPSP, different numerical estimates are not necessarily comparable. In some studies, preoperative status has been assessed, and incidence rates of new cases may be calculated. In a lot of studies, the counts have been made by cross-sectional or retrospective studies, and figures represent point- or period-prevalence. In some studies, the surgery has been performed at different points of time, while the assessment has been performed at one specific time, and the follow-up time thereby varies between patients. Furthermore, pain is usually expected to fade gradually, with lower prevalence rates when assessments are performed longer time after surgery. However, delayed onset pain may also occur[65], resulting in higher prevalence rates with time, depending on the time (interval) of assessment. Even based on conservative estimates, the problem of

PPSP arguably constitutes a health problem due to the large number of surgical procedures performed[4].

1.4.4 Etiology

Risk factors

Most of the reports deal with the outcome of one specific surgical operation, and risk factors may be relevant for this particular condition or procedure only. Examples are the impact of axillary lymph node dissection on persistent pain following breast cancer surgery[66-69] or the use of epidural analgesia during thoracotomies [70-72]. An exhaustive review of all risk factors for PPSP lies outside the scope of this thesis. Essentially, I will restrict this section to present current evidence on risk factors with potential relevance for PPSP in general, applying to a wide spectrum of surgical procedures.

Procedure related factors

Risk factors may be divided into procedure related (surgical and anesthesiological) factors and patient factors, the latter being a function of genetic and environmental factors.

Surgical factors

In a prospective study of 625 patients undergoing a wide spectrum of elective surgical procedures in the Netherlands, Peters et al. reported that *long duration of the surgical procedure* was independently associated with increased pain, functional limitations and poor global recovery at follow-up after six months[73]. Duration may however represent a proxy for invasiveness and complexity of the surgical task.

In clinical trials, favorable outcome with regard to persistent pain is reported for *minimal invasive surgery* in inguinal hernia repair[74,75], while similar gain has not been convincingly demonstrated for endoscopic thoracotomies[76] or laparoscopic hysterectomies[77] when compared to conventional open techniques. Selection of surgical techniques with less traumatizing of tissue would be assumed to cause less inflammatory pain. However, focus on surgical techniques have also been guided by the intent of reducing the risk of nerve injury, which is believed to be a major cause for PPSP[4].

Reports of pain associated to signs and/or symptoms of *nerve injury* are numerous, including cosmetic breast augmentation[78-80], breast reduction[81], breast cancer surgery[82-84], thoracotomy[85-88], and inguinal hernia repair[75,89,90]. In breast cancer surgery, the association between axillary lymph node dissection and PPSP has repeatedly been documented[67,68], with special attention being paid to the preservation of the intercostobrachial nerve. Although preservation of the nerve has been associated with less sensory disturbances, the question of injury and persistent pain is not settled[3,66,91,92].

In limb amputations, nerve injuries are inevitable, and incidences of persistent pain are reported as high as up to 85 %[65]. Postamputation pain, however, encompasses both residual limb pain and phantom limb pain. The two pain entities seem to be highly correlated[93] and tend to appear in a predictable temporal sequence[94]. A variety of pain mechanisms are probably involved in postamputation pain, of which cortical reorganization[95] and sustained peripheral nociceptive input may play complex, interrelated roles[93].

On the other hand: Despite obvious nerve section, all amputees do not develop PPSP, and in an observational study of nerve lesions in facial surgery, pain was only reported after 5% of verified lesions to the inferior alveolar nerve[28]. Likewise, in a prospective study of 120 breast cancer surgeries with a simplified assessment of sensory loss, such loss was not significantly associated to visually verified lesions of the intercostobrachial nerve[91]. Although prevalent among individuals with PPSP, sensory disturbances are found among pain free as well[89,96]. It has even been demonstrated that perioperative nerve damage in thoracotomies, documented with electrophysiological assessments at the time of operation, was not associated with chronic pain or altered cutaneous sensation 3 months later[34].

As can be seen, the operations referred above carry in common obvious risks for nerve injury. At the same time, these are among the procedures most frequently studied in publications on PPSP. Thus, the assumption that post-surgical pain is predominantly of neuropathic origin is not necessarily generalizable to other forms of surgery. Furthermore, for these specific operations it should be noted that a pre-operative chronic pain problem is usually not the primary indication for the procedures.

Investigating outcome from these operations serves the purpose of applying models with low risk of confounding persistent post-surgical pain with comorbid pain. In general, however, pain represents an essential indication for seeking medical assistance in the first place, and surgery is often the treatment.

Anesthesiological factors

Following the first evidence of central sensitization in 1983, from animal studies[97], and following clinical trials indicating improved acute[98] and long-term[99] postoperative pain outcome with the application of potent pre-incisional analgesia, Wall proposed the concept of *preemptive analgesia* in conjunction with surgery[100]. The intention of preemptive analgesia was to block or attenuate the afferent nociceptive barrage from peripheral nerves before sensitization of the central nervous system could take place. In such way, effective preemptive analgesia was assumed to attenuate pain in a period outlasting the duration of the medication. When applicable, local and regional anesthesia appeared to be the most rational approach, by acting peripherally or at the level of the spinal cord. Despite a large amount of trials, predominantly investigating acute post-surgical pain, results have been equivocal[101,102].

In preemptive analgesia, the timing, with initiation of analgesia before incision, is crucial. However, the tendency to focus entirely on early initiation of therapy, disregarding the potential sensitization taking place in the postoperative period, driven by nociceptive input from traumatized tissue and inflammation, has been criticized [103]. It may be claimed that the narrow focus on pre-operative analgesia accounts for the lack of efficacy. Consequently, the concepts of *preventive* and *protective analgesia* have been proposed[63,101], focusing on effective anti-nociceptive and anti-hyperalgesic treatment throughout the entire perioperative period.

Even though preemptive analgesia in general has not proven efficacious in human studies, there is some evidence of reduced incidence of PPSP. The use of spinal anesthesia, which offers effective block of nociception at the spinal level, has been associated with lower prevalence of persistent pain after hysterectomia[104] and cesarian section[105], when compared to general anesthesia.

Less persistent pain has also been reported after thoracotomy and breast cancer surgery when regional anesthesia has been applied as an adjunct to general anesthesia[72].

Recently, a systematic report from the Cochrane collaboration reviewed systemic pharmacological interventions for the prevention of PPSP. The meta-analysis suggested a modest, but statistically significant reduction in the incidence of PPSP following treatment with the NMDA (N-methyl-D-aspartate) receptor antagonist ketamine [106].

Patient factors

Sex

There is a tendency, although not consistent, towards more acute pain among women than men shortly after surgery and other invasive procedures[41]. However, unequivocal evidence for a systematic sex difference in the incidence of persistent post-surgical pain after identical surgery is lacking[41,73,74,107,108].

Age

Association between increased age and reduced risk for PPSP is reported from thoracic surgery[34], breast cancer surgery[109,110], and inguinal hernia repair[111].

Pain sensitivity

Most studies of associations between pain sensitivity and surgical pain have focused on acute post-surgical pain, but some have linked risk of PPSP to increased sensitivity to experimental pain measures. In general, results have been conflicting, although a review in 2010 estimated that 4-45 % (median 28 %) of variability in acute and persistent post-surgical pain may be explained by preoperative differences in sensitivity to experimentally induced pain[40,112].

It has been suggested that individual differences in pain sensitivity may influence the risk of chronification of post-surgical pain[75,113], or – conversely - that pain sensitivity may itself be influenced by changes in pain processing as a consequence of acute and persistent pain[9,100]. The two explanations are not mutually exclusive [114].

Psychological factors

A variety of psychological factors have been investigated, some related to personality or traits, others representing factors more liable to change over time and situations. *Anxiety* and *depression*[115,116], *fear of surgery* [73], *psychic vulnerability* [117] and *catastrophizing* [73] have been shown to be associated with established PPSP. Fear of surgery and psychic vulnerability have also been identified as predictive for PPSP when assessed preoperatively, and pre-operative *optimism* may be indicative of a favourable outcome[73].

Pain itself

The most prominent risk factor for pain is pain itself [63]. A strong association between the severity of *pain in the immediate postoperative period* and later development of PPSP is a consistent finding across a variety of different studies[73,79,118-120]. It is not settled whether this is a purely associative or causal relationship. Sensitization as a result of intense and prolonged pain and inflammation in the postoperative period may enhance the risk of persistent pain. The two may also share etiological factors predisposing for both acute and persistent pain.

Pre-existing pain, both in the form of preoperative local pain in the area of surgery[75,119] and remote pain, unrelated to the actual surgery[112,119,121-123] are associated to PPSP. These findings are compatible with assumptions of shared etiology and/or sensitization from persistent pain.

If acute post-surgical pain contributes to pain chronification, it offers the hope that improved perioperative pain treatment could possible reduce the incidence of PPSP. In a clinical trial with older orthopaedic patients, the potential gain of such preventive analgesia was demonstrated[124]. The intervention incorporated intensified pain assessments and treatment throughout the entire postoperative and rehabilitation period, including preemptive analgesia before physical therapy, with significantly reduced pain and improved functional outcomes in the intervention group. A recent trial concluded that acute pain management with follow-up continuing after hospital discharge could be more important than the specific analgesic method per se in preventing persistent post-thoracotomy pain[125].

2 AIMS OF THE THESIS

The thesis aimed to answer these major questions:

1. What is the prevalence of persistent post-surgical pain in a general population?
2. Which are the possible risk factors associated with persistent post-surgical pain?

Specific aims:

Prevalence

1. Estimate the prevalence of persistent post-surgical pain in a general population (Paper I)
2. Assess changes in persistent post-surgical pain over time (Paper III)

Risk factors

3. Identify demographic, psychological, and somatic factors associated with persistent post-surgical pain (Paper I)
4. Explore the relationship between persistent post-surgical pain and comorbid pain (Paper II)
5. Investigate the associations between persistent post-surgical pain, persistent pain from other causes and pain sensitivity (Paper II)
6. Assess associations between persistent post-surgical pain and self-reported symptoms of nerve injury (Paper I and III)
7. Assess associations between persistent post-surgical pain and signs of nerve injury identified with quantitative sensory testing (Paper III)
8. Estimate the proportion of subjects with persistent post-surgical pain which can be categorized as having neuropathic pain (Paper III)

3 MATERIAL AND METHODS

3.1 The 6th Tromsø study, 2007-2008

The Tromsø study is a prospective series of cross-sectional surveys and medical examinations, performed from 1974 up to now. At the outset, it was initiated as a response to high cardiovascular morbidity and mortality in North Norway, aiming to identify risk factors and means for prevention. It has later been expanded to cover osteoporosis, hormonal-, ophthalmologic-, respiratory-, occupational-, psychiatric-, and skin diseases, cognitive functioning and, in the 6th study, pain[126].

3.1.1 Sample

Tromsø 6 took place in 2007-2008, with 12,984 out of 19,762 invited individuals attending. Data in this thesis is based on 12,982 participants, due to withdrawal of consent from two individuals. The sample was recruited from four different groups, all with postal address in the municipality of Tromsø:

1. All previous attendants in phase 2 of a previous Tromsø Study (Tromsø 4, 1994-1995)
2. A 10% random sample of individuals 30-39 years old
3. All inhabitants 40-42 years and 60-87 years old
4. A 40 % random sample of inhabitants 43-59 years of age

Women constituted 53.4 % of the attendants, and 51.3 % of the invited. An overview over the recruitment procedures, response rates and sample composition has been published previously[127].

3.1.2 Questionnaires

Pain

All participants completed two questionnaires[128]. The first, four-page questionnaire (Q1) was distributed together with the invitation and completed before attending the examination. A second,

more comprehensive questionnaire (Q2) was either filled in during the visit or completed later at home and returned by mail.

Q1 included questions regarding general health, presence of diseases, familial diseases, muscular pain, emotional problems, lifestyle factors, education, medication, and consumption of health care. In this questionnaire, the participants were asked if they had undergone surgery during the last three years preceding the survey. Those who responded positively to this question were asked to complete follow-up questions in Q2, covering time of surgery, anatomical area of surgery and present sensory disturbances in close vicinity to the surgical scar. They were asked to rate the maximum pain intensity in the area of surgery with an 11-point numerical rating scale (NRS 0-10). The questionnaire also included NRS ratings of usual pain in the area of surgery, yes/no questions regarding presence of preoperative pain, and whether the present pain was similar to the preoperative pain or not. Individuals who had gone through more than one surgical procedure, were instructed to answer the questions with referral to the last operation performed. Site of surgery was reported by ticking one of 20 alternatives: head/face, neck/throat, back, heart, lungs, breasts, other surgery in the chest region, stomach/intestines, inguinal hernia, urinary tract/reproductive organs, gall bladder/biliary tract, other operation in the abdomen/genitals, hip/thigh, knee/lower leg, ankle/foot, amputation (leg), shoulder/upper arm, elbow/lower arm, hand, or amputation (arm, hand).

The answers on the questionnaire on surgery formed basis for the analyses presented in Paper I, Paper II, and the selection of participants for the follow-up study (Paper III).

Included in Q1 was a question of "constant or recurring pain with a duration of three months or more"[128]. It served as a question of entry for a separate section of Q2 covering chronic pain of any type. Responses to questions in this section formed basis for the main analyses in Paper II and were included as covariates in the analyses in Paper I and III.

Education

Education was used as a proxy for socioeconomic status, assessed with a 5-point ordinal scale: 1 = primary/secondary school, modern secondary school; 2 = technical school, vocational school, 1-2

year senior high school; 3 = high school diploma; 4 = college/university less than 4 years; 5 = college/university 4 years or more.

Body mass index (BMI)

BMI was calculated as weight in kilograms divided on square of height in meters (kg/m^2).

Diabetes

Blood samples were drawn from all participants in Tromsø 6, and diabetes mellitus defined as glycated haemoglobin c (HbA1c) greater than 6.5 %[129].

Hypoesthesia and hyperesthesia

The section in Q2 covering surgery included three categorical variables regarding sensory function: 1) "Do you have reduced sensitivity in an area near the surgical scar?"; 2) "Are you hypersensitive to touch, heat or cold in an area near the surgical scar?"; and 3) Does slight touch from clothes, showering or similar cause discomfort/pain?" Individuals responding "yes" to the first question were categorized as having hypoesthesia, while individuals responding positively to the second and/or third question were categorized as having hyperesthesia.

Psychological distress

Psychological distress, a compound variable containing items of both anxiety and depression, was assessed with the Norwegian version of Hopkins Symptom Checklist – 10 item version (HSCL-10), generating a continuous variable with values ranging from 1.00 to 4.00. In Paper I, the resulting variable was dichotomized with values exceeding 1.85 categorized as distress[130]. In Paper III, the continuous variable was applied. For individuals with 1 or 2 missing answers out of the 10 questions constituting the score, missing values were imputed with the mean score from the whole Tromsø 6 sample, in Paper III stratified on sex and age. When more than 2 answers were missing, the whole score was set to missing.

Hypertension

Hypertension was defined as either present systolic blood pressure $\geq$ 140 mm or diastolic blood pressure $\geq$ 90 mm Hg or present antihypertensive medication[131].

Painkillers

Use of painkillers, defined as intake of prescription analgesics at least once during the last four weeks, was included in the presentation in Paper I, based on questions from Q1. In the follow-up study, all participants were asked whether they had taken any analgesic medication within the past 24 hours (Paper III).

3.1.3 Assessments of pain sensitivity

The intended sample included all subjects participating in the 6th Tromsø Study (N = 12,982). However, due to capacity limitations during peak hours, technical problems or technicians' sick leave, some subjects were not examined. In these cases the technicians were asked to prioritize subjects < 60 years old, due to the lower sampling rate for these age cohorts. (Sampling rate was 100% for cohorts 60 years and up). No other criterion for skipping subjects was used.

After a short description of the testing procedure, subjects underwent a brief screening. The purpose of this screening was to exclude subjects who were unwilling to undergo testing, might have negative side-effects from the cold pressor test, or had medical problems that would lead to invalid results.

During testing, the subjects were placed in a comfortable chair, facing a poster with a horizontally oriented 11-point NRS. The participants first underwent assessment of either pressure pain sensitivity (N = 4,689) or heat pain threshold (N = 4,054), and afterwards the cold pressor test (N = 10,486), as described below. During the first 9 months of the study, pressure pain and cold pressor pain was assessed, and during the last 5 months heat pain and cold pressor pain.

Pressure pain

Pressure pain threshold was tested using a hand-held pressure algometer with circular probe of 1 cm^2. Pressure was applied to the cuticle of the fingernail of the ring finger on the non-dominant hand with pressure increasing by 30 kPa/s. The subjects were told to press a button when the pain intensity reached 5 on the 0-10 NRS. An upper safety limit of 800 kPa was set. Three measurements were made, and the threshold was calculated as the arithmetic mean of the second and third measurement.

Heat pain

Heat-pain threshold was tested using a somatosensory stimulator with a 30 x 30 mm Advanced thermal stimulator thermode. Stimuli were applied to the volar surface of the non-dominant forearm. Stimulation started from a baseline temperature of 32.0 °C and increased by 1°C/s. Subjects were instructed to press a button when the sensation changed from warmth to pain. Upon pressing the button, the temperature was registered, and the thermode temperature returned to baseline at a rate of 8 °C/s. An upper safety limit was set at 50.0 °C. The procedure was repeated 3 times for each subject. Threshold was calculated as the arithmetic mean of the second and third measurements.

Cold pressor pain

The cold pressor test (CPT) was performed by having the subjects submerge their dominant hand and wrist in circulating cold water and hold it there as long as they were able to, up to a maximum of 106 seconds. Endurance time was recorded. A precision thermometer calibrated the water temperature to 3.0 °C. During the stimulus, the subjects rated their pain intensity on the NRS. The first rating was obtained after 4 seconds followed by ratings every 9 seconds thereafter until the hand was withdrawn. Cold pressor tolerance was assessed as time endured with the hand submerged in cold water.

The manual behaviour of withdrawing the hand from the cold stimulus encompasses motivational aspects in addition to pain sensitivity alone. We therefore attempted to assess both perceived intensity (repeated ratings of pain intensity) and tolerance (time endured under cold stimulation). There is no established single measure for repeated pain intensity over time in the cold pressor test. Area under curve could easily be calculated, but would become negative biased for individuals with low endurance time. This could be solved by setting missing ratings after hand withdrawal to 10 (maximum). This however, may not accurately reflect pain intensity, as some subjects aborted the test while reporting relatively low pain intensities. As the best possible method for calculating an overall pain intensity, we decided upon computing a standardized overall pain intensity score (z-score), as described in detail in Paper II. Cold pressor tolerance data were analysed with survival statistics and reported as cox proportional hazard ratio (HR) as the outcome.

3.2 The follow-up study 2010

3.2.1 Power analysis

Before the follow-up study, a calculation of statistical power was performed: Power analysis indicated, with group sizes of N = 60 of pain and pain-free individuals respectively, an 80 % probability ($1 - \beta = 0.8$) of detecting a difference of 30 % vs.10 % in the prevalence of signs of nerve injury with < 5 % risk of detecting a false positive difference ($\alpha = 0.05$)[132].

3.2.2 Sample

A cohort of 1,217 participants reporting no pain (NRS = 0) and 498 individuals reporting pain in the surgical area, (NRS $\geq$ 3 at maximum), representing all anatomical areas of surgery, were classified eligible. Participants were invited by posting written invitations in the following sequence: 1) knee/leg and hand, 2) stomach/intestines and other abdominal, 3) ankle/foot, breasts and heart. Within each surgical group, individuals were invited by posting written invitations in randomized order. Randomization was performed manually, applying a table of random digits, and stratified by surgical location, in order to optimize sample size in each of the categories: soft tissue surgery and orthopaedic/extremity surgery, the latter indicated by our previous study (Paper I) to be prone to persistent pain[133]. Non-responders received one written reminder. The invitations were posted March 11th - June 1th and the examinations performed March 12th - July 9th 2010. Due to time constraints, and the need to utilize available laboratory capacity, some participants were additionally contacted by telephone, some of them the same day as invitations were posted.

3.2.3 Investigation

All assessments were performed by the same investigator (AJ) alone. Before examination, all participants went through a short semi-structured interview, aimed at confirming the questionnaire information from Tromsø 6 that was the basis for selections: type of surgery, time of surgery, later surgical procedures, comorbid pain and other health conditions, and analgesic medication. Written consent to the study was collected.

Questionnaires

In conjunction with the clinical examination, the participants filled in a questionnaire with ratings of the normal and the maximum pain intensity, at present, in the area of surgery, applying an 11-point NRS, and report of any present sensory disturbances in close vicinity to the surgical scar. The questions and response alternatives were identical to those applied in Tromsø 6, Q2. The participants also filled in Norwegian versions of the Brief Pain Inventory (BPI)[134], and Neuropathic Pain Symptom Inventory (NPSI)[24] with an explicit instruction to focus on pain in the surgical area. Finally, Norwegian questionnaires of psychological distress (10-item Hopkins Symptom Checklist, HSCL-10)[130] and pain catastrophizing (Pain Catastrophizing Scale, PCS)[135,136] were filled in after the clinical examination.

Quantitative sensory testing

Sensory abnormalities were identified by comparing QST-assessments made at the site of surgery (index site) with assessments at a reference site. When possible, a contralateral mirror area was selected for reference unless the surgery was performed in the midline of the body or contralateral surgery had been performed. In such cases, an individual evaluation was performed, and a test area near the area of surgery, judged on anatomical basis as unaffected by the operation, was selected for reference.

Orientational examination and definition of anatomical areas for testing

The area of surgery and a neutral, preferably contralateral, area was examined by warm (40.0 ^{o}C) and cold (20.0 ^{o}C) metal rolls, a cotton wad, and pinprick stimulation. The reference area (area 1) was investigated first. In the area of surgery, the orientational examination aimed at identifying both areas with attenuated and increased sensitivity (area 2 and area 3, respectively). If no signs of sensory aberrations were identified, one or two sites with neurological-anatomical relevant relation to the surgical intervention were defined, preferably one site distal to the surgical scar (area 2) and one more proximal (area 3). Area 1, 2 and 3 were defined by pen-marking the skin, by written anatomical descriptions and photo documentation. When two sites in the surgical area were defined,

one area was eventually selected as index area, based on presence of signs of sensory abnormalities on the orientational examination and on anatomical location.

Sequence of assessments

Within the predefined sites, assessments were made in the following sequence: Cold and warm detection thresholds, cold and heat pain thresholds, mechanical detection thresholds, mechanical pain thresholds, temporal summation of pinprick pain, and dynamic tactile allodynia. All assessments were first performed at the reference site, then at the index site(s).

Thermal thresholds

Cold and warm detection thresholds were assessed with the same equipment as in Tromsø 6, a baseline temperature of 32.0 ^{o}C and a ramp of 1.0 ^{o}C/sec. The participants pressed a button when the first sensation of cold and warm, respectively, were felt, and the thermode immediately returned to baseline before automatically initiating a new cold or heat sensation. First three consecutive cold stimulations were made, followed by three warm stimulations. Cold and heat pain thresholds were assessed with the same sequence, equipment, baseline and ramp, but faster return of temperature from threshold to baseline (8.0 ^{o}C/sec). All thermal thresholds were calculated as the arithmetically mean of the last two of three consecutive stimulations, which were all automatically recorded.

Mechanical thresholds

Mechanical detection and pain thresholds were assessed with vonFrey filaments 0.25-512 mN, applying a modified version of the method of limits presented by Rolke et al.[137]. For detection threshold, a logarithmically weighted ascending series of stimuli starting with 0.25 mN, 0.50 mN, 1.00 mN, and so forth was performed until the participant reported sensation of touch. The stimulus that generated sensation was recorded before descending stimuli intensities were applied until the participant reported no sensation. The first stimulus without sensation was recorded, and a new ascending series was started. The final threshold was defined as the geometrical mean of three ascending and descending series of stimuli. For mechanical pain threshold, the same procedure was applied, and the participant was asked to report whether the sensation was “touch” or “stinging”.

Temporal summation of pinprick pain

A 256 mN vonFrey filament was used for assessment of temporal summation. First, a single touch of the marked area was performed, and the participant was asked to rate the sensation on a 0-10 NRS. Next, a series of 20 touches were performed with a frequency of 2 touches per second. At the termination of the series, the participant was again asked to rate the sensation on the 0-10 NRS. Temporal summation ratio is reported as the ratio between the second rating and first rating. The value 0.1 was added to all NRS-assessments, to allow calculation of ratios even when the denominator (first assessment) was zero[48].

Dynamic allodynia

In all three areas, dynamic allodynia was assessed by two light strokes with a brush and with a cotton wad. The participants were asked to grade any pain on a 0-10 NRS. Results are reported as a dichotomous variable with all NRS-values $\geq$ 1 reported as presence of allodynia.

Pressure pain thresholds

Pressure pain thresholds were assessed with the same hand-held pressure algometer as in Tromsø 6, with circular probe of 1 cm^2. Pressure was applied in two areas remote from the surgical site: 1) just beneath the right occipital protuberantia and 2) the right upper trapezius muscle, with pressure increasing by 30 kPa/s. The subjects were told to press a button when they experienced pain. An upper safety limit of 1000 kPa was set. The pressure pain thresholds were defined for each area as the arithmetic mean of the last two out of three consecutive assessments.

Cold pressor test

For the cold pressor test, the same equipment and the same procedure as in Tromsø 6 was applied: The subjects were instructed to submerge their dominant hand and wrist in circulating 3.0 ^oC water and hold it there as long as they were able to, up to a maximum of 106 seconds. Endurance time was recorded.

Exclusions before analysis

Surgery

For our purpose, we defined "surgery" as a therapeutic intervention encompassing 1) a penetration of the skin barrier, and 2) instrumentation outside natural cavities and tubes. Consequently, if the interview at the beginning of the session revealed that the reported procedure was an endoscopy of the alimentary tract, a percutaneous intervention on coronary arteries or percutaneous implantation of stent-grapht of blood vessel, the participant was excluded from the study (Paper III, Fig. 1: "Exclusions 1"). Laparoscopies and arthroscopies were included.

Applicability of QST

In cases where the location of surgery was incompatible with QST, like vaginal or rectal surgery, only interview, collection of questionnaire data, and assessment of pressure pain thresholds and cold pressor test was performed.

For individuals where the areas available for QST were smaller than the area of the thermode (30 x 30 mm), the surgical procedure was defined as too small for QST-assessments, and QST was not performed (Paper III, Fig. 1: "Exclusions 2").

If comorbidity, prior injury, or surgery was judged likely to interfere with sensory testing, QST was either not performed, or collected data were later excluded from analysis.

Reoperations

The selection of the cohort for follow-up was based on questionnaire data on prior surgery and present pain at the time of the Tromsø 6 survey. For some of the participants, repeated surgery or new surgical procedures had taken place between the survey and the follow-up. If new procedure(s) affected the original surgical area or corresponding control area, the individuals were excluded from analysis (Paper III, Fig. 1: " Exclusions 3").

3.3 Statistics

NRS ratings of pain were either presented as numbers ranging from 0 to 10 or classified into four severity levels; no pain (NRS = 0), mild pain (NRS 1 to 3), moderate pain (NRS 4 to 6), and severe pain (NRS 7 to 10).

Statistical analyses were performed with cross tables applying Chi^2 for categorical variables, two-tailed t-tests and analysis of variance (ANOVA) for comparisons of means, Wilcoxons rank sum test and linear regression for comparison of ordinal data, Spearmans correlation coefficient (*rho*) for correlation analysis of ordinal data, and logistic regression for assessments of associations between pain and independent variables. Backward elimination was performed in multiple logistic regression analysis. Results from logistic regression analyses are reported in odds ratios (OR) with 95% confidence intervals.

3.3.1 Survival analysis (Paper II and III)

Individuals who endured either the entire cold pressor test period of 106 seconds, 50.0 ^{o}C heat, or 800 kPa pressure without aborting the respective stimuli, did all reach one or more test maxima. Hence, both cold pressor tolerance and heat and pressure pain thresholds are right-censored data. Both heat and pressure stimuli increased as a linear function of time. Thus, all cold pressor tolerance data, and, in Paper II, heat- and pressure pain data, were analysed with survival statistics, applying a cox proportional hazard model: Endurance time, or time until threshold, were entered as survival time. If maximal time or maximal stimulus intensity was reached, data was defined as censored (0). If the participant aborted the stimulus before maximal time/intensity, data was defined as failure (1). Results are reported as hazard ratios (HR) with 95% confidence intervals (CI). The HR indicates the proportional hazard, at any time point during the test, to abort the pain stimulus, compared to the reference group. Thus, an HR above 1 indicates higher proportional hazard, i.e. lower tolerance/higher sensitivity, while an HR less than 1 indicates higher tolerance/lower sensitivity.

3.3.2 Analysis of QST-data (Paper III)

Group data

Thermal thresholds were defined as differences (^{o}C) from baseline (32.0 ^{o}C), and assessed as positive, continuous variables for both cold and pain stimuli. In accordance with the methodology of the German Research Network on Neuropathic Pain (DFNS)[137], inequalities between assessments at surgical sites and reference sites were calculated as ratios (index site / reference site) with the exception of thermal pain thresholds, which were calculated as differences (index site – reference site).

Dichotomized (categorical) data

QST-data for each sensory test were dichotomized into normal/abnormal, applying reference values from DFNS[137]: For cold, warm and tactile detection, high thresholds were defined by ratios (index site / reference site) > 2.42, 2.39 and 2.62, respectively. For cold and heat pain, low thresholds were defined by differences (index site – reference site) of < - 10.3 ^{o}C and – 4.2 ^{o}C, respectively. Low tactile pain thresholds were defined by ratios < 1/0.53 and increased temporal summation by ratios > 1.94. Allodynia was defined as presence of pain and analyzed as a categorical variable (pain/no pain).

All pain in the surgical area were assessed as possible neuropathic pain. Probable neuropathic pain was defined as pain with one or more abnormal QST-assessments.

Parametric properties

Judgements of parametric properties of data were made with Shapiro-Wilk tests. Data distributions were considered non-parametric if the test showed $P < 0.05$. No threshold values were normally distributed as raw data. Thermal and mechanical detection thresholds in reference areas were normally distributed after log-transformation, while the index/reference ratios were normally distributed only for warm detection. Log-transformed pain thresholds in the reference area were normally distributed for tactile, but not for thermal stimuli. Temporal summation was not normally distributed neither before nor or after log-transformation. As most of the variables were not normally distributed, and for those that were, parametric methods produced equivalent results, we present all

data analyses with non-parametric methods for the sake of clarity. Data were compared with Wilcoxons rank-sum test and are reported as medians with ranges and interquartile ranges (IQR).

3.3.3 Level of statistical significance

For all analyses, statistical significance was defined as a *P*-value < 0.05.

3.3.4 Software

All data analyses were performed with STATA 12 (Paper I and II) or STATA 13 (Paper III) Statistical Data Analysis® statistical program (StataCorp, Texas, USA).

3.4 Approvals and consent

The Regional Ethics Committee and the Norwegian Social Sciences Data Services approved the study protocol. Written consent was obtained from the participants before entering Tromsø 6. The invitation letter for the follow-up study described the background and motivation for the study, the nature and duration of the session, and the economic compensation for travel expenditures, a present card worth NOK 200. The recipients were asked to sign a consent if they wanted to participate.

4 MAIN RESULTS

4.1 Prevalence of persistent post-surgical pain (Paper I)

Of the 2,043 individuals who had gone through surgery during the last 3-36 months prior to the survey and reported data on surgery, pain and sensory disturbances, 40.4 % (826 individuals) reported some degree of persistent pain (NRS $\geq$ 1), and 18.3 % (N = 373) reported moderate to severe persistent pain (NRS $\geq$ 4) in the area of surgery. Among those with moderate to severe pain, 57.4 % (N = 214) described the pain as different from any pre-operative pain. However, only 51 % (N = 421) of the individuals who reported persistent pain (NRS $\geq$ 1) did report chronic pain when asked without specific reference to the surgery.

4.2 Changes in persistent post-surgical pain over time (Paper III)

Persistent post-surgical pain is not necessarily a stable state. Over time, substantial bi-directional changes in pain intensity appeared in a significant proportion of the participants.

4.3 Demographic, psychological and somatic factors associated to persistent post-surgical pain (Paper I)

There were strong associations between persistent post-surgical pain and psychological distress. Persistent post-surgical pain was not associated with gender, hypertension or diabetes. In adjusted analysis, there were no associations with age or time from surgery (3-36 months). There was a statistically significant positive association between body mass index and persistent post-surgical pain, but the modest effect size did not indicate clinical relevance.

4.4 Persistent post-surgical pain and comorbid pain (Paper II)

Among subjects who indicated surgery as a supposed cause for their chronic pain (6.2 %, N = 208), the vast majority also reported other comorbid pain. Persistent pain in the area of surgery was more prevalent, and the intensity of pain was higher among individuals with comorbid chronic pain than individuals without ($P < 0.0001$).

4.5 Associations between persistent post-surgical pain and sensitivity to experimental pain stimuli (Paper II)

In overall analysis, chronic pain from other causes than surgery was associated with lower cold pressor pain tolerance, while the presence of persistent post-surgical pain was not, when comorbid chronic pain was adjusted for. Mean cold pressor pain intensity (mean of standardized scores), pressure pain threshold, and heat pain threshold were not associated with persistent post-surgical pain.

4.6 Associations between persistent post-surgical pain and symptoms of nerve injury (Paper I and III)

Strong associations between pain, pain intensity and self-reported sensory disturbances indicate neuropathy as a likely contributor to pain in a major proportion of cases (Paper I and III). Odds ratios were 2.68 (95 % CI 1.05 to 3.50) for hypoesthesia and 6.27 (95 % CI 4.43 to 8.86) for hyperesthesia (Paper I).

4.7 Nerve dysfunction (Paper III)

Sensory disturbances were present in a majority of cases, equally prevalent among individuals with and without persistent post-surgical pain. In addition, there was little correlation between subjective symptoms- and corresponding signs- of nerve dysfunction.

4.8 Neuropathic pain (Paper III)

Among 39 individuals with persistent pain in the operated area 21-64 months after surgery, 61 % (N = 26) had signs of nerve dysfunction indicating probable neuropathic pain, when applying the grading system proposed by Treede et al. in 2008[30].

5 DISCUSSION

5.1 Methodological discussion

5.1.1 Sample, selection, representativeness

Whole sample

In Tromsø 6, invitations were submitted to 19,762 inhabitants of the municipality of Tromsø. Of these, 12,982 individuals attended, yielding a response rate of 65.7 %, which is high for being a population-based survey and medical examination[138]. Non-attendees tended to be younger, and the proportion of men and individuals with marital status as single was higher than among attendees[126]. Invited age cohorts in Tromsø 6 (see materials and methods section) were favourable in terms of sampling individuals who had experienced surgery during the preceding years. Altogether, we consider that making generalisations from the sample are justified.

Surgical sample

All participants in Tromsø 6 were asked "Have you during the past 3 years undergone surgery?". If responding "yes", participants were requested to fill in a more detailed paragraph in questionnaire 2. There was no specification of the term "surgery". According to Oxford advanced learner's dictionary, surgery is "medical treatment of injuries or diseases that involves cutting open a person's body and often removing or replacing some parts"[139]. This definition is not exhaustive, as e.g. cosmetic surgery and diagnostic tissue biopsies are not comprised. As long as ambiguity persists, respondents may have had different interpretations of whether i.e. dental extractions, endoscopies or percutaneous intravascular interventions were to be covered by the question. This became evident in the follow-up study (Paper III), as 5 out of 14 individuals recruited after "heart surgery" had gone through revascularisations of coronary arteries by a non-surgical, catheter-based procedure, and consequently had to be excluded from QST-assessments. The questionnaire section referring to surgery encompassed 9 questions with one or more response options. Some participants may have undergone several surgical procedures during the past 3 years. The internal validity of these data relies

upon the participants' adherence to the instruction of referring to the most recent procedure when filling in the questionnaire.

Chronic pain sample

Estimates of chronic pain prevalence vary considerably between different reports and populations. Most likely, this is mainly due to lack of uniform pain definitions[140]. The question of entry for the chronic pain section in the Tromsø 6 questionnaire read "Do you have persistent or constantly recurring pain that has lasted for 3 months or longer?" Although the term "constantly recurring", leaves some room for different interpretations in cases of intermittent pain, the wording is, in our judgement, largely unequivocal. The proportion reporting persistent pain (32.7 %) is in line with other reports of chronic pain prevalence in Norway[141-143]. We consider both internal and external validity to be satisfying.

Comparison and combinations of data from surgical sample and chronic pain sample

In order to define a surgical sample, we specifically asked for surgery "during the past 3 years". The time frame was intended to reduce error due to inaccurate recall. This limit, however, excluded possible cases of persistent pain with longer duration. In Paper II, we compared numbers on PPSP based on self- report of chronic pain (no time limitation) and surgery last 3 years, respectively, as entry questions.

The follow-up study

Selection

Selection for the follow-up study (Paper III) was based on responses on the surgical questions in the Tromsø 6 questionnaire. The NRS ratings of pain in the surgical area, at maximum, were applied. The primary aim of the study was to compare individuals with and without persistent pain with regard to signs of nerve lesions. To reduce surgical heterogeneity in the patient sample, we intended to recruit participants from only a few surgical categories, including both orthopaedic surgery and soft tissue surgery. Intuitively, when selecting individuals with pain, applying a relatively high cut-off point for pain intensity would accentuate contrasts between the groups with and without pain,

highlighting potential differences. Our desire to do so had to be balanced against the need for a sufficient number of participants in the pain group. Raising the pain intensity limit would inevitably reduce the number of eligible individuals with pain. A pragmatic choice was made, by including individuals with NRS 3 or higher and contrasting those to individuals with no pain (NRS = 0). It could be argued that this level of pain intensity was too low to identify individuals with pain with sufficient clinical impact.

Data collection in Tromsø 6 was performed in 2007-2008. The follow-up study was performed in spring and summer 2010, which was as early as possible after data from Tromsø 6 had been made available. Median time from Tromsø 6 attendance to invitation to follow-up was 23 months (range 16-30 months). Pain ratings were considerably changed at follow up: Some individuals who were pain-free in Tromsø 6 reported pain at follow-up, and among individuals with pain in Tromsø 6, bidirectional drift in pain ratings had occurred. Analysis of associations between pain, self-reported sensory aberrations and QST-data were performed based on the current status at follow-up.

Intially, when designing the follow-up study, we planned to ask all possible eligible participants for written consent to read the parts of their medical records related to the specific surgery reported in the Tromsø 6-questionnaire. This approach was approved by the local ethics committee, and would, if we had followed this procedure, allowed a more specific selection of patients to the clinical investigation. But, later on, we found that there were at least three important arguments opposing this approach:

1. We would have to ask approximately 1,600 individuals for permission to read their medical records. The administrative and economical costs related to this work would have been substantial, and very many individuals would have to consider whether they should give researchers, with whom they had had no relationship, access to this sensitive material or not. Some might find the request troublesome, and many might refuse or simply not respond. Even if only 40-50% of the individuals would eventually give their consent, the workload of reading through the journals would become heavy and time-consuming.

2. The selection of participants for the clinical investigation was supposed to follow the screening of the journals. If a large proportion turned out not to give consent to read the medical records, the sample eligible for clinical testing would become decimated proportionally, possibly hampering our efforts to adequately size the study.
3. The reading of a very high number of medical records would expose sensitive information of more individuals than necessary, and should be avoided if possible.

We decided to change the design of the inclusion process: We would send invitations to samples selected exclusively on basis of questionnaire data from Tromsø 6, compensating for possible misclassifications by slightly sizing up the number of participants. The request to read the medical record, if necessary, would be presented at the end of the clinical investigation session. The local ethics committee approved our change of design and our revised written consent letter.

Invitations were posted stepwise, to include as many individuals as possible within each category. To reach the desired number of participants, new categories had to be added. Invitations started with “knee, leg”, and was followed by “hand”, “stomach, intestines”, “other abdominal”, “ankle, foot”, “breasts” and “heart”.

The total number of 53 individuals who had to be excluded was higher than expected, and must be seen as a consequence of our revised inclusion strategy: Five individuals had to be excluded because new surgery had been performed between assessments. Other reasons for exclusions were no real surgery (N = 11), surgical area not suited for QST (N = 7), surgical area too small for QST (N = 14), comorbidity, prior injury or surgery likely to interfere with sensory testing (9), and inappropriate reference area (1). In addition, 3 individuals were excluded due to poor cooperation (3) and other reasons (3).

Representativeness of responders

When comparing invited non-responders and responders (including individuals excluded after showing up on the follow-up study), there were no statistical significant differences with regard to sex, age, chronic pain from all causes, intensity of PPSP in Tromsø 6, psychological distress, or time from

surgery, although there were non-significant trends towards higher proportion of men, older age, and slightly shorter time from surgery among participants.

Overall, sample and selection

To reach the desired number of participants, a low cut-off for pain intensity had to be applied, possibly including participants with less severe post-surgical pain. A more heterogeneous sample than originally planned also had to be accepted. Furthermore, as a consequence of our revised sampling strategy, a relatively high number of participants had to be excluded, attenuating statistical power. This said, invitations were posted in randomized order, and analysis of responders vs. non-responders did not indicate systematic bias in the inclusion process.

5.1.2 Questionnaire data

Definition of persistent post-surgical pain

In Paper I, describing prevalence and impact of PPSP, and in Paper III, dealing with pain and signs of nerve lesions, NRS ratings of current pain in the surgical area were applied as definition of PPSP. In Paper II, the individuals' own report of "persistent pain" and presumed cause for the pain was applied. Analyses based on the two different definitions were compared.

The concept of PPSP implies an assumption of causation: The pain is caused-, or enhanced-, by surgery. The definition of PPSP proposed by MacRae demands that exclusion of the possibility that the pain represents a prolongation of pre-operative pain state should be attempted[60,64]. In a cross sectional study, the opportunities of doing so are limited. Per definition, single cross sectional studies can only demonstrate associations, not causation. As will be discussed later, pre-surgical local pain and comorbid pain has to be taken into account when analyzing PPSP in representative samples.

Pain defined as NRS

Applying NRS for defining pain has the advantage of both including low intensity pain and differentiating between individuals with varying levels of pain severity. In addition, graded scales are superior to dichotomous categorical variables for analyzing effect sizes. One-dimensional scales, however, have limitations in assessing the multidimensional experience of pain. This will be

elaborated on later. Rating pain at rest (spontaneous pain) and pain at movement (evoked pain) would have complemented the picture. Constraints on questionnaire volume however, restricted our questions to a very few, including pain at normal and pain at maximum.

Pain defined as "pain"

Pain defined solely by a number between 1 and 10 may not equal clinical meaningful pain, even when the "NRS-bar" is raised from 1 to 4. The ability of rating pain intensity on a numerical scale largely rests on the individual's ability to communicate the sensory-discriminatory dimension of pain. However, nociceptive sensations may present without unpleasantness, nor may they be perceived as a threat. Price argues that such sensations do not represent pain (Price, p. 6-8)[144], although they may be assessed above zero on a numerical rating scale. Flor and Turk distinguish between pain measurement (ratings) and comprehensive pain assessment, claiming that chronic pain needs comprehensive analysis of both pain and the impact of pain on the patient's life, encompassing assessment of pain and pain-related variables on behavior on both subjective (psychological), motor and organic (physiological) levels (Flor and Turk, pp. 139-175)[15]. Such assessments may help delineate pain with clinical relevance from nociceptive sensations and trivial pain. Ideally, one should aim for a more specific diagnosis of pain, applying more elaborate diagnostic tools like the Brief Pain Inventory (BPI)[134] and McGill Pain Questionnaire[145]. However, this was not applicable in our setting with a large multi-disciplinary survey.

Because pain per definition is a subjective experience, applying pain assessment tools always encompass some sort of decomposing of pain and/or weighing of pain dimensions. Alternatively, one may simply ask the person in question whether she has pain or not, as "pain", although unspecific, is intuitively understood by everyone. In paper II, where data on PPSP and comorbid persistent pain was integrated, self-report of "persistent pain", was the question of entry for the elaborate questionnaire section, intended to capture clinical meaningful pain. The question was answered by "yes" or "no" by 99.7% of the participants.

PPSP defined as individuals' own attribution of cause

In the same paper, persistent post-surgical pain was identified by the question: "What do you believe is the cause of the pain". "Surgery" was one of 20 pre-defined options, and it was possible to tic more than one box. While the pain definition based on NRS ratings of local pain, including all nociceptive sensations above 0, is supposed to be sensitive, although less specific, the use of the word "pain" would enhance the specificity by applying a clinical meaningful word. The subjective attribution of cause of pain, based on the individual's own assumptions in retrospect, may however have led to both over- and under-diagnosing of persistent post-surgical pain.

Definition of sensory disturbances

Validity of self-reported sensory abnormalities

In the questionnaires, sensory abnormalities were identified by three simple questions. 1) "Do you have reduced sensitivity in an area near the surgical scar?", indicating possible hypoesthesia; 2) "Are you hypersensitive to touch, heat or cold in an area near the surgical scar?", indicating possible hyperesthesia or allodynia; and 3) "Does slight touch from clothes, showering or similar cause discomfort/pain?", indicating allodynia. As question 2 and 3 are overlapping with regard to allodynia, it was not possible to identify individuals with hyperesthesia without allodynia. In most analyses, the two categories were combined to one, labeled "hyperesthesia".

Overall, questionnaire data

Questionnaires are key tools in collecting large quantities of data, particularly in epidemiological research. In Tromsø 6, with a high participation rate, comprehensive questionnaires were filled in by all participants, thereby collecting detailed data with a high degree of generalizability. Some sections of the questionnaires were validated questions, i.e. the Hopkins symptom checklist – 10 item score, while most questions were designed specifically for Tromsø 6, like the sections covering persistent pain and surgery. The lack of consistency between answers to different pain-related questions presented in different sections and contexts, demonstrates problems with internal validity. At present, there is no validated tool for diagnosing PPSP, and consequently no validated reference. To

approach meaningful estimates, we have run parallel analyses from the two different sections of the questionnaire, compared results, and in this way also highlighted some conceptual challenges.

5.1.3 Epidemiological data

The ideal aim for studying PPSP is to gain knowledge which can be translated into preventive measures. As presented in the introductory section, the complexity of the subject, and the divergent methodologies applied, contribute to the scarcity of definite evidence of both generalizable risk factors and the contribution of PPSP to the total pool of persistent pain in the population.

With respect to risk factors and pain mechanisms, the ideal study designs would be large, prospective, multi-center observational studies with exhaustive sampling of preoperative, perioperative and postoperative procedure- and patient-related data with long term follow-up. This thesis is based on another source of information: a large, cross-sectional population-based survey and medical examination, offering a large sample of individuals who had experienced a wide variety of surgical procedures, data on chronic pain, comorbidities, pain sensitivity and a wide spectrum of other health-related information, i.e. an epidemiological approach to prevalence and risk factors.

Strengths and limitations of epidemiological data

A common definition of epidemiology is "the study of the distribution and determinants of health-related states or events in specified populations and the application of this study to control health problems (Szklo and Nieto, p. 3)[146]. Among the advantages of addressing the public, are the opportunities to quantify the magnitude of a health related problem in a population and to describe relationships which may be less evident in data from selected, more homogenous samples. The number of participants is usually higher than in clinical studies, ensuring statistical power to prove associations of relatively low magnitude. Generalizations to a population may be more appropriate when based on data from representative samples drawn from the same population than from generalizations from clinical settings. Epidemiological data may also serve as confirmation or correction of conclusions drawn from studies on clinical samples.

On the other hand, identifying specific diagnostic entities may be difficult. In a large epidemiological study, the level of detail in sampled information has to be limited. While the ultimate strength of epidemiological research may lie in describing prevalent conditions easily identified by unequivocal questions or simple assessments, identification of less prevalent entities may prove more difficult.

Cross-sectional studies gain correlation knowledge, which is related to 2 of the 9 viewpoints on causality proposed by Bradford Hill (Szklo and Nieto, pp. 382-292) [146]. The stronger the statistical correlation, and the more consistency in correlation from different investigations, the more likely a causal relationship may actually exist. Additional evidence has to be collected from other scientific sources to prove causation: specificity of effect, temporality, dose-response relationship, scientific plausibility, coherence and analogy with current knowledge, and experimental evidence. Standing alone, none of the criteria are universally sufficient nor necessary to prove causation, but have to be evaluated in concert[147].

In this work, selection of individuals eligible for the follow-up study was based on combinations of a series of questions covering surgery, anatomical site of surgery, time of surgery, and grading of persistent pain in the area of surgery. All questions carried some risk of inaccurate recall, interpretation and report. The interpretation of "pain" has been discussed earlier in this section. As presented paragraph 5.1.1, "surgery" was also, by some participants, conceived otherwise than intended.

5.1.4 Experimental pain assessments

Heat and pressure pain

Heat and pressure pain thresholds were assessed both in Tromsø 6 and in the follow-up study. In Tromsø 6, all participants had the heat assessments performed at the same anatomical site, intended to explore inter-individual differences in heat pain sensitivity. In the follow-up study, assessments were made in different anatomical locations, selected according to the surgical procedure performed,

with the intention to identify site-to-site differences within each individual, indicating local sensory aberrations.

Pressure was applied to the cuticle of the 3. finger on the non-dominant hand in Tromsø 6, and to the right occipital bone and right trapezius muscle in the follow-up study. Although referred to as "thresholds", the assessments of pressure pain sensitivity in Tromsø 6 did not actually identify pain thresholds. The participants were told to press a button when they experienced the sensation equaling 5 on the 0-10 NRS, as increasing pressure was applied to the cuticle. Consequently, in more accurate terms, an assessment of sensitivity to a supra-threshold pain stimulus was made. In contrast, the assessments of pressure pain sensitivity in the follow-up study measured the lowest pressure stimulus generating pain, i.e. the pain threshold.

Ideally, to enhance adherence to instructions and precision of assessments, a test sequence should be preceded by introduction of stimuli and exercise of responses in a neutral anatomical area, remote from the test site. Rolke et al. calculated thermal thresholds as the mean of three measurements made after such introductory demonstrations[48,137]. Due to time constraints, our test model was simplified, without pre-testing in a remote site. By calculating the mean of the last two of three consecutive assessments, the first stimulus served as a test. Both in Tromsø 6 and the follow-up study this approach was followed for thermal and pressure stimuli.

Cold pressor pain: Tolerance, intensity

In contrast to the phasic thermal and pressure stimuli with low to medium intensity, the cold pressor test represents a tonic stimulus inducing intense pain in most subjects, often accompanied by autonomous responses as changes in heart rate and blood pressure[57]. The relatively easy applicability of the test, its ability to mimic clinical pain, to allow assessments of both threshold, sensitivity above threshold and tolerance, and its association to both resting cardiovascular responses and chronic pain [148] makes it well suited for investigating relationship to persistent pain conditions. In line with this, an association between clinical pain and cold pressor tolerance was demonstrated (Paper II).

Reliability and stability of tests

In Tromsø 6, two hundred and sixty-three individuals were recruited for a repeat examination of heat-pain threshold and cold pressor tolerance. The mean elapsed time between the first assessment and follow-up testing was 54 days (range 23-107 days). Re-examination was performed twice on the second visit for 189 of the subjects. The repeated assessments demonstrated high test-retest stability for the cold pressor test: alpha 0.82 between first and second measurements and 0.93 between second and third assessments (on the same day). In contrast, heat pain threshold, while demonstrating high internal consistency within the same session (alpha 0.95-0.96) had low stability over time (0.57 between first and second visit and 0.80 within the same day)[149]. Re-testing of pressure pain sensitivity was not performed.

Overall, experimental pain assessments

Internal validity of experimental pain assessments rests heavily upon the quality and standardization of instruction, standardization of stimuli, and report and documentation of responses. Stability in assessments over time is crucial for both internal and external validity. According to our findings, cold pressor test proved satisfactory with regard to both ease of instruction, performance and report, and stability. Thermal threshold and sensitivity to phasic, medium intensity pressure pain appeared less reliable, although a formal assessment of stability of pressure pain sensitivity was not performed.

At the time being, evidence indicates that tests applying supra-threshold stimuli and "dynamic" tests of pain sensitivity and modulation are the most useful in relation to PPSP[40,112]. Comprehensive and time-consuming tests are less applicable in large scale studies, with limited time for instruction and assessments. Experience from Tromsø 6 and the follow-up study however, proved that the cold pressor test can be applied in such settings, with data relevant for investigating clinical conditions.

5.2 Ethical considerations

5.2.1 Justification of study

There is an inherent contradiction between "individual ethics", concerned with the well-being of the patient at hand, and "collective ethics", concerned with the obligation to seek understanding and improve treatments for all patients[150]. In experimental pain research, one needs to expose individuals to pain to collect data. Putting emphasis only on individual ethics would eventually obstruct all research which implies pain or discomfort, and even blinding, placebos and randomisation. The Helsinki Declaration §5 points to the equal *rights* of individuals and groups to be represented in research[151] . Chronic pain is a major health problem, and chronic pain patients are not known to be a privileged or highly prioritized group. The contribution of PPSP to the total burden of chronic pain in the population is unknown, and knowledge of prevalence and consequences is needed, as well as clues to better understanding of the phenomenon. Consequently, we argue that the potential benefits for chronic pain patients in general outweighs the potential disadvantages for the individuals volunteering for the study, provided that the execution of the study follows high standards of ethics and safety.

5.2.2 Study design

Both Tromsø 6 and the follow-up study were observational studies without medical interventions. Individuals were compared on tests of sensory functions and responses on questionnaires. Accordingly, there were no risks of exposing individuals to harm by pharmacological treatment or by withholding beneficial treatment to one group. Rather, the question was whether participation in the study might have any known or unknown disadvantageous consequences for any of the individuals.

5.2.3 Advantages, disadvantages and safety for participants

All participants in the follow-up study were offered a present card worth NOK 200 as compensation for travel expenditures and parking tax. The invitation letter explained that the session would last approximately two hours, and we do not consider 200 kroner to represent undue economic incentive. In accordance with the recommendation from the National Ethics Committee, everyone

showing up received the card, regardless of whether they completed the tests and questionnaires or not [152].

All participants were exposed to experimental pain. For the most part, the intensity of the pain stimuli in operated areas and control areas were low, but as large individual differences in pain processing and perception exists, a few individuals experienced more intense pain during QST. Common for all tests were that the stimulus could be interrupted immediately on request, and so was done. In most instances, the pain subsided instantly, but in a few cases, the attenuation was somewhat slower.

For most individuals, the cold pressor test is rather challenging. All the participants in the follow-up study had experienced this test before, in Tromsø 6. Still, only two of the 128 participants were unwilling to perform the test again. Another individual was excluded from this test by the investigator, on medical grounds. CPT is considered safe, and this was also the statement in the applications to the Regional committee on research ethics. Spasms of coronary arteries during CPT are described, in one report even with coronary infarction as an outcome [153]. At the same time, CPT has been considered a safe procedure for diagnosing such spasms in patients with suspected angina pectoris [154].

In Tromsø 6, more than 10,000 individuals underwent the CPT. Eighty-one adverse events were recorded, most of which were minor symptoms like transient discomfort or dizziness. Eight subjects (0.08 % of the sample) fainted. One of these was hospitalized overnight for observation. None of the eight participants experienced heart infarction or other sequelae[155]. For comparison, the frequency of complete fainting during venipuncture was reported to be 0.2 % in an American study[156]. In Tromsø 6, blood pressure was monitored continuously during the CPT. Preliminary analyses indicate that a slowing of the heart rate and a decline in blood pressure in most instances preceded the loss of consciousness, and probably was the cause of the fainting. In theory, this may impose a risk for participants with certain severe heart conditions. The individual excluded by the investigator reported

another heart condition, most likely with no risk of serious adverse events, but was still excluded for the sake of maximal safety.

5.2.4 Informed consent

As presented in the methods section, signed consent was collected both before Tromsø 6 and before entering the follow-up study. At the beginning of each session, the signed informed consent-letter was presented again. The content was repeated and explained to the participants, making sure that they had understood, with special attention paid to the right to refuse tests or withdraw. This oral information served a dual purpose: both to "read the rights" to the volunteers, and to make them feel calm and comfortable with the situation before testing. No one withdraw from the session as a consequence of this repeated information.

5.2.5 Health information, privacy and autonomy

At the end of each follow-up session, the investigator requested for written consent to read the medical record to verify information regarding type of surgery, time of surgery, complications or reoperations, if needed. When asked, only one out of 128 participants hesitated to give written consent, and was accordingly given support to refuse.

5.2.6 Scientific conduct

Ethics are also about optimizing the probability of completing the project with a reliable conclusion. Pocock points to methodological flaws as "(…) the major ethical failing of many clinical trials"[150]. He defines three main outcomes that a trial should avoid: 1) bias, 2) too few patients and 3) no published findings. Although the follow-up study was not a clinical trial, the points made by Pocock are relevant. As discussed in the methodological discussion, we do not find bias, but an unforeseen number of exclusions significantly reduced statistical power, and the follow-up study could be criticized on this ground.

5.3 Discussion of results

5.3.1 Prevalence and extent of problem

As mentioned in the introductory section, methodological differences may account for a large portion of the diversity between different reports of incidence and prevalence of persistent pain after surgery.

Studies on groin hernia repair may serve as an example: Incidence rates are reported between 0 and 63 %[62]. The lowest assessment is from a long term follow-up of consecutive surgeries, with no documented time of pain assessment. The report was aimed at describing 9 years' experience with a novel surgical technique. Chronic pain was defined as "pain (…) serious enough to interfere with a patient's daily activities beyond the first 90 postoperative days". Incidence of PPSP was reported as 0, alongside the statement that 53 % "took no pain medication", indirectly indicating a prevalent use of analgesics[157]. The highest prevalence of 62.9 % at 1 year and 53.6 % at 2 years, was reported in a prospective study with pain as the primary outcome. In this study, pain was reported both with an 11-point NRS and a categorical scale describing pain and impact on physical function[158].

Aasvang has documented significantly higher incidences of pain in reports with pain as the primary outcome compared to reports with pain as secondary outcome[111]. This finding may suggest possible underestimations of PPSP in studies aiming at other main outcome variables. On the other hand, as our findings in Paper I indicates, specific, surgery-related questions and a 0-10 NRS with all ratings above 0 defined as pain, may bring about inflated and misleading representations of clinical relevant pain.

The definition of PPSP proposed by Macrae[60,64] defines criteria for duration and etiology, but does not specify criteria for pain. Clinical studies often give reports of moderate or severe pain, in addition to "all pain" when NRS or VAS is used for pain definition. Given our survey of a large population-based sample and no opportunity to definitely verify temporal relationships and pain etiology, estimates had to be based on combinations of questionnaire responses.

In our first publication, we reported 40.1% with persistent pain in the surgical area (NRS ≥ 1 when at worst, N = 826 of 2,043). As stated earlier, we do not consider this figure as representative for the clinical problem of PPSP, particularly not since only 50.1 % confirmed having chronic pain when the question was presented without relation to surgery. Taking the pain intensity into account, we found that 18.3 % (373 individuals) had moderate to severe pain (NRS ≥ 4). Of those, 214 (10.5 % of 2,043) indicated that this pain was different from the pre-operative pain. These numbers fall in line with numbers pooled from clinical studies of different surgical procedures[4]. Answers to the retrospective question of pain quality are clearly liable to recall error. Still, it might help leaving out individuals experiencing prolongation of preoperative pain as their main problem. Based on the questions above, our best delineation of clinical relevant PPSP might possibly be: 1) individuals with moderate or severe pain (NRS ≥ 4), and 2) pain different from pre-operative pain, and 3) persistent pain when asked without specific reference to surgery. This pragmatic restriction leaves 6.8 % (138 individuals) with persistent pain 3-36 months after surgery in our mixed surgical sample.

5.3.2 Pain sensitivity: Cause, consequence, or irrelevant?

The inter-individual variability in pain associated to seemingly comparable physical stressors and trauma are striking[159]. Although apparently identical traumas (e.g. a standardized procedure of inguinal hernia repair) may encompass some anatomical and procedural variations, it is tempting to ascribe the large variation primarily to differences in pain sensitivity. Systematic differences in both clinical and experimental pain sensitivity between sexes and ethnic groups are well documented[41,160]. There are, however, several obstacles for making valid deductions from findings in experimental findings to the clinical setting.

Firstly, as described in the introductory section, in experimental settings the subject possesses a control of the pain stimulus, which is not present in clinical pain. Hence, the experience of experimental pain is qualitatively different from clinical pain. Secondly, the specific experimental pain modality may or may not be associated to the clinical pain entity in question. Furthermore, for each pain modality, assessments may be based on pain threshold, pain ratings of supra-threshold intensities, or pain tolerance (intensity or time). Several studies indicate that both modality[161] and intensity[40] of

the experimental stimuli is paramount when associations between clinical and experimental pain are explored. While some promising results have been demonstrated with supra-threshold stimuli and comprehensive assessments of pain modulation, threshold assessments may be of less value[162].

Enhanced pain sensitivity may increase the risk of clinical pain. On the other hand, it may also be a consequence of long-standing pain due to peripheral and central sensitizing processes or attenuation of pain inhibiting mechanisms. A predominantly genetic cause for individual differences in pain sensitivity would serve as an argument for inborn predispositions for clinical pain. For different clinical pain phenotypes, the heritability has been estimated, but uncertainties persist due to differences in the definition of the phenotypes[163]. In experimental pain settings, heritability may be different for different pain modalities[43].

Many trials have been performed to predict post-surgical pain by experimental pain assessments. Only a minority have focused on persistent post-surgical pain, and results have been conflicting[40,112]. In recent years, however, there are a few reports of successful prediction of PPSP by applying experimental pain models: Aasvang et al. demonstrated that the pain response to tonic supra-threshold heat stimuli was among the factors predictive for persistent pain 6 months after groin hernia repair[75], and Yarnitsky et al. found that an attenuated conditioned pain modulation was predictive for persistent post-thoracotomy pain[113].

Without pretending to predict future pain, we assessed the association between PPSP and pain sensitivity by applying a tonic, supra-threshold pain stimulus, the cold pressor test, which by the majority is perceived as intense pain (Paper II). We found that PPSP was associated with lower cold pressor tolerance, but not when adjusting for other chronic pain. In the cox regression analysis, the hazard ratio was reduced when we adjusted for comorbid pain, indicating that comorbid pain may actually explain most of the variance in cold pressor tolerance, although low statistical power may also account for the negative finding.

While response to the intense cold pressor stimulus was associated to clinical pain, we did not find any association between PPSP and heat or pressure pain thresholds. In line with the

aforementioned reports on pain modalities and pain intensities, we believe that the lower pain intensities applied in tests of heat and pressure made associations to PPSP unlikely to appear.

5.3.3 Comorbid pain

Our data indicate that comorbid pain is present in the vast majority of cases of persistent post-surgical pain (Paper II). Macrae's proposed definition of PPSP[60] underlines the importance of excluding other sources of pain, such as continuation of preexisting pain. As different pain conditions may frequently be interwowen, this task may prove more difficult. Limiting the focus of clinical PPSP studies to individuals with no pre-operative pain is appealing, and certainly minimizes the risk of reporting prolonged pre-operative pain, but may lead to considerable underestimations of PPSP, as long as pain is one of the most frequent indications for medical assistance and surgery.

Comorbid and/or pre-existing pain may predispose for PPSP. Alternatively, common etiological factors may predispose for both PPSP and other persistent pain. Pain sensitivity may represent one such confounder. In our study, the association with cold pressor pain tolerance was stronger for comorbid pain than for PPSP. This does not prove causality. Pain sensitivity may also represent a mediator; a factor influenced by persistent pain, which in turn affects the risk of chronification of post-surgical pain. As median duration of persistent pain in Tromsø 6 was 108 months, our data supports this interpretation. Furthermore, as shown in Table 2, individuals with other chronic pain, restricted to pain with duration longer than the time elapsed from surgery, reported localized pain in the area of surgery more frequently and with higher intensities than individuals reporting no chronic pain or pain from surgery alone. All together this suggests a change in central pain processing related to long-lasting pain, eventually influencing both report of localized pain in the surgical area and tolerance for experimentally induced cold pain. Our findings are in accordance with prior reports emphasizing the significance of both pre-operative pain in the surgical field[164], other remote pain[66,119,120,122,123], and number of comorbid conditions[165] for development of PPSP. However, our cross-sectional study design does not allow inferences on causal direction.

Table 2

Intensity of persistent pain in area of surgery and co-morbid chronic pain

Pain in area of surgery	**Other chronic pain**			
	No chronic pain[1]	**Chronic pain[2]**	**Missing**	**Total**
No (NRS 0)	67.3 (694)	47.4 (272)	*33*	60.1 (999)
Mild (NRS 1-3)	23.4 (242)	19.7 (113)	*13*	22.2 (368)
Moderate (NRS 4-6)	7.5 (77)	17.9 (103)	*7*	11.3 (187)
Severe (NRS 7-10)	1.8 (19)	15.0 (86)	*2*	6.4 (107)
	100.0 (1,032)	100.0 (574)	*55*	100.0 (1.661)

Data is presented as % (N). Willcoxon's rank sum test : P < 0.0001.

[1] No chronic pain or pain from surgery alone

[2] Chronic pain other than pain from surgery alone; pain duration exceeding time from surgery

To secure representativeness, we argue that individuals with comorbid pain should be incorporated in studies of PPSP. This, however, requires prospective study designs with thorough pre-operative mapping of clinical pain with regard to location, quality, intensity, and pain interference with physical, emotional and social functioning. Recently, Werner and Kongsgaard have made a laudable attempt to propose a revised definition of PPSP, taking pre-existing pain into account[166].

5.3.4 Significance of nerve damage: Self report data and QST-data

Pain ratings were strongly associated to self-reports of sensory disturbances (Paper I and III), indicating a link between nerve lesions and pain. However, pain was not associated to sensory disturbances identified with quantitative sensory testing, and there was little evidence of association between self-reported sensory disturbances and related QST-findings.

We know that nerve lesions do not necessarily result in pain. We also know that the amount of objective demonstrable nerve injury, although associated to sensory disturbances, is not necessarily correlated to pain[28,34,91]. Given our relatively broad range of test modalities, the lack of coherence between symptoms (self- reported sensory disturbances) and signs of sensory dysfunction (QST) is still surprising. Beforehand, a risk of reporting false positive associations (Type I error) was considered more likely, as analyses of data from our test battery encompassed multiple comparisons, intended to identify any sensory disturbance.

Report bias cannot be excluded. Compared to people without pain, individuals with pain may be more vigilant and prone to report sensory aberrations in the painful area. In our QST model, aberrations were identified with site- to site comparisons within the same individual. The spatial distribution of sensory abnormalities were not assessed. Wide ranges for normal site- to site-variations in sensory thresholds[137] may be one explanation for the negative findings. Another explanation may be that increased or attenuated pain thresholds for sensory stimuli, which both may represent consequences of traumatic lesions, may have offset each other, masking differences between individuals with and without pain in group comparisons. Methodological aspects, like potential selection of sub-optimal areas for QST-testing, might have contributed to unsystematic measurement

errors in QST-assessments, reducing group differences. Together with possible systematic over-assessment of group differences in self report of sensory disturbances (above), this may have attenuated possible associations between pain, self-report and QST-findings. Finally, due to the nature of the inclusion criteria, i.e. questionnaire filled in 3-36 months after completed surgery, some cases of sensory disturbances caused by preoperative events cannot be ruled out.

In sum: Questionnaire data strongly indicates nerve dysfunction as important, but this finding is neither confirmed nor rejected by our QST-findings.

Among the individuals who reported persistent pain in follow-up, 61 % had sensory disturbances identified with QST. According to the diagnostic criteria proposed by Treede et al.[30], our findings would indicate that the majority of individuals with persistent pain had "probable" neuropathic pain, even though QST-aberrations were equally prevalent among individuals without pain. A substantial overlap in findings from sensory testing between groups with low, intermediate and high probability of neuropathic pain has been reported from a clinical study by Rasmussen et al[32]. Other studies have also documented high prevalence of sensory aberrations among pain-free patients[89,96]. In our group of 26 individuals with PPSP and sensory disturbances, the median rating of pain, at maximum, was 3 (range 1-8) on the 0-10 NRS, and median NPSI-score was 1.8 (range 0.0 – 24.7) on the 0.0-100.0 scale. Given the unsettled debate on definition of neuropathic pain, we consider our finding a maximum estimate of proportion neuropathic pain.

5.3.5 Age

We found that the prevalence- and intensity of PPSP was slightly lower among older age groups (Paper I and II), consistent with reports of persistent pain following thoracotomies[34,87], breast cancer surgery[109,110], and inguinal hernia repair[111]. In a recent, prospective multicenter study with a cohort of mixed surgical patients, Duale et al. identified older age as an independent protective factor against neuropathic PPSP[167]. Also recently, in a population-based study covering an unselected sample of individuals after major surgery, younger age was reported to be a risk factor for prolonged opioid use[168]. After some procedures, however, age-related changes in physical activity may confound

results[111]. In contrast to the majority of findings, a retrospective study of individuals who had gone through thoracotomies in childhood or adolescence, reported a negative association between age at surgery and prevalence of pain in adulthood[169].

5.3.6 Sex

Compared to men, women were significantly more sensitive to all pain modalities tested (Paper II). Although chronic pain was more prevalent among women, we did not identify significant sex-differences in prevalence of PPSP (Paper I and II). These findings may seem paradoxical, but are in line with other research:

Chronic pain from a variety of causes, and with different bodily localizations, are generally more frequently reported by women than men[142,143,170]. Women also demonstrate higher sensitivity for many modalities of experimentally induced pain[41]. Studies of acute post-surgical pain essentially report increased risk of pain among women, both in mixed surgical samples and when outcome of specific surgical procedures are assessed[41,63]. For PPSP, however, results are conflicting:

In one systematic review of PPSP after inguinal hernia repair, Aasvang and Kehlet[111] refers to three retrospective studies indicating increased risk for PPSP among women compared to men[171-173], and one randomized controlled trial reporting the opposite[74]. Ochroch et al. performed a prospective cohort study of 120 patients for up to 48 weeks after thoracotomy, and found significantly more pain among women than men throughout the whole study[174]. Middelfart et al. also reported a higher frequency of PPSP among women than men in a retrospective study 5-10 years after gall bladder surgery[175]. Ritter et al. assessed pain and functional measures preoperative and repeatedly up to 5 years after knee surgery and found that women had higher pain scores at all time points compared to men, but the changes from pre- to postoperative pain were similar between sexes[176]. A randomized controlled trial of cholecystectomia[107], and retrospective studies of hip replacements[108] and knee arthroscopies[177] failed to demonstrate significant sex differences in pain ,while a randomized controlled trial of knee arthroscopies identified female gender as a risk factor confounding analgesic

treatment effects[178]. Men and women did not differ in 6-month incidence of PPSP in a large prospective study of a mixed surgical sample by Peters et al.[73].

As demonstrated above, a distinct pattern of gender differences in the occurrence of PPSP is difficult to detect, regardless of type of surgery or study design. To a certain extent, this fact contrasts to the literature on chronic pain from other causes. The studies above have applied different tools for assessing pain, some have assessed preoperative pain, others not. Still, these methodological differences do not seem to explain differences in outcome.

5.3.7 Persistent post-surgical pain: Common term for disparate conditions?

Mechanisms involved in the transition from acute to chronic pain are complex and only partly understood. One reason for the growing interest in PPSP is the potential to serve as a model for investigating the transition from acute to chronic pain[61,63]. However, some cases of PPSP are not necessarily products of dysfunctional pain processing in the early or late postoperative period, but rather pathological pain from the very outset, at surgery. Even though PPSP may have developed in different ways, and different risk factors may have been involved, the outcomes may be indistinguishable when assessed and subjected to statistical analysis. In the context of the wide repertoire of pre-, per- and postoperative factors potentially influencing the pain trajectory, one may speculate that risk factors, like sex, with high impact in other pain conditions, may not prove statistically significant as general risk factors for PPSP.

6 CONCLUSION AND FUTURE PERSPECTIVES

- ✓ Persistent pain following surgery is common. 18.3 % reported moderate to severe persistent pain in the area of surgery (NRS $\geq$ 4) 3-36 months after surgery.
- ✓ Bi-directional changes in intensity of persistent post-surgical pain appear to take place over time.
- ✓ Both the presence- and intensity- of persistent post-surgical pain is strongly associated with psychological distress.
- ✓ Most cases of persistent post-surgical pain are coexistent with other chronic pain.
- ✓ When comorbid pain is adjusted for, there is no evidence for any association between persistent post-surgical pain and sensitivity to the three experimental pain modalities heat pain threshold, pressure pain threshold, or cold pressor tolerance.
- ✓ Persistent post-surgical pain is strongly associated with self-reported sensory disturbances, indicating a possible neuropathic component of the pain.
- ✓ Sensory aberrations compatible with nerve injury can be confirmed with quantitative sensory testing in a majority of the operated individuals, equally prevalent among subjects with and without persistent pain in the surgical area, and there is little evidence of correlation between self-reported sensory symptoms and aberrations verified by testing.

6.1 Clinical implications

- ✓ Even though this thesis do not confirm causal relationships, comorbid pain should be searched for and recognized as an established risk factor associated with persistent post-surgical pain, requiring special pre- and perioperative attention.
- ✓ As yet, routine pre-operative screening of pain sensitivity to predict risk for persistent post-surgical pain is not warranted.
- ✓ The thesis supports current evidence indicating nerve dysfunction in a large proportion of cases with persistent post-surgical pain. However, nerve injury does not appear sufficient for development of such pain, as signs of nerve injury were just as common among individuals without persistent post-surgical pain.

6.2 Research implications

- ✓ Clinical and epidemiological research on PPSP should focus on clinical relevant pain, applying validated pain scoring tools.
- ✓ Comprehensive pre-operative assessments are needed to determine incidence rates of persistent post-surgical pain with improved precision.
- ✓ Future studies of relationship between experimental pain sensitivity, persistent post-surgical pain, and other chronic pain should be done in prospective clinical studies and population-based cohort-studies to detect temporal changes in pain sensitivity and clinical pain.
- ✓ Data on self-reported symptoms of sensory dysfunctions as well as QST should be collected both pre- and postoperatively and should include assessments of spatial distributions of sensory abnormalities.
- ✓ As persistent post-surgical pain in most cases is coexistent with comorbid pain conditions, comprehensive pre-operative assessments of comorbid pain should be routinely included in future research on persistent post-surgical pain.

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