UiT The Arctic University of Norway

Faculty of Health Sciences

Relationships between physical activity and chronic pain: The role of endogenous pain sensitivity

A population-based perspective: The Tromsø Study

Anders Pedersen Årnes

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“You will exchange

joy for my pain”

-Kirk Franklin

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Anyone who has ever read a PhD-thesis has read a personal story about pain. I will add only that it has been fun, difficult, interesting, frustrating, exiting, terrifying, and everything else all at once. I cherish the experience, and count myself lucky to have had this opportunity. They say it takes a village to raise a PhD-student into a real scientist. So too with me. I live a blessed life surrounded by kind-hearted people that have enabled me to do a thing.

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Abstract

Background and aims: Chronic pain is a major global health concern, yet causal mechanisms are not well understood. Physical activity is popular as prevention and treatment, possibly acting through a positive effect on endogenous pain modulation. This has not been examined in the general population.

Materials and methods: We used data from the sixth and seventh surveys of the population-based Tromsø Study (Tromsø6 and Tromsø7, respectively) to perform cross-sectional and longitudinal analyses of the association between physical activity and pain tolerance. We also performed counter-factual mediation analyses to assess the direct effect of physical activity on chronic pain types, and any potential indirect effects on chronic pain mediated through the effect of physical activity on pain tolerance.

Results and conclusions: This thesis found evidence supporting higher habitual PA in leisure time, and higher exercise intensity and duration, to be associated with higher cold-pain tolerance. This association appeared to be dose-response shaped in leisure-time PA. The same was not seen in accelerometer-assessed PA. Leisure-time PA relationships appeared to be stable when measured in the same individuals at multiple time-points, and more PA over time was related to higher pain tolerance compared to being less active. There were indications that direction of PA change matters. However, PA did not appear to counteract an overall drop in pain tolerance over time. Effect estimates appeared in general to be slightly larger for men than women. Higher PA levels were associated with lower risk of moderate-to-severe chronic pain types. For such chronic pain types, a small part of this effect was mediated through an effect on pain tolerance, suggesting pain tolerance might have a mechanistic role in the effect of PA on chronic pain. The clinical significance of this indirect effect is unclear.

Sammendrag

Bakgrunn og mål: Kronisk smerte er en betydelig global helseutfordring, men årsaksmekanismene er ikke godt forstått. Fysisk aktivitet brukes ofte i forebygging og behandling, og virker muligens gjennom en positiv effekt på endogen smertemodulering. Dette er ikke undersøkt i den generelle befolkningen.

Materialer og metoder: Vi brukte data fra den sjette og syvende undersøkelsen av den befolkningsbaserte Tromsøundersøkelsen (henholdsvis Tromsø6 og Tromsø7) for å utføre tverrsnitts- og longitudinelle analyser av sammenhengen mellom fysisk aktivitet og smertetoleranse. Vi utførte også kontrafaktiske medieringsanalyser for å vurdere den direkte effekten av fysisk aktivitet på forskjellige typer kroniske smerter, og mulige indirekte effekter på kroniske smerter som formidles gjennom effekten av fysisk aktivitet på smertetoleranse.

Resultater og konklusjoner: Denne avhandlingen fant bevis som støtter at høyere vanemessig fysisk aktivitet i fritiden, og høyere intensitet og varighet av trening, er assosiert med høyere kuldesmerte-toleranse. Denne sammenhengen så ut til å ha en dose-respons-form for fysisk aktivitet i fritiden. Vi fant ikke tilsvarende resultater for akselerometermålt fysisk aktivitet. Assosiasjonene med fysisk aktivitet i fritiden så ut til å være stabile når de ble målt i de samme individene ved flere tidspunkter, og mer fysisk aktivitet over tid var relatert til høyere smertetoleranse sammenlignet med å være mindre aktiv. Det var indikasjoner på at retningen av endring i fysisk aktivitet har betydning. Det så ikke ut til at fysisk aktivitet motvirket en generell nedgang i smertetoleranse over tid. Effektestimatene generelt så ut til å være litt større for menn enn for kvinner. Høyere nivåer av fysisk aktivitet var assosiert med lavere risiko moderate-til-alvorlige typer kroniske smerter. For slike typer kroniske smerter ble en liten del av denne effekten formidlet gjennom en effekt på smertetoleranse, noe som antyder at smertetoleranse kan ha en mekanistisk rolle i effekten av fysisk aktivitet på kroniske smerter. Den kliniske betydningen av denne indirekte effekten er uklar.

List of Papers

Paper one

Årnes AP, Nielsen CS, Stubhaug A, Fjeld MK, Hopstock LA, Horsch A, Johansen A, Morseth B, Wilsgaard T, Steingrímsdóttir ÓA. Physical activity and cold pain tolerance in the general population. Eur J Pain 2020.

Paper two

Årnes AP, Nielsen CS, Stubhaug A, Fjeld MK, Johansen A, Morseth B, Strand BH, Wilsgaard T, Steingrimsdottir OA. Longitudinal relationships between habitual physical activity and pain tolerance in the general population. PLoS One 2023;18(5):e0285041.

Paper three

Årnes AP, Fjeld MK, Stigum H, Nielsen CS, Stubhaug A, Johansen A, Hopstock LA, Morseth B, Wilsgaard T, Steingrímsdóttir ÓA. Does pain tolerance mediate the effect of physical activity on chronic pain in the general population? The Tromsø Study. (Pain: Submitted after revision 22 November 2023).

Abbreviations

CPA = Computerized cuff-pressure algometry

CPM = Conditioned pain modulation

CPT = Cold-pressor test

DAG = Directed acyclic graph

DLW = Doubly labelled water

EIH = Exercise-induced hypoalgesia

GRIP = Graphical index of pain

HR = Hazard ratio

HUNT = Norwegian Health Survey of North Trøndelag

ICC = Intra-class correlation coefficient

ICD = International classification of diseases

LTPA = Leisure-time physical activity

MICE = Multiple imputation with chained equations

MVPA = Moderate-to-vigorous physical activity

NIPH = Norwegian Institute of Public Health

OPA = Occupational physical activity

OUS = Oslo University Hospital

PA = Physical activity

PAEE = Physical activity related energy expenditure

PAFID = Physical activity frequency intensity duration scale

PAQ = Physical activity questionnaire

PH = Proportional hazards

Q1, 2 = Questionnaire

QST = Quantitative sensory testing

RCT = Randomized controlled trial

RR = Risk-ratio (relative risk)

SGPALS = Saltin-Grimby physical activity level scale

TSP = Temporal summation of pain

VM = Vector magnitude

WHtR = Waist-height-ratio

WHO = World Health Organization

1. Introduction

This thesis and its included papers considers how physical activity relates to pain sensitivity, and to chronic pain through it. The introduction gives an overview of key concepts, definitions and epidemiology regarding chronic pain, pain sensitivity, and physical activity, and suggests a rationale for how these three may be connected.

1.1. Chronic pain definition and impact

Pain is currently defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" [181]. In all its complexity, chronic pain has come to be recognized as a condition unto itself with a defining framework and taxonomy that is not co-dependent on other primary diagnoses. This has been systematized by IASP through its contribution to the 11th edition of the International Classification of Disease (ICD-11) [228; 229]. Chronic pain has traditionally been regarded as pain persisting for a length of time beyond what is to be expected with normal tissue healing and hence not serving the physiological warning function that acute pain does [170]. Historically, the most frequently applied criterion has been pain with an onset of three months or more [216] which has been operationalized in the current IASP classification of chronic pain is "persistent or recurrent pain lasting longer than 3 months" [229]. IASP further suggest a division according to aetiology, underlying pathophysiological mechanisms, and affected anatomical site or organ system.

Additional criteria can be added to further specify chronic primary pain according to spread, location, and/or place of origin of pain. The taxonomy details specifiers that can be added to record severity, temporality, and psychosocial aspects of the pain. For severity, numeric rating scales of 0-10 for intensity, pain-related distress, and interference are used to qualify the pain as mild, moderate, or severe. Using markers of severity, such as disability and reported intensity, to qualify severe chronic pain has previously been connected to more severe outcomes in terms of employment status, daily functioning, and general health outcomes [209; 226].

Nevertheless, chronic pain does not represent a single homogenous state but rather a wide array of clinical conditions originating from a complex underlying causation, can occur with

or without varied types of tissue damage, with an underlying aetiology that is poorly understood [146]. Divided into several specific sub-categories such as nociceptive pain (related to actual or potential tissue damage), neuropathic pain (from disease or injury of the nervous system) or, more recently and controversially, nociplastic pain (from maladaptive neuroplastic changes facilitating experienced pain absent of tissue damage or disease) [36], it is nevertheless common to experience overlap of several concurrent types of chronic pain. This has been referred to as "mixed pain" [55].

Due to the ambiguous and multifaceted nature of pain along with a historical lack of common standards for defining it in the epidemiological setting, uncertainty remains regarding prevalence and incidence rates [216], which are nevertheless certain to be high [63]: Yearly incidence rates of chronic pain are estimated to be as high as 8-10% in adults [46; 63], with reported prevalence rates ranging from 5.1-64.4%, likely depending on the definition used [49; 182; 194; 216]. Norwegian surveys have put the national prevalence at 7-60% [30; 54; 66; 72; 84; 119; 120; 163; 188], again highly dependent on the defining criteria.

Although the Global Burden of Disease study does not separate chronic pain as a category by itself and may thus fail to include several chronic pain conditions, it has previously identified lower back and neck pain as the leading global cause of disability [244]. For the most part it categorizes chronic pain together with musculoskeletal disorders, which are characterized by it. These have been ranked as the primary cause of years lived with disability globally, and sixth in cause of lost quality of life [41]. In the 2019 Global Burden of Disease study, low back pain and headache disorders were ranked in the top ten leading causes of disease-adjusted life-years for age groups 10-49 years [42]. For those aged 50-74, low back pain and other musculoskeletal disorders featured as number six and 11, respectively. Furthermore, most prominent contributors to the global burden of disease such as major depressive disorder, cancer, diabetes, and substance abuse are important comorbidities of chronic pain [184]. Estimated costs of chronic pain due to healthcare consumption and productivity losses are substantial, in several western countries reported to range between 2.7-10% of national GDP [13; 57; 70; 85; 155; 182; 194; 223]. Finally, chronic pain has been linked to excessive mortality when controlling for other variables [137]. Regardless of the taxonomy employed, it is beyond doubt that chronic pain remains a leading cause of healthcare utilization and health-adjusted life-years lost globally, resulting in considerable suffering, distress, social dysfunction, societal expenditure, and loss of independence, productivity, function in daily living, income and self-esteem [30; 182].

To adequately meet this immense challenge, there is a need to understand what is causing the protective, transitory, and useful experience of pain to become persistent and detrimental to so many.

1.1.1. Proposed mechanisms causing chronic pain

Pain does not equal nociception. Nociception denotes "The neural process of encoding noxious stimuli" [1]. However, the brain houses neural networks that interpret a mass of afferent signalling and other information in light of prior knowledge to formulate an opinion of how the organism is doing [31]. Figure 1 illustrates how this coordination of several tiers of the central nervous system may conceptually act upon and modulate afferent signalling before a consensus is arrived upon for interpreting the sensation as painful. Thus, pain is also influenced by individual factors such as experience, expectation, memory, and context. Only after the brain has arrived at an interpretation that is likely to facilitate the preservation of homeostasis is a stimulus experienced as painful for the individual.

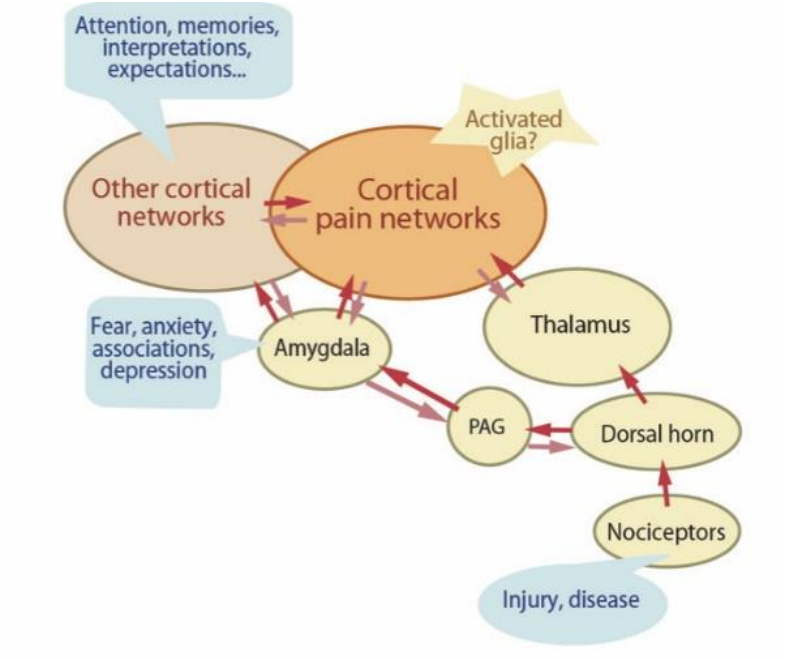


Figure 1: The Pain Network. From: Brodal P. A neurobiologist's attempt to understand persistent pain. Scand J Pain 2017, with permission.

The mechanisms that cause chronic pain to develop are not well understood [171]. It is thought that chronic pain can arise when a sufficient amount and magnitude of changes occur in one or more parts of the pain network described by Brodal in such a manner that it is brought into a state of perpetual alarm; however small the final triggering change might be, it

would be acting on a network that is already vulnerable [31]. Indeed, the nodules of this network need not necessarily receive nociceptive input to produce experienced pain if the system is brought to a sufficiently heightened state. Concurrently, there is little evidence that pain correlates well with level of nociceptor activation [170]

Known risk factors for chronic pain include a wide range of clinically separate conditions and predisposing factors, in an extensive causal framework. Such risk factors have been suggested to include biological factors like genetics, sex, age, and hormone levels [36; 148]; obesity [148; 251]; a previous history of pain [148] and factors related to socioeconomic status like low education level, low social support, employment status, hazardous occupation; risk behaviour such as smoking, excessive alcohol consumption; and also psychological distress and comorbidity [36; 64; 91; 148] as well as sleep disorders and insomnia [24; 36; 148; 240].

1.2. Endogenous modulation of pain

Another potential predictor or risk factor of chronic pain includes individual capacity for pain modulation, or nociceptive somatosensory function. Individual pain sensitivity expresses the functioning of peripheral, spinal, and supraspinal pain pathways as well as central modulatory control [31; 250]. Therefore, this thesis uses the term endogenous modulation of pain and the more general term pain sensitivity synonymously, although a more nuanced approach might define them as separate but overlapping phenomena. The endogenous system of pain signal modulation is one important contribution to the interpretative process made by the central nervous system to arrive at experienced pain [36]. Deficiencies in either inhibitory or facilitatory descending pathways are hypothesized to be one of the reasons why there is an apparent lack of proportionality between nociceptive signalling input and the amount of pain experienced by patients [9]. In acute pain, there is systemic inflammation and sympathetic upregulation as well as central release of substances with excitatory function, which facilitates generation of nociceptive transmission [50]. If continuous or persistent, such nociceptive signals can cause complex changes throughout all pain-processing levels both peripheral and central, working to increase overall nociceptive excitability and neural plasticity, and increasing pain sensitivity to an exaggerated degree [50].

As any facilitatory signal can in theory contribute towards bringing the pain network into a state of disequilibrium that subsequently induces chronic pain, it is hardly surprising

that persistent pain development seems to be correlated with alterations to sensory processing and subsequent plastic neural changes [31; 146; 159].

1.2.1. Quantitative sensory testing of pain

Options to directly measure pain signal conductivity are limited in humans. For this reason, a range of techniques commonly referred to as experimental quantitative sensory testing (QST) of pain has gained popularity as means of a proxy for use in human research and in the clinical setting. Such tests are standardisable and can be controlled with regards to stimulus intensity, application localisation, pattern and frequency of stimuli, and stimulus duration [8]. The goal is to induce pain in the test subject through systematic nociceptive stimulation to measure response parameters. To do so, a wide variety of test modalities can be applied, at different anatomical sites [9].

When combined, the modalities and parameters listen in Figure 2 are intended to produce estimates of different aspects of somatosensory function through stimulating different nociceptive tissues and mechanisms. Resulting estimates vary according to which modalities and parameters are combined, the clinical conditions present in test subjects, and the anatomical site at which parameters are measured – especially if relative to some painful site.

Is it not unusual to separate test parameters into groups of tests to provide data on static sensory capacity or dynamic sensory modulation [227; 249]. Static parameters such as thresholds and pain-magnitude ratings have been suggested more suitable for establishing basal somatosensory function, whilst dynamic parameters aim towards stimulating the sensory system in order to activate and measure more complex, centrally conditional processes of pain modulation [9; 175]. For instance, temporal summation of pain (TSP) is believed to express pain facilitation, whilst the pain-inhibits-pain paradigm conditioned pain modulation (CPM) is thought to express capacity for pain inhibition [249]. Nevertheless, all QST parameters engage pain signalling between the periphery and the brain and no QST parameter can fully inform us of the structures, mechanisms, or levels of afferent signal processing which are producing the resulting estimate [38].

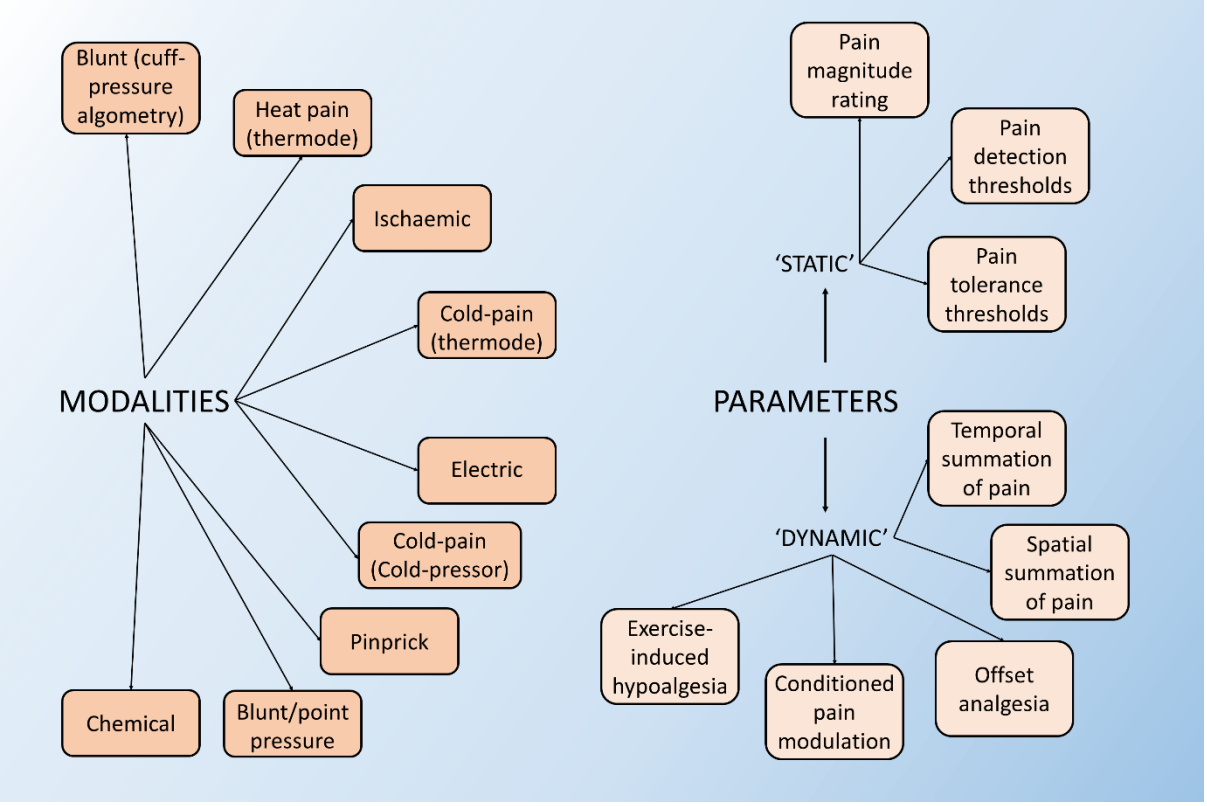


Figure 2: Categories of quantitative sensory test modalities and parameters.

1.2.2. Endogenous pain modulation and chronic pain

Defective pain facilitatory and inhibitory functioning is thought to pose a potential risk factor for chronic pain development [171]. For instance, post-traumatic deficiencies in endogenous pain modulation seen in animal studies of traumatic brain injury are thought to reflect mechanisms which contribute to the high prevalence of chronic pain as observed in human traumatic brain injury patients [94]. Some evidence finds altered function in mechanisms of endogenous pain modulation to be prevalent with several types of chronic pain conditions, which is often evident with comparisons of quantitative sensory testing of pain in clinical and healthy populations [38]. These conditions include low back pain [202], fibromyalgia [164], osteoarthritis [178], chronic orofacial pain [150], irritable bowel syndrome, headache/migraine and temporomandibular disorders, amongst others [131]. However, empirical reviews commonly find a high degree of heterogeneity between studies investigating the relationship of endogenous pain modulation and chronic pain, typically attributable to differences in methodology, site of examination, and the parameters

investigated [164; 178; 202], but also to the range of age and gender of included participants [131].

Furthermore, there are large within-group differences in estimates of endogenous pain modulation for both chronic pain patients and healthy controls, meaning that far from all patients exhibit signs of centrally conditioned hypersensitivity [38].

We should bear in mind that the concurrence of altered pain processing and chronic pain states does not equate to a predictive role of experimental pain processing for chronic pain development. As Brodal summarizes, translating findings regarding endogenous pain modulation into clinical application is not straightforward. For instance, grey matter alterations in neural networks which commonly occur in most chronic pain conditions presumably primarily reflect neural plasticity associated to the condition [31]. Still, deficient descending inhibition of pain has been predicted to contribute to a centrally conditioned hypersensitivity to pain and subsequently increased risk of chronic pain [227], marking it as a potential piece of the causal framework of why chronic pain develops.

1.2.3. Prediction of chronic pain by endogenous pain modulation

Whether alterations in QST-estimated endogenous pain modulation predict subsequent chronic pain has often been examined in humans according to whether they predict poor pain outcomes after surgical intervention. Baert et al. reviewed whether capacity for central modulation of pain predicted poorer outcomes after total knee replacement. 'Central modulation of pain', measured as low pre-surgical QST (electric sensations, pressure and heat pain) pain thresholds predicted more pain after knee replacement [14]. However, post-surgical QST-measures were not reported. A study by Petersen et al. in 2019 further investigated the ability of QST to predict chronic postoperative pain development in 200 patients undergoing total knee arthroplasty [174]. Cold and heat detection and pain detection thresholds as well as mechanically induced TSP were used to predict chronic pain defined as <30% improvement in peak 24-hour pain intensity VAS score at 12 months compared to preoperative ratings. Only TSP remained significantly associated with 12-month pain intensity.

In a 2021 review, Petersen et al. further looked at whether a variety of QST modalities and both static and dynamic parameters could predict postoperative pain at least three months after several types of surgery [175]. TSP and CPM were the parameters most frequently

predictive of chronic postoperative pain, but with a high degree of heterogeneity in findings between the included studies the results were not consistent. Static QST parameters rarely predicted postoperative chronic or moderate-to-severe chronic pain intensity but included mainly thermal detection thresholds and pain detection thresholds. Only six studies investigated the predictive capacity of pain tolerance thresholds, and then mainly with regards to future pain intensity. Included studies showed a high variability in the types of exposure and outcome measures they employed.

Georgopoulos et al. reviewed the ability of QST estimates to prospectively predict pain, disability, and negative affect in a wide range of chronic musculoskeletal disorders commonly marked by chronic pain including knee osteoarthritis and post-operative pain [61]. QST modalities, parameters, and anatomical sites were all highly varied, with mechanical and cold pain detection and tolerance thresholds at or near painful sites being the most common combinations. In models plausibly adjusted for confounders, the ability of QST to predict future pain had a pooled effect estimate of r= 0.18 (95%CI: 0.11 to 0.25), with estimates from studies adjusting for baseline pain being somewhat lower. Prediction of disability was higher, at 0.35 (95%CI: 0.21 to 0.49). Adjusted models proved better at predicting pain in clinical conditions such as low back pain, whiplash-associated disorders, and osteoarthritis than for post-operative pain. Cold-pain detection thresholds predicted future disability to an estimated r= 0.48 (95% CI: 0.19 to 0.77). In general, dynamic QST models testing near or at the painful anatomical site provided the strongest predictions. The authors concluded that QST had some ability to predict musculoskeletal pain and disability.

Thus, there are some indices from animal and human studies alike suggesting that QST measures might be able to predict subsequent persistent pain. However, applied methodologies and subsequent parameter estimates vary widely and sample sizes are limited, yielding inconsistent evidence of which mechanisms, measured by which parameters, are more suitable for making such predictions. Furthermore, the underlying causes of such neural hyperexcitability in chronic pain and why it occurs in one individual but not the other, remain uncertain [31].

1.3. Physical activity

It has become customary to reference the World Health Organization (WHO) in defining physical activity as "*Any bodily movement produced by skeletal muscles that requires energy expenditure*" [2]. All physical activity (PA) occurs throughout several different domains of life, including leisure- and occupational time, in commuting/transport, in general activities of daily living (including domestic activities and education), and exercise [32; 200]. The latter is typically defined as a subtype of PA which occurs with a certain regularity, is structured and deliberate, and is undertaken to achieve certain specific purposes related to aspects of athletics or health [200]. PA during leisure (LTPA) is defined as such activity that is not required in daily living and that is performed voluntarily at the participant's discretion [32]. This encompasses exercise and recreational sports participation, as well as other types of activities that increase metabolic strain above being at rest without necessarily being categorized as exercise by the individual. Not only volume (frequency×intensity×duration), but also the domain in which volume is performed, is a relevant metric when assessing PA (Figure 3).

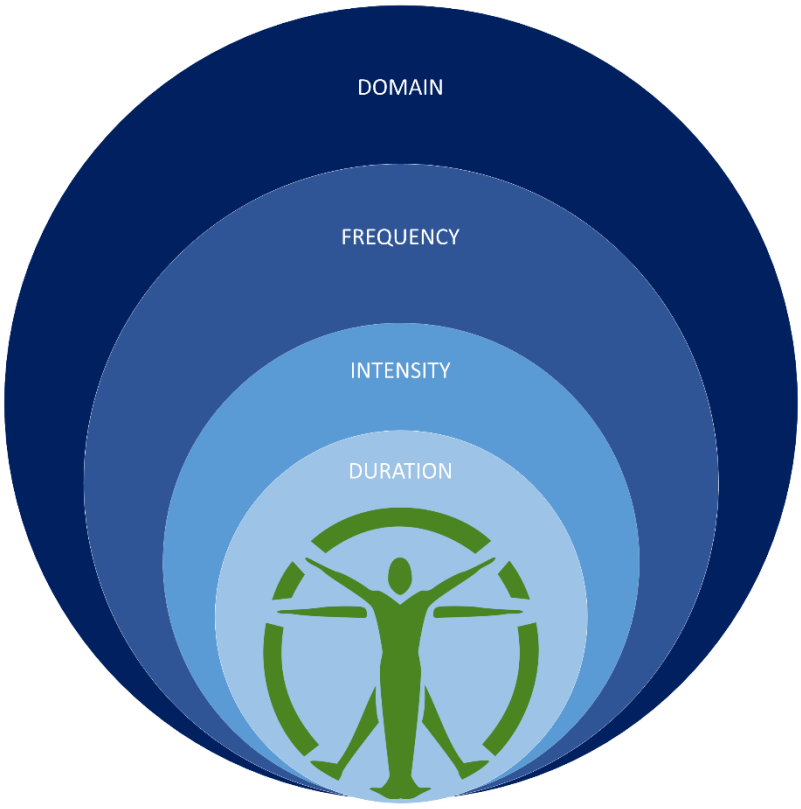


Figure 3: The characteristics of physical activity

1.3.1. Measuring physical activity

Across the domains of life, total PA volume can be quantified by measuring the intensity, frequency, and duration at which the PA is performed. Assessment methods can be divided into measurement of physiological markers (e.g. heart rate, movement, calorimetry), questionnaires (including diaries), and direct observation [247]. The former usually requires specialized equipment and some form of measurement device. Doubly labelled water (DLW), an indirect manner of measuring energy expenditure, is considered the gold standard when assessing total amount of PA-related energy expenditure (PAEE) in free-living conditions [247; 248]. Reasons for choosing one methodology over the other relate to inherent costs, the time, equipment, technicians, and expertise needed, and the context in which the data gathering is to be performed. They also differ by what they measure; i.e. what data outcomes each methodology is most suited to produce. These categories have often been separated into 'subjective' and 'objective' PA measurement methodologies (Figure 4), though this should not necessarily be interpreted as a divide between 'true' versus 'less true' estimates.

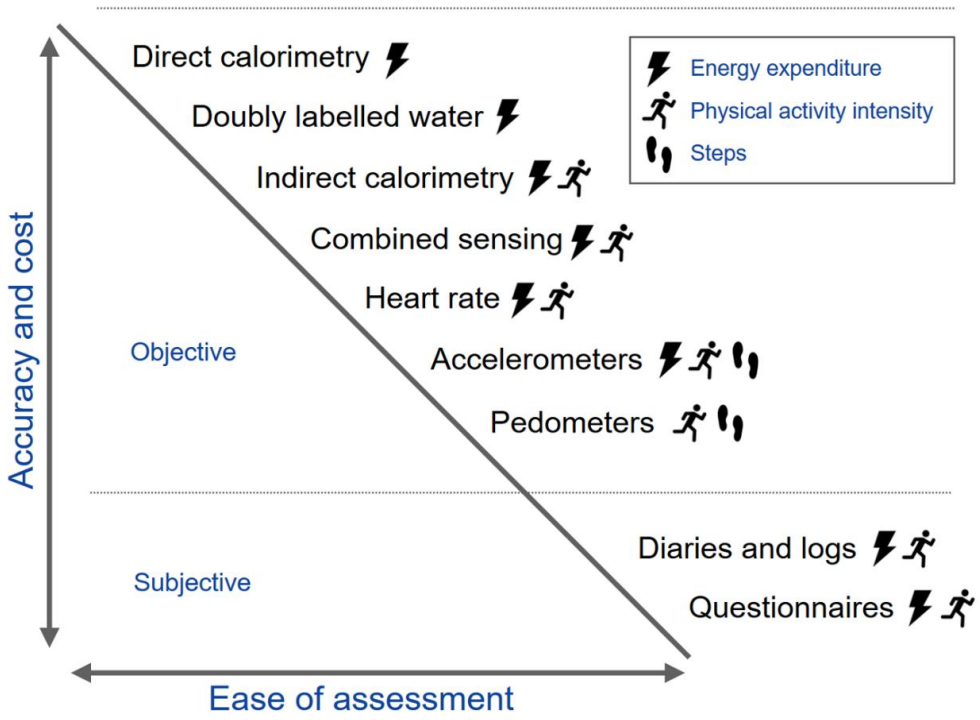


Figure 4: Methods for assessing physical activity. With permission from André Henriksen.

The most common methodology for measuring PA in large surveys is by querying the subjects themselves, through interviews, types of diaries, or most commonly through questionnaires [247]. These are relatively cheap and easy to employ in large samples, and incur a low burden on participants. They are thus a feasible alternative in population-based studies. However, questionnaires in general suffer low reliability and validity when estimating absolute levels of PA with correlations to DLW estimates of energy expenditure being low [247]. Common challenges to PA questionnaires includes falling reliability with length of recall, and over-reporting of PA volumes and under-reporting of sedentary time (possibly due to social desirability bias), incommensurability of different levels, and floor effects [200]. Questionnaires can nevertheless be adequate for ranking groups according to relative activity levels [190; 247] and can show strong predictive validity with regards to morbidity or mortality outcomes.

Accelerometry is generally regarded as an acceptable device-based alternative for measuring activity volume in free-living conditions [219]. Accelerometers are small devices that can easily be worn on one or several locations on the body for short to intermediate time-periods. Accelerometer can produce estimates of PA patterns and related estimates of PAEE, which generally show fair correlation to estimates derived from DLW [177; 219]. As with all types of measurement, there are many investigator-dependent choices that must be made when employing accelerometers. I will return to the properties of such methodologies in chapters 3 and 5.

1.3.2. Physical activity and health outcomes globally

According to the 2020 WHO guidelines, adults should undertake 150-300 minutes of moderate intensity, or 75-150 minutes of vigorous intensity, or an equivalent combination of the two, aerobic PA per week [32]. Previous WHO guidelines (2010) also included performing the moderate-to-vigorous activity in bouts of at least 10 minutes or more, as continuous activity was thought to incur additional benefit. This has since been removed as the value of total PA volume has become more apparent. Additionally, regular performance of muscle-strengthening PA is recommended. Such cut-offs are based on evidence of what PA levels provide beneficial impact on muscular and cardiorespiratory fitness, bone health and body composition, balance and daily functioning, cardiometabolic health and mental

health [2; 32].

In global estimates, more than 25% of the world's adult population fail to meet the minimum currently recommended PA level, and more so for high-income countries, females, younger age groups, and people with lower education level [2; 32; 183]. Recommended type and volume of PA differs minimally across age groups and conditions such as pregnancy, disability, and chronic illness, with the overarching theme being that doing something is better than doing little or nothing, and that PA is considered a safe and effective way of improving health outcomes for all groups [32].

Furthermore, lack of PA might infer its own health risk. As seen, insufficient activity (defined as failing to meet some minimum requirement of PA stipulated in given guidelines [198]) has generally poorer health outcomes than participating in higher amounts of PA. Being insufficiently active is associated with 20-30% increased mortality risk compared to meeting WHO recommendations [2]. However, prolonged periods of sedentary behaviour, defined as "having a MET value between one and 1.5 (for example, equivalent to sitting or lying down)" [231] have previously been associated with poorer health outcomes independently of PA level. Increased levels of sedentary behaviour significantly increased risk of all-cause mortality, cardiovascular disease mortality and incidence, cancer mortality and incidence, and diabetes type 2 incidence, and more so for those with low levels of PA, who could be described as physically inactive [25; 106]. Thus, the WHO guidelines also include a recommendation to reduce sedentary behaviours [32]. Taken together, this indicates that leading a lifestyle characterized by regular PA is generally advisable.

1.3.3. Physical activity and chronic pain

In a review of animal studies, Lesnak and Sluka summarized how regular PA reduced or prevented hyperalgesia in neuropathic, inflammatory and non-inflammatory muscle pain models [129]. Furthermore, certain pain inhibitory mechanisms which are active in habitual PA, such as increased activation of mu-opioid receptors through exercise, show some overlap in animals and humans [129; 130].

In humans, PA is a mainstay non-pharmacological modality for treating chronic pain conditions, and there is a growing body of evidence regarding its effect on chronic pain. Large population studies have commonly found higher levels of PA to be associated with lower risk of chronic pain in adults [54; 66; 89; 118; 232].

PA interventions in chronic pain have also been extensively reviewed: A 2017 Cochrane review of 21 earlier Cochrane reviews summarized the safety and efficacy of PA interventions for chronic pain severity, impairment, quality of life, and resulting healthcare use [59]. The 21 included reviews assessed effects in people suffering a broad range of specific chronic pain conditions: rheumatoid arthritis, osteoarthritis, fibromyalgia, low back pain, intermittent claudication, dysmenorrhoea, mechanical neck disorder, spinal cord injury, post-polio syndrome, and patellofemoral pain. These looked at any kind of aquatic or land-based exercise or PA intervention such as range-of-movement, strength, balance, or aerobic-enhancing exercise.

The included studies were characterized by a high variation of duration for both intervention period and exercise sessions, frequency (times per week) of the intervention, and both quantification and target of intervention intensity. This high variability as well as lack of detailed intervention information left the reviewers unable to use total PA volume in analyses, and illustrates how common such heterogeneity is in studies of PA interventions.

In total, there was evidence in support of a small to moderate effect of PA interventions lowering average pain intensity and increasing physical function, small to large effects for improving quality of life, as well as a mix of no effect and significant effects for mental health, depression, and anxiety. However, most included participants of the reviewed reviews reported only mild to moderate pain at baseline, low to moderate effect sizes, and inconsistency of results due to frequent high risk of bias and heterogeneity in interventions and follow-up [59].

One later Cochrane review of 13 randomized controlled trials (RCTs) looking specifically at aerobic exercise interventions for fibromyalgia found moderate-quality evidence of improvement in health-related quality of life, with low-quality evidence for small decreases in pain intensity and improvement in physical function [23]. Three of the included studies found effects on pain and function to persist over time.

Another review found aerobic and strengthening exercises to be effective for pain reduction in fibromyalgia, chronic whiplash-associated disorders, and chronic idiopathic neck pain [51]. This review excluded approximately half of the included studies from meta-analysis due to differences in the interventions employed [51]. They concluded that ideally, exercise should be performed 2-3 times per week, and that exercise in many cases could be of a higher intensity (moderate to vigorous) than previously reported if the increase was properly managed. Overall, effect sizes on pain intensity were generally modest (< 20% / 10

mm VAS change).

In reviewing exercise for hip osteoarthritis pain, moderate effects were found for those exercise interventions that adhered to the recommendations of the American college of sports medicine regarding intensity/workload, duration, and frequency of exercise [157]. Another meta-analysis on exercise in knee osteoarthritis found a standardized mean difference of 0.50 (0.39, 0.62) on pain reduction and similar effects on disability, with the best results occurring with aerobic or targeted single-type exercises performed three times per week for at least four weeks [104].

Finally, Mertens et al. found exercise effective for range of motion, function, and pain improvement in frozen shoulder, but 14 out of 33 included studies could not be included in the meta-analysis due to heterogeneity of exercise type and dose [145].

Few of the reviews mentioned above found any upper limit to the benefit of additional volume, beyond occasionally diminishing returns from adding to an already substantial one. Thus, it seems likely that the same effect PA has on health in general also carries over onto chronic pain.

1.3.4. The physical activity health paradox

There might be one exception to the pattern of effect of any type and increase in volume of PA which is not explored in the types of studies included in the reviews above. Potentially, PA domain plays an important role in the health effects of PA; in particular, PA as performed in the occupational context (OPA). This lack of, and possibly even detrimental, effect of OPA on health has been termed the "physical activity health paradox" [87].

In contrast to LTPA, OPA often has different intensity level (lower) and/or duration (longer) requirements that are outside the parameters required for cardiorespiratory improvement. Research indicates that high OPA elevates 24-hour heart rate and blood pressure measurements, negatively impacts heart rate variability and autonomic cardiac control, and increases immediate as well as risk of long-term rise in inflammatory markers, which are all possible risk factors of cardiovascular disease [75; 87]. Also, OPA is often performed in contexts that are less voluntary than LTPA, with a lower degree of autonomy regarding work tasks, intensity, duration, and frequency, and in environments characterized by different psychosocial milieus than LTPA, and with less self-regulation of recovery time [87].

Concurrently, evidence indicates high levels of OPA to be associated with increased risk of cardiovascular morbidity and mortality [88] as well as all-cause mortality [78]. Two studies found higher OPA to predict higher risk of long-term sickness absence in Danish workers whilst the opposite was true regarding their LTPA levels, despite adjusting for socioeconomic proxies like education level, type of work, employment grade, and job title [69; 86]. Those with the highest OPA had almost twice the risk of those with the lowest, whilst high LTPA reduced the risk of long-term sickness absence by 23-40%.

There is reason to suspect this would be similar for chronic pain. Indeed, one exploratory study found that workers spending more work-time at higher heart rates more frequently reported experiencing pain than those reporting less [144], whilst a population study found that higher levels of OPA was associated with increased risk of chronic low back pain [82]. Possibly then, not all types of PA influence pain in a similar fashion, and the effects of LTPA and OPA may be reversed in pain (Figure 5).

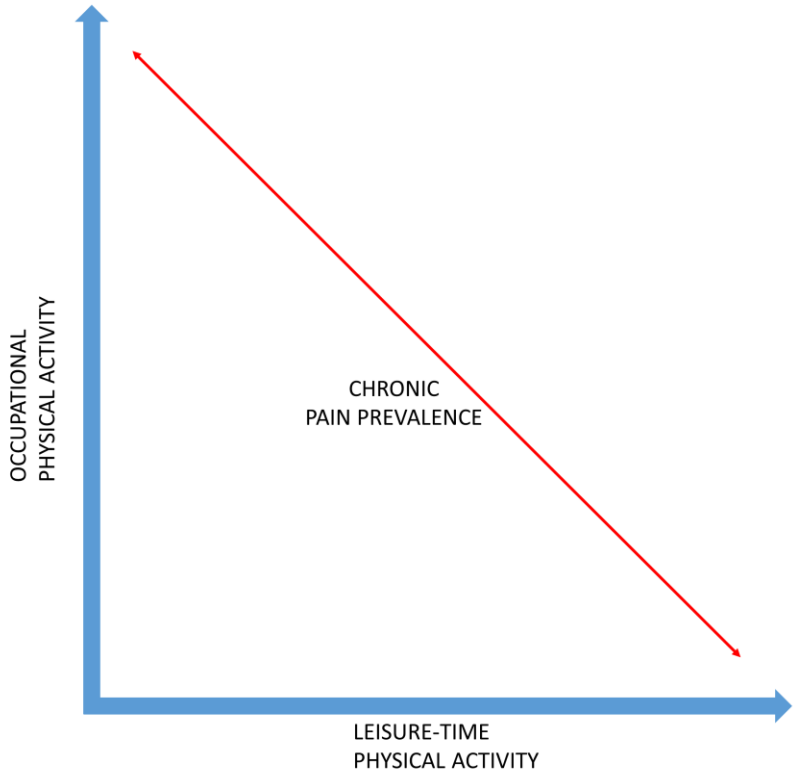


Figure 5: The physical activity paradox in chronic pain

1.3.5. Physical activity and pain sensitivity

In healthy humans, acute bouts of exercise have been found to induce a period of hypoalgesia immediately after the exertion [160; 185]. This effect has been termed exercise-induced hypoalgesia (EIH), commonly occurs as a generalized decrease in pain sensitivity, and lasts for a short while (≤ 30 minutes) during and after the exercise bout [185]. Several reviews have reported such short-term reduction in pain sensitivity and increased tolerance thresholds using various QST modalities [111; 160; 185]. Looking at habitually active nonathletes, a review by Vaegter and Jones found that these might experience greater EIH, lower pain intensity and unpleasantness ratings, and larger CPM responses [236]. Despite a high quantity of studies on EIH, (>150 were identified by the reviewers), these are commonly conducted on small samples (n ≤ 50), and show very high heterogeneity in both exercise modality and QST outcomes assessed.

CPM has itself been shown to partially predict the EIH response [126] but the mechanisms nevertheless appear partially independent of each other [185; 234]. Strenuous exercise might be painful and thus trigger a CPM response, but EIH nevertheless also occurs after exercise that has been perceived as not painful [45]. There are thus PA-specific mechanisms which correlate with increased endogenous pain inhibition.

Such effects may be further enhanced by regularly engaging in PA. Regularly active animals show a wide range of plastic adaptations that are thought to be protective for the development of chronic pain [207]. Habitually active humans also appear less pain sensitive than less active controls when comparing static QST measures. Tesarz et al. reviewed 15 studies each including 6-67 athletes, comparing their pain sensitivity to normally active controls. They found significant, moderate-to-large effect sizes for higher pain tolerance in athletes, but found no significant differences in pain detection thresholds after excluding studies with high risk of bias [222]. Effects were more uniform in endurance athletes, with studies using cold-pain modalities having strong and consistent findings. Furthermore, painful heat stimuli were rated as less intense by endurance athletes than by nonathletes in a study which also found athletes had reduced activation of, and different functional connectivity between, brain regions normally connected to nociception [58]. Less consistent effects were seen when measuring PA using accelerometry [26; 44; 167; 245].

A few controlled trials have also found effect on QST parameters when intervening

on PA across several weeks [74; 77; 102; 165; 196]. Studies of PA interventions on chronic pain have also found concurrent improvement in pressure pain sensitivity thresholds [20], but the quality of evidence was low to moderate.

Potential mechanisms which may explain how PA could influence pain sensitivity have frequently been examined in animals. One of the most widely promoted hypotheses is activation of the endogenous opioid system during exercise, which subsequently lowers pain sensitivity post-exercise. In animal studies, PA has been found to increase the release of opioidergic agents and serotonin, reduce central neuron excitability and modulate CNS neuronal signalling [124; 207; 208]. This is a suggested reason why interventions like long-term treadmill exercise reduces acquired hyperalgesia after induced nerve injury in animal models of neuropathic pain [129]. Such findings are reversible by administering opioid receptor antagonists to counteract endogenous opioids [213], and appear to be accompanied by neuroplastic changes in spinal cord and dorsal root ganglia to facilitate increased inhibition [206].

PA mediated activation of endocannabinoid receptors also seem to contribute to exercise-induced hypoalgesia, as antagonist administration in animals hinder increases in nociceptive thresholds caused by exercise [129]. An equivalent of the opioid-serotonin-driven analgesic mechanism, activated by regular PA, has been proposed to counteract hyperalgesia in humans [207]. Several other central and peripheral neurogenic exercise-mediated mechanisms have been proposed to contribute to endogenous pain modulation, for an overview see [129].

Furthermore, higher level of inflammatory markers has been associated with increased pain sensitivity [201]. PA has been found to alter macrophage phenotype to produce anti-inflammatory cytokines, acting as an up-regulator of the immune system and thus reducing inflammation-driven nociceptor sensitization [130; 180]. Exercise has also been found to cause acute cardiovascular response through elevated blood pressure and baroreceptor activation, which appear to be associated with subsequent changes in pain sensitivity [114].

Additionally, due to the interpretative nature of pain, several psychological factors might play important roles in pain sensitivity. For example, one small study (n=52) found marathon runners' significantly higher tolerance to pain compared to non-runner controls to be partially explained by their pain-specific self-efficacy [100]. Both self-efficacy and coping skills have previously been correlated to pain tolerance, and indeed to pain tolerance during exercise [15;

158]. Furthermore, pain acceptance training was found to increase pain endurance and tolerance during the cold-pressor test (CPT) [246]. Self-efficacy, coping skills, and pain acceptance are characteristics that are relevant to PA and exercise, especially at higher levels of PA intensity, due to its sometimes unpleasant or painful nature [222]. Several authors have connected these cognitive aspects to the pain tolerance threshold parameter in particular, and have hypothesized them as a possible contributing explanation to the relatively frequent finding of elevated pain tolerance thresholds for those who are physically active despite seeing no differences in pain detection thresholds or intensity ratings [40; 76; 222; 236].

In sum, these possible pathways constitute a complex interaction of numerous mechanisms through which acute and regular PA might impact endogenous pain sensitivity and modulation.

1.3.6. Physical activity interactions with sex and chronic pain

There appear to be sex-dependent differences in chronic pain and pain sensitivity. A substantially larger proportion of chronic pain sufferers are women, with one review finding an excess prevalence of 5.5% for women across seven chronic pain syndromes [151]. Several other reviews corroborate the finding that women suffer a higher risk of experiencing chronic pain than men [18; 52; 132]. One of these also found women to have a 47% greater risk to report their pain as more severe [132]. There are several proposed causes of this discrepancy. These include sexually dimorphic neural mechanisms in structure and functioning of both descending pain modulatory circuitry, neural circuitry in the spinal cord, and other pain signal transduction pathways (in particular in pain-related activation of mu-opioid receptors), as well as the neuroimmune system (spinal cord microglia) [18; 52; 152]; sex hormones, their interaction with pain signalling pathways in the central nervous system, and hormonal cyclic gender differences [18; 52; 148; 211]; and sex-specific biological differences in immune system functioning and its impact on pain states [211].

In both a 2012 and a 2020 review, Mogil noted that when one considers effect size directions in an extensive body of typically underpowered studies, evidence of sex differences frequently appears and almost unwaveringly does so in the form of higher pain sensitivity in women [151; 153]. Women have also been found to have greater temporal summation of pain as well as lower levels of conditioned pain modulation [18]. Overall, effect sizes for these

gender differences range from small to large, varying with study design and risk of bias due to study quality, as well as the methodology employed [18].

These sex differences are theorized to be relevant both for clinical and experimental pain [152]. As some mechanisms share similarities with certain proposed mechanisms for how PA influences pain sensitivity (the opioidergic system in particular), it might be possible that PA relates differently to chronic pain and pain sensitivity according to sex, and concurrently relates differently to chronic pain according to sex. Whether EIH or pain sensitivity change induced by habitual PA is sex dependent has not been extensively explored.

Some small, experimental studies have failed to find sex-dependent differences in EIH magnitudes or interaction effects with PA level or fitness on pain sensitivity measures [127; 128; 233; 235]. In contrast, Sternberg et al. found analgesia in CPT to be induced by treadmill-running in young female but not male students regardless of their athletic ability (n=63; 33 women) [217]. They did not observe similar results for heat withdrawal. Koltyn et al. found pressure pain thresholds to increase and pain ratings to decrease significantly for women after isometric maximal and submaximal hand exercise, whilst men experienced only decreased pain ratings and only after maximal exercise (n=31; 16 women) [113]. Vaegter, Handberg, and Graven-Nielsen found an exercise intensity-dependent EIH effect for pressure pain thresholds which was greater in women than men after cycling but not after isometric exercise (n=80; 40 women) [234]. All in all, evidence is inconclusive regarding possible gender differences in the acute effect of PA on pain sensitivity [185]. Less is known regarding long-term PA and pain sensitivity. Furthermore, in the population as a whole, the association between PA and chronic pain prevalence differs between men and women [54]. It is unknown how much of this difference is due to an underlying sex-difference in pain sensitivity.

There is inconsistent evidence regarding how chronic pain influences the relationship between PA and pain sensitivity, particularly EIH, in part due to a lack of high-quality studies [12, 13]. Localized chronic pain has been connected to impaired EIH response at the same anatomic region but intact EIH response in remote, nonafflicted sites, whereas widespread or generalized chronic pain has been associated with global EIH dysfunction and even increased pain sensitivity following exercise [185; 236]. However, these findings are not universal and there are large variation between patients, EIH function across clinical conditions, and EIH response based on type and anatomical site of exercise [185; 199; 236]. One review found no

significant EIH when localized musculoskeletal pain was present, looking only at sensitivity thresholds before and after isometric exercise [52]. In chronic pain populations, sparse evidence suggests that more habitual PA is associated with lower pain exacerbation from acute exercise, and that higher physical fitness is associated with less pain symptoms [236].

1.4. A happy triad: Physical activity, chronic pain, and pain sensitivity

In summary, animal studies have suggested plausible models for how PA might be protective against chronic pain and its development. So too in human studies, albeit with a considerably higher degree of heterogeneity regarding the quality of evidence as well as the nature of interventions, outcomes, and comparison groups. A purely "pharmacocentric" approach to chronic pain management has not been effective [37; 184]. In consequence, there is a need for enhanced interdisciplinary approaches to chronic pain that emphasize effective self-management [4]. PA remains an important, safe, and effective non-pharmacological treatment option for a broad range of chronic pain conditions [59], and is even associated with lower use of opioids in chronic pain management [21]. Such health-related behaviours remain some of the most important, modifiable risk factors on the causal and prognostic pathways to chronic pain [148].

It is possible that countering pathophysiological changes in the nervous system could prevent or minimize the development of chronic pain [50]. The evidence furthermore indicates that many of the contributing causes to chronic pain, including peripheral and central physiological changes that occur in acute pain, can be influenced by PA, both prior to as well as after the genesis of chronic pain. There is a biological rationale for how PA affects modulation of pain sensitivity with similar observed associations between PA level and pain sensitivity in humans. These effects appear to occur with both acute and after long-term exposure to PA. Pain sensitivity in turn has some tentative ties to the risk of subsequent chronic pain development, although prediction of future chronic pain by QST measurements remains a remote possibility [175; 227].

In order to better assess the causal nature of PA in pain, it is necessary to investigate if PA affects QST sensitivity in such a way that this constitutes an underlying mechanism by which PA alters pain [124] (Figure 6).

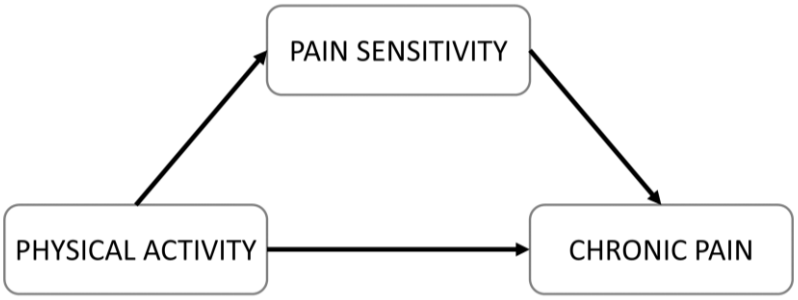


Figure 6: Conceptual model of thesis

Common traits in previous studies of PA and pain sensitivity includes small and frequently single-sex samples of young, healthy volunteers, or otherwise homogeneous samples of chronic pain patients. These are frequently under-powered to detect interaction effects, and are therefore not ideal to reveal moderation of the PA-pain sensitivity relationship by sex or clinical pain. Studies are frequently of moderate-to-low quality and rarely employ more than one estimate of habitual PA. Furthermore, the relationship between PA and pain sensitivity has not previously been estimated in a heterogeneous population-based setting.

Few large studies on PA interventions for pain sensitivity have been performed. If long-term exposure to PA indeed improves pain tolerance, traces of this should be found in the population as a whole. If it only does so in certain contexts, larger studies in more heterogeneous settings could explore this too. A population-based approach to investigating the effect of PA on pain sensitivity over time could therefore contribute important knowledge.

Finally, there have been no studies looking at how an effect of PA on chronic pain might be mediated by pain sensitivity, and whether the definition of chronic pain impacts such mediation.

2. Aims and objectives.

Based on the lack of knowledge identified above, the aim of this project was to be the first to investigate cross-sectional and longitudinal relationships between physical activity level, pain tolerance and chronic pain in a general population, and to longitudinally explore whether impacting pain tolerance represents a mechanism through which physical activity reduces the risk of chronic pain.

To achieve these aims the following objectives were identified:

Paper 1:

1. Establish whether subjective and device-measured PA levels are cross-sectionally associated with pain tolerance.
2. Assess whether this relationship is conditional on sex and chronic pain.

Paper 2:

1. Assess how longitudinal change in PA level is associated with subsequent pain tolerance.
2. Explore whether pain tolerance changes over time and whether such change is moderated by PA level.

Paper 3:

1. Investigate the extent to which PA impacted the risk of chronic pain indirectly via pain sensitivity.
2. Investigate whether the type of chronic pain mattered to this indirect pathway.

3. Materials and methods

This PhD-project is based on data from the Tromsø Study including both cross-sectional and longitudinal data from the two most recent surveys of this population study. This section provides a description of the study setting of the Tromsø Study and its population, how samples from the study population were selected for the papers of this thesis, the methodology used to collect data and how these were used in the thesis papers, and key ethical aspects of the papers. In the next chapter I discuss the properties of the tools used to gather these data.

3.1. Setting and study population

The Tromsø Study is a population-based study conducted in the municipality of Tromsø, Northern Norway. Tromsø, the largest city of Northern Norway, lies at 69° North, far above the arctic circle, and so is subject to two months of midnight sun and two months of polar night yearly. The Tromsø Study is run and owned by the Department of Community Medicine at UiT - The Arctic University of Norway, and was initiated with its first survey in 1974 as an epidemiological response to the high cardiovascular mortality rates, particularly amongst men, in the region [96]. Since then, it has been repeated several times, with the seventh and latest iteration (Tromsø7) taking place in 2015-2016. Although the study began with an initial weight of focus on cardiovascular disease and risk factors in men, it has been gradually expanded to include both women (Tromsø2) and a broad range of data on other health outcomes. The vast majority of Tromsø Study participants are of Caucasian ethnicity, with a minority being of indigenous Sami origins [43; 90; 96]. Further description of the Tromsø Study and its setting has been published elsewhere in greater detail [96].

Data are gathered through inviting large proportions of the municipal inhabitants to extensive physical examinations, biological sampling, and administering questionnaires both digitally and on-site at a dedicated study locale.

3.2. Data collection – Tromsø6 and Tromsø7

This thesis includes data from the two latest surveys of The Tromsø Study, namely Tromsø6 (2007-2008; [43]) and Tromsø7 (2015-2016; [90]). In Tromsø6, all municipal inhabitants 40-

42 and 60-87 years of age were invited to participate. In addition, random samples of 10% of inhabitants 30-39 and 40% of 43-59 years of age were invited, as well as those who participated in Tromsø4 who had not otherwise been included [43]. Tromsø7 invited total birth cohorts aged 40 years and older [90].

Using the same general setup, both Tromsø6 and Tromsø7 were conducted using on-site visitation centres staffed by administrative staff and research technicians who were given prior training for 3-4 weeks [43; 90]. Participants received mailed invitations with suggested dates and times for their visit but were also free to 'drop in' at a time convenient to them during opening hours. See Appendix 1-5 for the invitation letters, information, and consent form mailed to participants. Eligible attenders of visit1 were invited to a follow-up visit (visit2), 2-4 weeks after. Participants received no monetary reimbursements.

On both survey occasions, questionnaire data were gathered from two questionnaires. In Tromsø6 and Tromsø7, participants received a mailed first questionnaire (Q1 - Appendix 6) together with the survey invitation. In Tromsø6, a second paper questionnaire (Q2 – Appendix 7) was filled in during the visit or later at home and returned by mail. In Tromsø7, the first questionnaire (Q1 – Appendix 8) could be done by paper or digitally, whilst the second (Q2 – Appendix 9) was only available digitally.

3.3. Tromsø6 and Tromsø7 samples and participant characteristics vs non-participants

Survey sample selection has been described in more detail elsewhere for Tromsø6 [43] and Tromsø7 [90]. Invitation and participation patterns are shown in Table 1. This shows curvilinear participation proportion by age.

To summarize, of the 19,765 persons aged 30-87 years invited to Tromsø6, 12,984 participated for a participation proportion of ~66% (53% women). In Tromsø7, of the 32,591 persons aged 40 years or older invited, 21,083 participated for a participation proportion of ~65% (53% women). 79% of Tromsø6 attendees also attended Tromsø7 (n=8,906; 54% women).

Table 1: Invitees and attenders Tromsø6 and Tromsø7. The Tromsø Study: visit1.

Age-groups	Women			Men			Total		
	Invited	Attended	%	Invited	Attended	%	Invited	Attended	%
Tromsø6									
30-39	541	297	54.9	544	212	39.0	1,085	509	46.9
40-49	2,969	1,913	64.4	2,988	1,663	55.7	5,957	3,576	60.0
50-59	1,705	1,289	75.6	1,702	1,147	67.4	3,407	2,436	71.5
60-69	2,635	2,108	80.0	2,702	1,995	73.8	5,337	4,103	76.9
70-79	1,456	988	67.9	1,197	841	70.3	2,653	1,829	68.9
80-87	831	335	42.7	492	196	39.8	1,323	531	40.1
Total	10,137	6,930	68.4	9,625	6,054	62.9	19,762	12,984	65.7
Tromsø7									
40-49	5,195	3,378	65.0	5,562	3,054	54.9	10,757	6,432	59.8
50-59	4,534	3,245	71.6	4,327	2,790	64.5	8,861	6,035	68.1
60-69	3,586	2,677	74.7	3,543	2,502	70.6	7,129	5,179	72.7
70-79	2,001	1,361	68.0	1,897	1,315	69.3	3,898	2,676	68.7
80-89	981	389	39.7	639	325	50.9	1620	714	44.1
90-104	242	24	9.9	84	23	27.4	326	47	14.4
Total	16,539	11,074	67.0	16,052	10,009	62.4	32,591	21,083	64.7
Overall	26,676	18,004	67.5	25,677	16,063	62.6	52,353	34,067	65.1

Values are numbers and proportions.

Reproduced from:
Eggen AE, Mathiesen EB, Wilsgaard T, Jacobsen BK, Njolstad I. The sixth survey of the Tromso Study (Tromso 6) in 2007-08: collaborative research in the interface between clinical medicine and epidemiology: study objectives, design, data collection procedures, and attendance in a multipurpose population-based health survey. Scand J Public Health 2013;41(1):65-80.
And:
Hopstock LA, Grimsgaard S, Johansen H, Kanstad K, Wilsgaard T, Eggen AE. The seventh survey of the Tromso Study (Tromso7) 2015-2016: study design, data collection, attendance, and prevalence of risk factors and disease in a multipurpose population-based health survey. Scand J Public Health 2022:14034948221092294.

3.4. Research questions and study sampling

The research questions that were identified to achieve the objectives of this thesis are illustrated in Figure 7. At most, 22,271 unique participants contributed data to the papers included in this thesis.

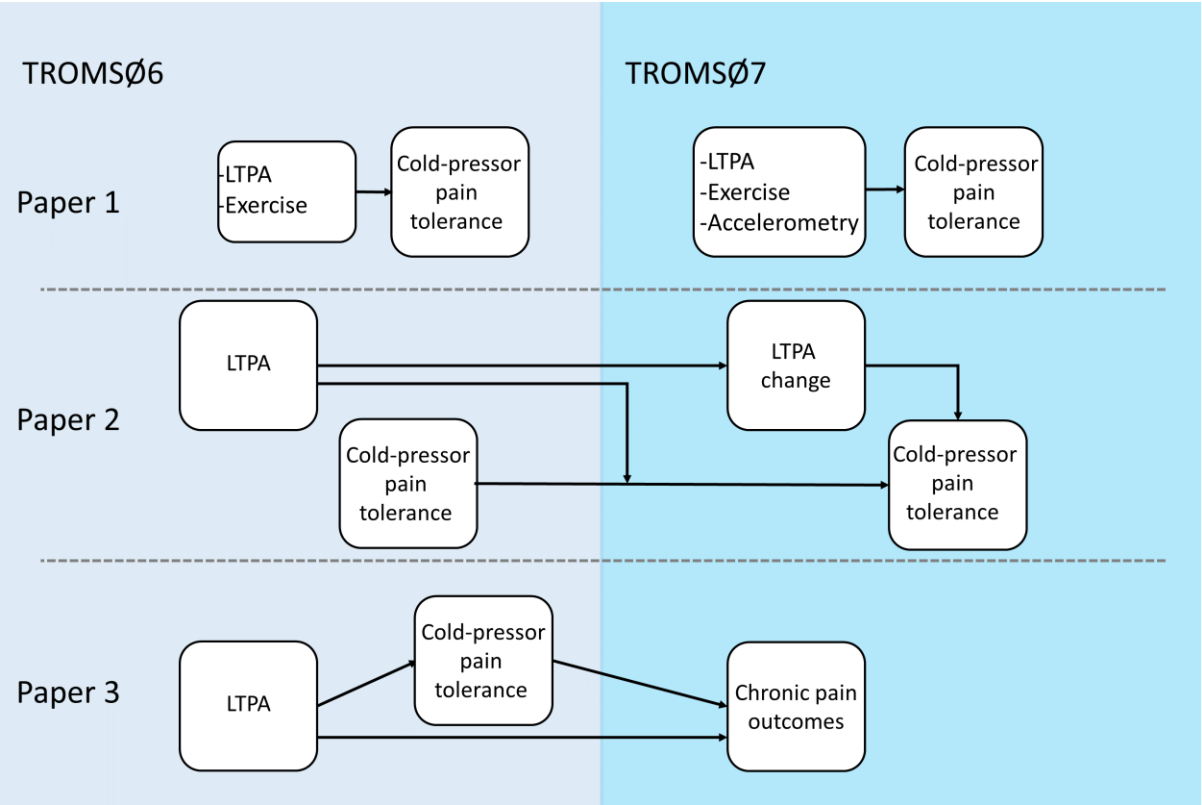


Figure 7: Schematic representation of study questions explored in the thesis. LTPA=Leisure-time physical activity.

3.4.1. Paper I

In Paper I we investigated 1) whether different levels of PA were cross-sectionally associated with different pain tolerance level, and 2) whether this depended on the type of PA-measurement used. We also assessed whether sex and chronic pain moderated the relationship.

Paper I thus constituted a pooled cross-section of data on individuals who participated in CPT in Tromsø6 or Tromsø7 (n=22,271), and who provided concurrent measures of self-reported PA in Tromsø7 and/or accelerometer-measured PA data in Tromsø7. For those participants who provided data in both Tromsø6 and Tromsø7, we used their cross-sectional data from Tromsø7.

3.4.2. Paper II

In Paper II we assessed 1) the relationship between longitudinal habitual PA change and subsequent pain tolerance, and 2) whether PA moderated any change in pain tolerance over time in the longitudinal relationship between habitual PA and pain tolerance in repeated measurements of individuals. We also assessed whether these relationships varied according to sex or chronic pain status.

Paper II therefore included individuals with data on CPT in either Tromsø6 or Tromsø7, and LTPA in Tromsø6. Primary analyses further required self-reported LTPA in both Tromsø6 and Tromsø7, as well as CPT in Tromsø7 (n=6,608). Secondary analyses included participants with self-reported LTPA in Tromsø6 and CPT in Tromsø6 or Tromsø7 (n=10,254).

3.4.3. Paper III

In Paper III we investigated whether CPT tolerance acts as a mediator for the effect of PA on risk of chronic pain. We investigated whether such effect varied with different definitions of chronic pain. We also examined how effects changed when using baseline sample without any present chronic pain, and also according to sex.

Paper III thus included individuals who participated in both Tromsø6 and Tromsø7 (N=8,906), who had information on LTPA in Tromsø6, CPT in Tromsø6, and chronic pain in Tromsø7 (n=6,834).

3.5. Inclusion of variables and methodology

3.5.1. Exposure: Physical activity

The exposures variables of the studies of this thesis were measures of habitual physical activity. The Tromsø Study has employed two main methodologies for measuring PA levels in the population: self-reported (all surveys), and device-measured (Tromsø7).

Self-reported PA

Participants reported on habitual physical activity level in Tromsø6 and Tromsø7 through two self-reporting instruments. The first is the modified Saltin-Grimby Physical Activity Level Scale (SGPALS), which asks participants to recall and rank their average physical activity

level for the past 12 months according to four mutually exclusive categories. The instrument differentiates between activity performed during occupation and in leisure time, and provides exemplars for each of the categories (Table 2).

The SGPALS was originally developed to assess physical activity levels in middle-aged males who were former athletes and has been widely used, amongst others in Nordic countries in general and in Norway in particular [68].

Table 2: Saltin-Grimby Physical Activity Level Scale (SGPALS)

Leisure-time physical activity Tromsø6: *"Exercise and physical exertion in leisure time. If your activity varies much, for example between summer and winter, then give an average. The question refers only to the last twelve months."* Leisure-time physical activity Tromsø7: *"Describe your exercise and physical exertion in leisure time over the last year. If your activity varies throughout the year, give an average."*			
Sedentary: "Reading, watching TV/screen or other sedentary activity?"	Light: "Walking, cycling, or other forms of exercise at least 4 hours a week? (including walking or cycling to place of work, Sunday-walking, etc.)"	Moderate: "Participation in recreational sports, heavy gardening, snow shoveling etc at least 4 hours a week."	Vigorous: "Participation in hard training or sports competitions, regularly several times a week?"

As there is no established gold standard for measuring PA, the validity of questionnaires has frequently been assessed by their concurrent validity with other measures of PA or measurements of physical fitness, and by their predictive validity for risk factors of morbidity and mortality [68].

Concurrent validity appears overall adequate. SGPALS correlates strongly with another much-used PA questionnaire – the long version of the International Physical Activity Questionnaire [65]. Furthermore, in a study of 138 Danish adults, the Danish version of SGPALS was significantly associated with accelerometer-measured PA level, with a moderately good ability to rank individuals according to accelerometer-estimated energy expenditure (r=0.71), total PA (0.64), and moderate-to-vigorous PA (MVPA) (0.53) [141]. Two Tromsø Study-based papers reported weak-to-moderate correlations to accelerometer-assessed total, light, and moderate-to-vigorous PA [47; 190]. In the study by Emaus et al., All types of accelerometer-estimated PA increased significantly with increasing SGPALS levels

[190]. In comparison, correlations of PA questionnaires (PAQs) to accelerometry rarely exceed 0.6 [204].

Regarding fitness, SGPALS showed significant moderate correlation with treadmill-assessed VO_{2max} (ml/kg/min) among 313 Tromsø6 participants, at r=0.40 for women and r=0.44 for men [47]. Resting heart rate correlations were lower, at r=-0.24 for women and r=-0.17 for men. In a random subsample from Tromsø3 (1986-87; n=609), bicycle-assessed fitness increased ($p<0.001$) and heart rate (significantly for women only) decreased with LTPA [134]. In a walking test on 422 participants from Oslo, SGPALS had an age-adjusted correlation coefficient of 0.3 to VO_{2max} [65].

Earlier findings show that increasing level of SGPALS is negatively associated with lower population risk of breast cancer in women (relative risk (RR) 0.63 (0.42 – 0.95) [224], incidence of fractures (RR 0.6 (0.4 – 0.9)) [98], diabetes mellitus type 2 [95], current and future work ability [10] and long-term sickness absence [86], coronary heart disease and associated risk factors like smoking, self-reported stress and mental health challenges, body composition, smoking, resting heart rate, fasting plasma-glucose, and blood lipids (serum triglycerides, low-density lipoproteins and total cholesterol [6; 7; 65; 103; 134; 186]. Although such correlations have sometimes been weak, they have mostly been consistent in their direction [65; 134], including across several sub-cohorts over 25 years [6]. Low correlation coefficients are to be expected between LTPA and cardiovascular risk factors given their high variability with diet, health status, and heritability [65]. Furthermore, SGPALS also shows strong predictive effect on coronary/cardiovascular, cancer, and all-cause mortality independently of other risk factors in large cohorts [92; 187; 191; 197].

Regarding the reliability of SGPALS, one small reproducibility analysis has found 86% agreement between two self-reports separated by one month, in 29 participants of a population-based cohort [203]. In the study by Emaus et al., test-retest intra-class correlation coefficients between SGPALS and accelerometry were 0.62 for total amount PA, 0.31 for light PA, 0.65 for MVPA, 0.75 for vigorous PA, and 0.86 for VO_{2max} (ml/kg/min), showing an overall moderate to good reliability [47].

The other self-reported PAQ used is the Physical Activity Frequency, Intensity, and Duration questionnaire (PAFID). This instrument was developed for self-reporting on exercise in the Norwegian Health Survey of North Trøndelag (HUNT) [117]. Here, participants respond to three items regarding the average frequency, duration, and intensity of their habitual exercise

if such is performed (Table 3).

Table 3: Physical activity frequency, intensity, and duration questionnaire (PAFID)

Frequency Tromsø6 and Tromsø7: *"How often do you exercise (i.e. walking, skiing, swimming or training/sports)?"*				
1: "Never"	2: "Less than once a week"	3: "Once a week"	4: "2-3 times a week"	5: "Approximately every day"
Intensity Tromsø6 and Tromsø7: *"If you exercise - how hard do you exercise?"*				
1: "Easy - you do not become shortwinded or sweaty"	2: "You become shortwinded and sweaty"	3: "Hard - you become exhausted"		
Duration Tromsø6 and Tromsø7: *"For how long time do you exercise? (give an average)"*				
1: "Less than 15 minutes"	2: "15-29 minutes"	3: "30-60 minutes"	4: "More than 1 hour"	

PAFID is a newer and less used PAQ. When combined into a single index, it shows strong positive association to accelerometer estimates of total, light, and moderate-to-vigorous PA ($p<0.001$) [190].

It shows poor correlation ($r=0.24$) but statistically strong association to VO_{2max} (ml/kg/min) ($p<0.0001$) [135]. In Kurtze et al., VO_{2max} increased with higher levels reported for each item separately [117]. Similar to SGPALS, PAFID here showed consistent, though at times weak, correlations with accelerometry estimates of activity level such as energy expenditure and total amount of PA.

In a small validation study (n=102) from HUNT, test-retest agreement was $r=0.80$ for frequency, $r=0.82$ for intensity, and $r=0.69$ for duration, suggesting good to very good reliability [117].

SGPALS was coded as a four-level categorical variable of LTPA with categories equalling those of the questionnaire. Furthermore, the PAFID-instrument yielded three distinct categorical variables of habitual exercise frequency, intensity, and duration, each with a number of categories corresponding to that of the instrument items.

Exposures for Paper I included LTPA from the SGPALS and all three PAFID variables to examine if any single component of exercise might be more relevant for pain than others. For PAFID frequency, we combined categories one and two, and categories three and four,

yielding a three-level categorical exposure variable: “never or less than once per week”, “one to three times per week”, and “approximately every day”. For PAFID duration, we combined categories one and two into one category, yielding a three-level categorical exposure variable “0-29 minutes”, “30-60 minutes” and “more than 60 minutes”. The recoding was done in order to preserve statistical power in modelling. PAFID intensity was used as a four-level categorical without recoding.

Exposure for Paper II was LTPA from the SGPALS. Categories three and four were combined into the new category “Moderate-to-vigorous LTPA” (MVPA). The resulting three-level categorical variable was used as is, in addition to a LTPA-change index computed by multiplying the three-level categorical from Tromsø6 with the same from Tromsø7 and adding all products as separate categories in a new nine-level categorical variable, the LTPA change index.

Exposure for paper III was SGPALS LTPA, used as a continuous variable.

For all use of self-reported PA, comparison between groups were done against the lowermost category.

Device-measured PA in the Tromsø Study

In addition to the questionnaires, accelerometry was also used to gather data on physical activity in the 7th survey of the Tromsø Study.

All participants who attended visit2 were invited to wear the triaxial ActiGraph accelerometer (ActiGraph wGT3X, ActiGraph, LLC, Pensacola, Florida, United States) for eight consecutive days (recordings started at 00:00 the day after the accelerometer was issued). In the Tromsø Study, the ActiGraph was placed at the right hip by means of an elastic band. Instructions to participants detailed to perform all activities as usual, but that the ActiGraph was to be removed when showering, bathing, swimming, diving, going to the sauna, or performing sports with high amounts of physical contact. Accelerometers would then be returned by mail in provided envelopes.

Total sampling time was set at 24 hours every day for seven consecutive days. The sampling frequency of acceleration was set to 100 Hz (100 samplings per second), recorded in three axes (sagittal, vertical, coronal). Triaxial accelerometers provide vector magnitudes (VM), i.e. the square root of the sum of squared activity counts. Raw data were recoded into 10 second acceleration epochs for each of the axes using ActiGraph proprietary software

(ActiLife, ActiGraph, LLC, Pensacola, Florida, United States). Raw data were further processed using the Quality Control & Analysis Tool (QCAT), a custom-made software developed in MATLAB (The Math Works, Inc., Natick, Massachusetts, United States), where epochs were summed into 1-minute epochs before further processing.

Non-wear time was defined using the Hecht 2009 algorithm [79] on the 1-minute epochs. This algorithm states that at least two of the following conditions must be fulfilled for a minute to classify as wear-time: 1) >5 VMs during this minute, 2) at least two minutes with >5 VMs during the following 20 minutes, and/or 3) at least two minutes with >5 VMs during the preceding 20 minutes. Required wear-time was set to a minimum of 4 days, with a daily wear-time of at least 10 hours, for accelerometry measurement to be regarded as valid.

Level of PA intensity was classified according to cutoffs for VM counts per minute as proposed by Sasaki et al. [195] MVPA and Peterson et al. [176] for sedentary as follows: sedentary behaviour <150; light 150-2,689; moderate 2,690-6,166; vigorous 6,167-9,642; very vigorous >9,642. This allowed computing minutes spent in each intensity per valid wear time day. A total of 6,333 invited individuals consented to participate in accelerometry in Tromsø7, of whom 43 were excluded post-hoc due to lost accelerometers and technical errors, and 165 due to non-valid data (mainly, less than four days with at least 10 hours of wear time).

Triaxial Actigraph GT3X-estimated total PA, MVPA, and PAEE show moderate correlation to PAEE estimated using DLW, with triaxial accelerometry achieving higher correlations than uniaxial [34]. This is comparable validity to that of other triaxial accelerometer brands [177]. Furthermore, cutoffs for activity intensity can exert strong influence on estimates of time spent [34], and placements on the body can significantly affect PAEE-estimates, of which hip placement showed the best criterion-validity [115]. Santos-Lozano showed moderate to high ability of the GT3X to correctly classify PA intensities when validating cut points against indirect calorimetry [193]. However, accelerometry has a risk of underestimating volume in certain PA types in free-living, such as heavy lifting/carrying, swimming, and biking, thus underestimating PAEE [73]. Accelerometer data further make no distinction between domains of PA.

Very high correlations between two GT3X units simultaneously worn on the hip suggests strong reliability for measuring overall and intensity-specific PA levels, with r = 0.93–0.99 for 7-day wear-time [254].Thus, accelerometry-based estimates of PA correlates moderately well to both questionnaires and DLW-estimated PAEE, appears to have good

reliability, but the estimates produced are dependent on a number of choices made in relation to the device, data-collection process, and processing of data.

From the accelerometer data we extracted total VM counts per minutes as a measure of total physical activity, and average daily minutes of MVPA performed in bouts of at least 10 minutes. The choice of requiring MVPA bouts of at least 10 minutes was driven by the fact that at the time the prevailing WHO recommendations included performing MVPA in ≥10-minute bouts.

These two accelerometry variables were used as exposures in Paper I. They were both standardized into z-scores before being used as continuous variables. The process involves subtracting the mean of the variable from the value of each case value, yielding a mean of zero, and divided by the standard deviation. This produces transformed variables so that each observed value indicates the difference from the original variable's mean in number of standard deviations [3]. This equals changing variable units from single VM counts or MVPA minutes, to number of standard deviations from the original means. This was done to ease the interpretation of coefficients as the number of decimals would decrease substantially, and has no effect on statistical significance testing. Both standardized variables were added as continuous independent variables.

3.5.2. Outcome and mediator: Quantitative sensory testing of pain, and pain tolerance

In Tromsø6 and Tromsø7 the Norwegian National institute of public health (NIPH) and Olso University Hospital (OUS) contributed with a research project called the Tromsø Pain Study. This project sought to acquire population data on both clinical pain and QST. The latter involved extensive test protocols which required dedicated space, equipment, and personnel on-site during both surveys. Research stations were equipped, staffed, and supervised in a collaboration between the Tromsø Study staff and the NIPH and OUS researchers. This included providing research personnel with protocol training prior to the start of the survey, which included performing the protocol on each other as one of the key training items. Subsequent QST performance was continuously monitored according to research technician ID to ensure the possibility timely intervention given any sign of systematic differences.

Tromsø6 had two research stations dedicated to QST, with a QST protocol that was initiated with a CPT of tolerance threshold on the dominant hand concurrent with a blood-pressure measurement protocol. This was followed either by a pressure pain test of the

opposite hand's ring finger cuticle (or optionally index- or little finger), using a handheld pressure algometer, or by a heat pain threshold test applying a 3x3 cm thermode to the volar forearm. At times, a lack of capacity at the QST stations in Tromsø6 caused some participants to be turned away. When this occurred, staff were instructed to prioritize testing participants <60 years of age, which was the least sampled group at the time [212].

Tromsø7 had four dedicated QST research stations in order to better accommodate the extended protocol as well as to avoid the periodic lack of capacity in Tromsø6. The QST protocol in Tromsø7 was more extensive, exchanging some modalities and testing more parameters than previously. Differences included performing CPT of tolerance threshold on the non-dominant hand, as well as computerized cuff-pressure algometry (CPA) using blood-pressure cuffs around both calves if possible. During the procedure participants were tested in the following order: CPA threshold on dominant leg, CPA tolerance on non-dominant leg, CPA tolerance on dominant leg, CPA conditioning stimulus (70% of same side tolerance threshold) on non-dominant leg, CPA tolerance on dominant leg, CPT tolerance threshold on non-dominant hand, CPA tolerance on dominant leg.

In both surveys, CPT testing employed a 13-litre plexiglass vat with water continuously circulated by a cooling circulator (Julabo FP40HE, Julabo Labortechnik GmbH Germany, 22 l/min), with temperature control provided by a precision thermometer placed in the vat. The water was maintained at 3° Celsius. Participants were screened before inclusion to the CPT, with exclusion criteria including reluctance to participate, bilateral loss of sensitivity in the hand, bilaterally breached skin of the hands caused by particular conditions (painful eczema, open sores, etc.), Reynaud's syndrome or cold allergy if believed by the participant to be an obstacle for testing, and inability to follow instructions.

Cold pain tolerance threshold was defined as the maximum achieved test-tolerance time before withdrawing from or completing the CPT. Maximal allowed tolerance time was set to 106 seconds in Tromsø6 and 120 seconds in Tromsø7, resulting in two corresponding continuous variables containing seconds endured in each test as their values. Corresponding dichotomous indicator variables were also created with values 1 given to all those who withdrew their hand from the water before the maximum time was reached, and 0 for all who did not withdraw. The resulting continuous variables were marked by a pronounced right skew, as seen in Figure 8. This was owed to the right-censoring imposed by the maximum allowed time.

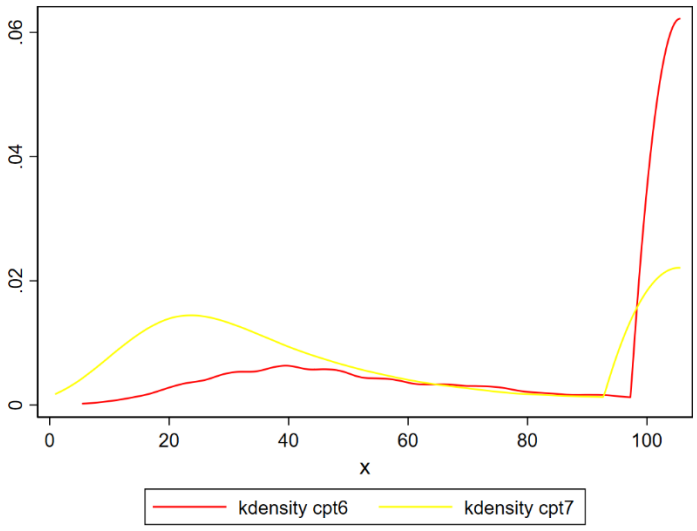


Figure 8: Tolerance times in the cold-pressor test for Tromsø6 and Tromsø7.

QST data, and CPT tolerance data in particular, have not previously been collected at population level like that of the Tromsø Study. The reliability of such data are therefore not well established. In general, cold-pain QST has shown good-to-excellent long-term reliability (Intra-class correlation coefficients (ICCs) 0.77-0.79) [140]. One small study re-examined cold-pain tolerance in 155 men and 108 women at a mean of 54 days after their Tromsø6 participation. Test-retest correlation was 0.82 between Tromsø6 and first re-test, and 0.93 between first and second re-test performed on the same day [162]. One study comparing CPT data a controlled laboratory setting in Tromsø6 (n=10,486) and Haifa, Israel (n=648) versus home-administered CPT in the US (n=1,826) found distributions of CPT tolerance times to have comparable distribution patterns [142]. It should be noted that, in population data from the Tromsø Study, CPT tolerance has been found vary according to both meteorological conditions as well as seasons [48]. Averaging measurements throughout the year should attenuate these variations.

A 2012 review by Moloney et al. examined 21 papers of reliability and reproducibility of thermal QST [154]. They found fair-to-good reliability in six papers on repeated CPT pain thresholds. Notably, the authors did not specify any search terms for tolerance thresholds.

One later study on test-retest reliability of CPT measures found no significant differences in cold-pain tolerance estimates in healthy students (n=59) when measured at 2-week intervals [110]. The study found excellent 2-week test-retest reliability at both 4°C and

6°C, with correlation coefficients that were higher for cold-pain tolerance than for thresholds (0.81 vs. 0.62 for 4°C and 0.86 vs. 0.73 for 6°C).

When designing the papers of this thesis, the static parameters from Tromsø6 were available. Among these, CPT had the highest participation rate. During the PhD-project, the static parameters from Tromsø7 CPT were also made ready for analysis. We subsequently chose to use CPT tolerance as our main exposure and eventual mediator. This would also provide the highest statistical power possible. Furthermore, tolerance thresholds appeared in the literature to produce stronger and more consistent associations to physical activity [222].

Thus, CPT tolerance served as both outcome and mediator in the papers of this thesis. Paper I used the continuous CPT variables and their corresponding dichotomous indicator variables from Tromsø6 and Tromsø7 as the main outcomes. As the maximum allowed time in Tromsø7 was 120 seconds and we wished to have similar dependent variables, this was censored at 106 seconds and all participants achieving ≥106 seconds were identified as 'survivors' by being given a 0 on the corresponding dichotomous indicator variable.

Paper II used the continuous CPT variables from Tromsø6 and Tromsø7 as the main outcomes.

Paper III used the continuous CPT variable from Tromsø6 as a mediator. A mediator is a variable which represents a pathway, or a mechanism, through which an exposure might affect an outcome as an indirect part of the total effect of the exposure on that outcome [242].

3.5.3. Outcome and moderator: Chronic pain

Chronic pain served as both outcome and moderator in the papers of this thesis.
In both Tromsø6 and Tromsø7, one questionnaire item in Q1 asked "Do you have persistent or constantly recurring pain that has lasted for 3 months or more?" (Appendices 6 and 8, item 4, p. 1). This yielded a corresponding dichotomous variable.

Tromsø7 also used a novel tool for self-reporting pain and pain characteristics, namely the Graphical Index of Pain (GRIP) ([215]. GRIP was created to be a web-based questionnaire that would be easy for surveys to administrate and participants to use, with a long-term goal of improving the global standardization of pain measurements. GRIP consists of a body map

which is two-tiered, with 10 first-tier, and 167 or 168 second-tier, body regions for men and women respectively (see Figure 9 for all tier 1 regions and Figure 10 for examples of tier 2 regions). Participants received login information along with their written and mailed invitation to the first visit of Tromsø7, along with instructions for completing the questionnaire. The GRIP was only digitally available. More than 96% of Tromsø7 participants returned the questionnaire [215].

The initial entry screening question of GRIP stipulates respondents should only address such pain that has been suffered the past four weeks. First-tier regions are accompanied by anamnestic information regarding the pain. Amongst other, this included time since first onset was reported from the options "four weeks", "1-2 months","3-5 months", "6-11 months", "1 year to five years", "If more than 5 years, how old were you". Furthermore, intensity, bother, (anchors: "No pain" / "The strongest imaginable pain" and "No bother" / "The greatest imaginable bother"), and impact on daily activities were measured on 11-point numerical rating scales.

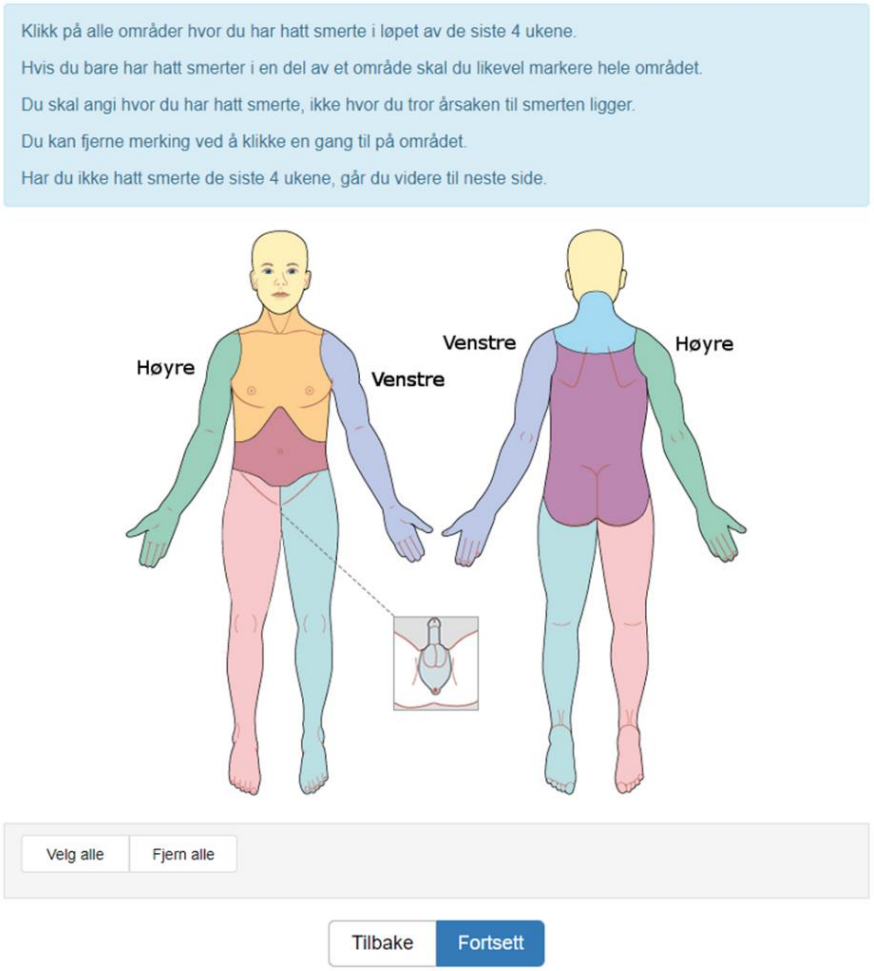


Figure 9: Graphical Index of Pain, tier 1 anatomical regions.

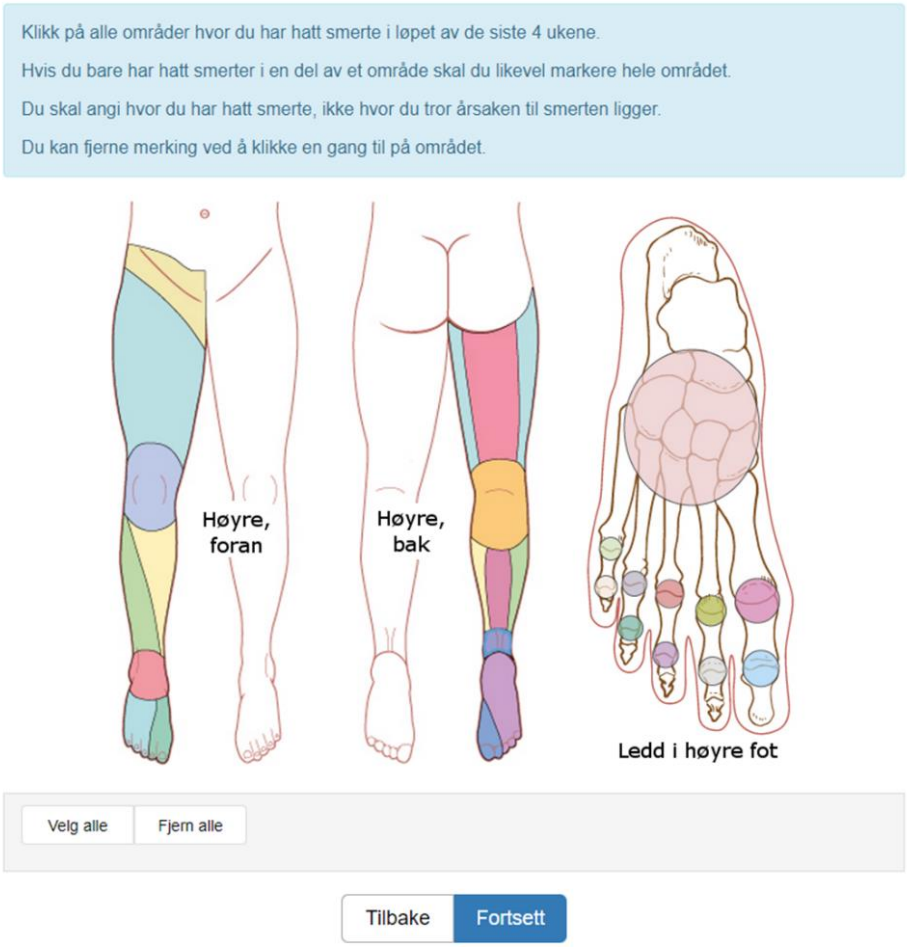


Figure 10: Graphical Index of Pain, tier 2 anatomical regions, examples.

GRIP data were used to construct four different chronic pain outcomes. First, chronic pain was defined as pain in any first-tier region pain persisting or recurring for longer than 3 months. Second, widespread chronic pain was defined as chronic pain which was experienced in ≥7 number of tier-one sites (0-19 possible sites), and in four or more body regions (axial, left upper, right upper, left lower, or right lower possible regions). Third, in an approximation of ICD-11 criteria [228], moderate-to-severe chronic pain was defined as chronic pain with onset ≥ 3months, intensity >3, bothering >3, impact on activities of daily living >3. Fourth, widespread moderate-to-severe chronic pain was created by combining all previous criteria. All four definitions yielded a corresponding dichotomous "yes/no" variable.

As a novel tool, GRIP has not yet been studied for validity or reliability. In general, there is long-standing use of body manikins for gathering pain data and GRIP was developed as a standardized high-resolution version of the numerous types of analogue and digital tools that have been used previously [215]. Digital questionnaires and the use of body manikins has

been suggested to provide better completeness and adherence, and equally good information on pain location as compared to paper questionnaires [101; 139; 237]. As 96% of Tromsø7 participants across all included age-groups responded to GRIP, its design does not appear to be a barrier for respondents. This could suggest that GRIP is a feasible tool for reporting on clinical pain in large population studies.

Based on the literature referenced in the introduction, Paper I used chronic pain as a moderator of the relationship between PA and CPT tolerance. A moderator is a variable which *interacts* with the exposure to produce a different effect on the outcome – the effect being studied depends on the level of another variable, the moderator [35; 243]. Such possible interaction between LTPA and chronic pain was in Paper I examined using the dichotomous variable derived from Q1, as well as using GRIP-defined moderate-to-severe chronic pain.

Paper II also used the Q1-derived dichotomous chronic pain variable to assess interaction with LTPA.

Paper III used the four GRIP-derived dichotomous variables chronic pain, widespread chronic pain, moderate-to-severe chronic pain, and widespread moderate-to-severe chronic pain as four separate outcomes.

3.5.4. Covariables: Confounders, moderators, and colliders

In any epidemiological study there is a chance that a third variable can exert distortive influence on the relationship between an exposure and the outcome. Part of the apparent effect of the exposure on the outcome might then be owed to this unseen influence of another variable – this is the confounder effect [35]. If confounders are not properly accounted for in statistical models, they will bias corresponding effect estimates of the dependent variable.

In Paper I we selected potential confounders based on a combination of pre-existing rationale for what might plausibly affect the relationship between PA and pain tolerance as well as an evaluation of how those potential confounders affected model estimates. For Paper II we based confounder selection solely on pre-existing literature and co-author discussions, whilst in Paper III we added to such discussion a pre-hoc directed acyclic graph (DAG). DAGs can be useful tools for visualizing exposures, outcomes, and potential sources of bias [133]. This allows researchers to make explicit model choices, and readers to critically appraise those

choices. The DAG thus detailed how we believed potential candidate confounders, mediators, moderators, and colliders would behave in our models.

The Tromsø Study gathered data on age and sex from the National Population Register of Norway. Age is a known important confounder in most epidemiological studies in general [35] and for several pain sensitivity modalities [71; 123], although evidence regarding tolerance thresholds is less equivocal. Sex is an established determinant of pain sensitivity and chronic pain [18; 151; 153]. Age and sex were therefore included as potential confounders in all papers of this thesis. Sex was furthermore included as a potential moderator of the associations being studied.

Body composition has been associated with chronic pain and in some instances pain sensitivity [109; 205; 251]. Waist circumference and height were measured for all participants, generating continuous variables for both. We recalculated these into waist-height-ratio (WHtR) as this is has been suggested to be a better proxy for body composition than other measures like body-mass index [218]. WHtR is calculated by dividing waist circumference in centimetres on body height in centimetres. We included WHtR as a confounder in Paper I. However, in Papers II and III we had come to consider the possibility that body composition might mediate an effect of physical activity on pain sensitivity and chronic pain, and therefore elected not to include it as a confounder.

Participants further self-reported on education level as: “primary or secondary school up to 10 years”, “technical/vocational/high school up to three years”, “college/university less than four years”, “college or university for four years or more”. This generated a four-level categorical variable. Data on smoking was acquired from participants reporting whether they were daily smokers: “never”, “former” or “current daily smoker” as a categorical variable; and number of cigarettes smoked per day for present or former daily smokers as a continuous variable. Habitual alcohol consumption frequency was reported as: “never”, “monthly or less frequently”, “2–4 times a month”, “2–3 times a week”, “4 or more times a week” as a categorical variable, and habitual number of units consumed when drinking alcohol: “1–2”, “3–4”, “5–6”, “7–9”, “10 or more” as another categorical variable.

Proxies of socioeconomic status, such as education level and substance use or abuse, e.g. smoking and alcohol consumption, are general predictors of health and functioning as well as of chronic pain and higher sensitivity to pain [105; 109; 116; 122; 205]. As seen in the introduction, physical activity is also related to markers of socio-economic status. We

therefore included them as potential confounders in all the papers of this thesis. In Paper I, we adjusted for smoking by creating a combined variable for daily smoker status and average daily number of cigarettes smoked for smokers, with categories: “never smoked daily”, “smoked daily previously”, “smokes between 1 and 10 cigarettes daily” and “smokes more than 10 cigarettes daily”. Alcohol was included by creating a categorical variable of approximate tertiles indicating the average number of units consumed each week by multiplying average alcohol consumption frequency with average number of units consumed.

For Papers II and III, only the average alcohol consumption frequency variable was used as it was observed to contribute equally well to models without incurring loss of information by requiring responses on an additional variable. The same was the case for the daily smoker status variable.

Participants further reported on yearly household income: “What was the households total taxable income last year? Include income from work, social benefits and similar” with options “Less than 125000 NOK”, “125000-200000 NOK”, “201000-300000 NOK”, “301000-400000 NOK”, “401000-550000 NOK”, “551000-700000 NOK”, “701000-850000 NOK”, and “more than 850000 NOK”, which generated an 8-level categorical variable. We included household income as a potential confounder in Paper III due to peer advice that alcohol, smoking, and education might not fully capture socioeconomic factors, and because it is independently associated with chronic pain [105]. Income was recoded into a 3-level variable for the sake of not sacrificing modelling power: “0-300k”, “300k-700k”, and “above 700k”.

Self-reported health was reported as: “very bad”, “bad”, “neither good nor bad”, “good”, “excellent”, generating a five-level categorical variable. Papers I and II included it as a potential confounder because co-morbidities (e.g. diabetes) which might impact self-reported health could potentially also impact pain sensitivity. Furthermore, factors like stress and health status have a potential impact on PA levels [19]. The two lowermost groups were combined into a single category “very bad or bad” due to very small numbers in the lowermost category, yielding a four-level categorical variable. We refrained from including this in Paper III due to the possibility of opening a backdoor path to the exposure, given that chronic pain likely affects self-reported health. This would likely induce bias in our results.

In Papers I and II, we added chronic pain from Q1 as a potential confounder to address its impact on pain sensitivity and explore its potential role in moderating the effect of PA. However, in Paper III, we omitted baseline chronic pain as a confounder due to the likelihood

of it being a mediator of the effect of PA on chronic pain at follow-up — a phenomenon known as Lord's paradox [173]. In such scenarios, adjusting for the baseline variable introduces bias by removing its indirect effect from the total estimate of PA's impact on chronic pain.

SGPALS also contains an item for reporting habitual OPA: “If you have paid or unpaid work, which statement describes your work best?” with options “Mostly sedentary work? (e.g. office work, mounting)”, “Work that requires a lot of walking? (e.g. shop assistant, light industrial work, teaching)”, “Work that requires a lot of walking and lifting? (e.g. nursing, construction)”, and “Heavy manual labour”. We included SGPALS OPA level as a four-level categorical potential confounder for Papers II and III, since the physical activity paradox had been brought to our attention and we wished to assess the effect of LTPA independently of OPA. Participants who had no employment or who on another item reported being retired or on disability pensions, unemployment benefits, or sick leave, were assigned to the added categories “retired” or “disability/sick leave”, respectively, so as not to lose those cases from analyses.

Finally, a categorical variable indicating baseline or follow-up (Tromsø6 or Tromsø7) was added as a potential confounder to Paper II in order to represent time, as time might influence longitudinal change in pain sensitivity and moderate the effect of physical activity on pain sensitivity.

3.6. Statistical analyses

Table 4 outlines the modelling decisions of all three papers. Modelling choices are further discussed below. All statistical analyses included in the thesis were performed using Stata 15-17 (StataCorp, College Station, TX, USA). Additionally, R (R Foundation for Statistical Computing, Vienna, Austria) was used for select analyses of Paper II.

Table 4: Models at a glance – modelling choices of Papers I-III

	Paper I	Paper II	Paper III
Study design	Cross-sectional	Longitudinal	Longitudinal
Model types	1. Cox regression survival analysis	2. Tobit analysis of covariance 3. Tobit mixed model	1. Counterfactual mediation analysis
Exposure	- LTPA SGPALS Tromsø6+Tromsø7 - PAFID Tromsø7 - Accelerometry Tromsø7	- LTPA SGPALS change Tromsø6-7 - LTPA Tromsø6	- LTPA SGPALS Tromsø6
Outcome	- CPT tolerance threshold Tromsø6+Tromsø7	- CPT tolerance threshold Tromsø6+Tromsø7	- Chronic pain - Widespread chronic pain - Moderate-to-severe chronic pain - Widespread moderate-to-severe chronic pain Tromsø7
Confounders [a]	- Sex - Age - Education level - Smoking status - Average alcohol consumption - Self-reported health - Chronic pain / moderate-to-severe chronic pain - Waist-height-ratio	- Sex - Age - Education level - Daily smoking status - Alcohol consumption frequency - Self-reported health - Chronic pain - OPA - Measurement time	- Sex - Age - Education level - Daily smoking status - Alcohol consumption frequency - OPA - Household income
Confounder criteria	Previous rationale and ±10% coefficient change	Pre-hoc modelling rationale, prior knowledge	Pre-hoc modelling rationale, prior knowledge, DAG of model
Mediator			- CPT tolerance Tromsø6
Moderators	- Sex - Chronic pain - Moderate-to-severe chronic pain	- Sex - Chronic pain - Time	- Sex (stratification)

[a] Models in paper I were adjusted for concurrent covariates (Tromsø6 or Tromsø7), models in papers II-III were adjusted for baseline covariates (Tromsø6).
LTPA=leisure-time physical activity; SGPALS=Saltin-Grimby physical activity level scale; PAFID=Physical activity frequency intensity duration scale; CPT=Cold-pressor test; OPA=Occupational physical activity level; DAG=Directed acyclic graph.

3.6.1. Descriptive characteristics

Descriptive characteristics of participants were tabulated and summarized in tables and results of Papers I-III according to likely relevant subgroupings in the dataset, to let readers critically assess variations in absolute distributions.

3.6.2. Modelling in Paper I

We used survival analysis with Cox proportional hazards (PH)-models to examine the relative risks PA groups had of withdrawing their hand from the CPT before the maximum allowed test time was reached. This time-to-event analysis was chosen above an ordinary regression-type model as we were not only interested in the final observed proportion of 'hand withdrawers' to 'survivors' in the different PA groups, but also the speed (i.e. the hazard rate) with which these groups experienced the event [60]. Using survival regression yields outcome estimates in the form of relative group hazard rates, the hazard rate ratio (HRs), providing an overall comparison of group hazards for experiencing the event (here: hand withdrawal). In this context, all participants achieving the maximum allowed CPT time of 106 s were counted as having been at risk of but not having experienced the event of interest during the test time. Earlier studies have similarly modelled CPT tolerance in the Tromsø Study using survival analysis [99; 168; 192].
We estimated one model for each of the SGPALS LTPA, PAFID, and accelerometer-derived standardized bouted MVPA and total VM counts as described in chapter 2.5.1; in total six separate models. Candidate confounders were added to bivariate statistical models. If the model main effect estimate for the exposure on the outcome changed by ±10%, the variable was added as a confounder in the final model.

The Cox PH-model requires that there be no dependency between HRs and survival time – here, that the effect estimates did not vary according to the time of CPT. We used the Schoenfeld residuals-based goodness-of-fit test as well as visual inspection of log–log survival plots to ensure that this proportional hazards assumption was not violated [108; 172].

Sex- and chronic pain interactions were assessed by multiplying each to the PA exposures and adding the cross-products to the models to check for statistically significant effect of the interaction variable (interaction analyses). We also used likelihood ratio-tests of models with and without the interaction terms to assess whether it contributed meaningful explanatory effect to the model.

Sensitivity analysis included investigating associations between LTPA and CPT tolerance in the accelerometry sub-sample, to see whether it differed in the sub-sample compared to the sample of the LTPA model. Another sensitivity analysis assessed impact on interactions when using the moderate-to-severe chronic pain definition in replicated models.

3.6.3. Modelling in Paper II

This paper utilized two different types of models to perform two sets of analyses. Both were based on a model class called Tobit regression. This model, first proposed by J. Tobin in 1958, was originally developed for use in economics specifically to handle instances of dependent variables containing censored data [225]. Censoring occurs when observations are present and included in data, but certain levels are set to a pre-determined value - the censor value [29]. So-called 'right' censoring occurs in the CPT data due to the imposed cut-off in the variable by the maximum allowed time limit. Here, there is an upper bound to possible values in observations, i.e. to the 'right' of the possible range. In total, 68.3% of CPT-participants were right-censored in Tromsø6 and 38.2% in Tromsø7, i.e., they reached the maximum time allowed. As shown in the graph of Paper II, this substantial amount of censoring means that the CPT variables from Tromsø6 and Tromsø7 were not normally distributed. In such circumstances, ordinary linear regression is not a suitable model due to the linear model assumptions of normality of data, and would lead to inconsistent parameter estimates that do not approach the 'true' population parameters as samples size increases[29]. Tobit regression allows us to avoid throwing away available information and therefore cause a bias in the estimates. It also more accurately estimates what the true distribution of CPT tolerance might be in the population if we did not impose the right-censoring but rather let participants continue for as long as they wished. It thus estimates the 'true', or 'latent', distribution of the uncensored outcome in the population, given the observations of the censored variable [225].

Our first model estimated a linear Tobit regression model with right-censoring to assess how levels of the LTPA change index were associated with CPT tolerance at follow-up.

The second model used a mixed Tobit regression model to assess whether a change in pain tolerance over the time between Tromsø6 and Tromsø7 was associated with PA level. Since data contained repeated measurements of the same individuals from two surveys, we added a random intercept to adjust for this dependency. A likelihood-ratio test confirmed a

better model fit with the random intercept added to the model. The random effect model is calculated using quadrature, and it is recommended to evaluate its accuracy through varying the number of integration points used. As doubling the number from seven to 14 yielded negligible effect-estimate differences, we believed random effects to be adequately estimated. As mixed models can use incomplete cases to improve accuracy of estimates, we also included participants with the outcome measured at only one survey occasion.

We added cross-products for LTPA and sex or chronic pain (from Q1) respectively to assess interaction effects in the same manner as was done in Paper I. The same was done with time, as measurement occasion (Tromsø6 vs. Tromsø7), in the mixed model, to assess whether the effect of time on CPT tolerance varied according to level of LTPA.

We performed sensitivity analysis by estimating an identical model using regular mixed linear regression to compare estimates for the censored vs. the 'true' or population-latent outcome variable.

As noted by Barros et al., the Tobit class of models is more sensitive to assumptions of normality than ordinary linear regression [16; 17]. We therefore used their statistical package `tobitdiag` for R to plot and inspect Martingale-type residuals for potential deviation from normality in residuals We found some indication of deviation, and discuss the implication of this in chapter 5.

3.6.4. Modelling in Paper III

Paper III assessed whether there was an indirect effect of habitual LTPA on chronic pain through CPT tolerance. The research question of such models assumes that there is or can be a causal relationship between exposure and outcome. This assumption is made based on subject matter knowledge and cannot be confirmed by modelling alone. However, steps can be taken in the study design to incorporate the temporality requirement of causality as far as possible through ensuring that exposure precedes the mediator which precedes the outcome [241].

Mediation analysis is a suitable methodology for assessing indirect effects via a third variable representing a causal mechanism, akin to answering questions of "how" something happens (e.g. an effect of PA on the risk of experiencing chronic pain) [241]. When doing mediation analyses with binary outcomes, classic product- and difference methods suffer increasing risk of biased results when the outcome is common (generally >10%), due to the

"noncollapsibility" of the odds ratio [67; 242]. This causes the odds ratio to fail to approximate the risk ratio to a higher degree the more common the outcome is and the more covariates are added to the model [242]. As chronic pain outcomes have high prevalence rates (>10%), a relative risk mediation model should be used, which can be broken down into direct and indirect effects using the counterfactual framework [241]. These models provide natural direct effects on the outcome by fixing the mediator, CPT tolerance, to the level it would be when exposure LTPA=0 (sedentary) and then changing LTPA by a one-level increase to assess the direct effect of this change on the chronic pain outcome. They also provide natural indirect effects on the outcome through changing the mediator CPT tolerance by what it would change with a one-level increase in LTPA, whilst keeping the value of LTPA constant and thus capturing only the effect of LTPA on the chronic pain outcome that occurs through the corresponding change in CPT tolerance [241]. All models were examined for possible exposure-mediator interaction by adding their cross-products and assessing whether they were statistically significant or model estimates changed substantially. As no signs of interactions were found, models were specified without exposure-mediator interactions.

In total, we specified four separate models for each of the four chronic pain outcomes: chronic pain ≥ 3 months, widespread chronic pain, moderate-to-severe chronic pain, and widespread moderate-to-severe chronic pain ≥ 3 months. Sensitivity analysis examined whether estimates changed when analysing a baseline sample without prevalent chronic pain. Models were further stratified on sex to compare similarity of estimates for men and women.

Counterfactual mediation analysis assumes that no unmeasured confounders are contributing a substantial bias to estimated parameters between exposure, mediator, or outcome (Figure 11) [241]. We performed an explorative simulation to assess how much influence such unmeasured confounding would have to exert on our exposure, mediator, or outcomes in order to substantially alter the effect estimates of our models. Simulating a dataset of 10,000,000 observations of the associations identified in our actual models, we used it to observe the effect of adding first one normally distributed continuous, and second one binary, unmeasured confounder. Assuming quite substantial confounding associations between these, and X, M, and Y, we could then simulate how much bias such strong confounders would introduce to the direct, indirect, and total effects identified in our actual models. We could then assess the probability of any such substantial confounders being left out of our models, and how that would subsequently impact model estimates.

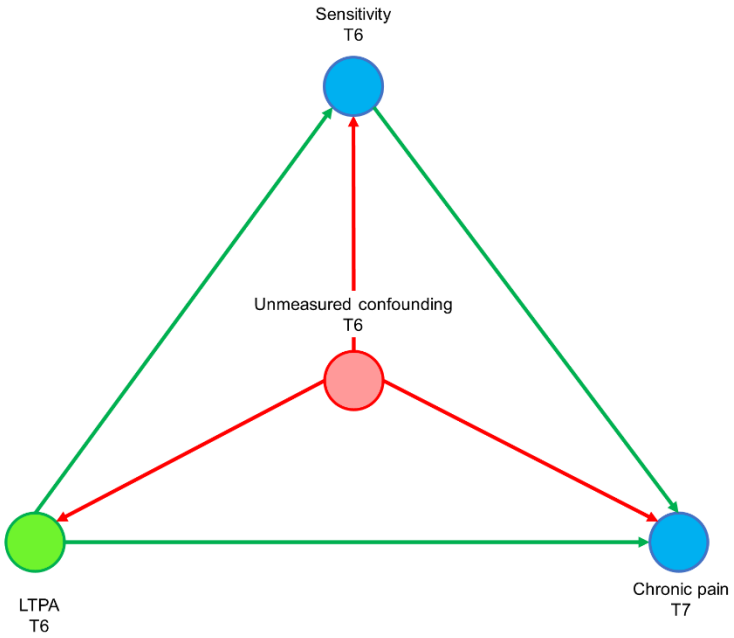


Figure 11: The mediation model, with potential unmeasured confounding

3.6.5. Missing data and imputation

Overall, missingness occurred most frequently in exposures and outcomes, due to item nonresponse in self-reported PA and chronic pain questionnaires, and nonparticipation in accelerometry or CPT. Due to a delayed start-up of data gathering at the beginning of the study, 4% of participants of Tromsø7 have missing on GRIP (n=820; 385 men, 435 women) [215].

Paper I missing data

There were 25,158 unique participants in Tromsø6 and Tromsø7 combined. In total, 2,887 of these did not participate in CPT in either Tromsø6 or Tromsø7. Amongst the 22,271 persons eligible for inclusion, 916 were missing SGPALS LTPA, 389 were missing PAFID frequency, 1,624 were missing PAFID intensity, and 1,676 were missing PAFID duration. The subgroup with accelerometer data numbered 5,785, leaving 16,486 non-participants. Regarding the sensitivity analysis of chronic vs. moderate-to-severe chronic pain, 2,987 participants of the sample had no GRIP data due to not participating in Tromsø7. An additional 642 participated before GRIP-data collection had commenced. Of the remaining

18,642, 2,022 had missing data on one or several of the GRIP characteristics used to compute the chronic pain outcome, leaving 16,620 complete cases used in the complete-cases sensitivity analyses of moderate-to-severe chronic pain. These were then compared to a model with MICE-imputed missing GRIP data.

Paper II missing data

Of the 22,271 participants of Tromsø6 and/or Tromsø7 with CPT at either time-point, 11,539 did not have LTPA data from Tromsø6. The remaining 10,732 were eligible for the secondary analysis. The primary analysis required repeated CPT and LTPA data from Tromsø6 in Tromsø7 which caused a further 3,868 participants to be excluded, leaving 6,864 participants for analysis.

Paper III missing data

Of the 8,906 that participated in both Tromsø6 and Tromsø7, 2,072 were missing information on either exposure, mediator, or outcome, leaving 6,834 for inclusion in analyses. Among these participants, of all included covariates household income the previous year had the highest proportion missing in the final sample (n=289; 4.2%).

As outcomes were constructed using varying numbers of GRIP items, additional missing information was incurred for each of the outcome models depending on the number of GRIP items used. In total, 6,625 had information on chronic pain (3% missing), 6,459 on chronic widespread pain (6% missing), 6,259 on moderate-to-severe chronic pain (8% missing), and 6,052 on widespread moderate-to-severe chronic pain (11% missing). At most, of the 8,906 repeat participants, 32% were missing cases in the final models.

Multiple imputation

To assess the impact of missingness on model estimates, we performed multiple imputation with chained equations (MICE) [252] for the four models of self-reported PA in Paper I and for the four models of chronic pain outcomes in Paper III, using predictive mean matching. This replaces each single missing observation with an aggregate of several possible values through creating multiple datasets containing plausible values based on observed information and uncertainty in the original dataset [252]. In Paper I, we imputed 100 datasets with 10 iterations each and known nearest neighbours = 10. In Paper III, we imputed 30 datasets with

10 iterations each and known nearest neighbours = 20. Both imputations used a burn-in of 10 iterations.

3.6.6. Missing on covariates in final samples

All papers reported frequencies and proportions of missing information on covariates for all analyses in appendices. This missingness occurred due to item nonresponse for covariates. Table 5 shows numbers and proportions missing for covariates in Papers I-III.

Table 5: Missing information on covariates for Papers I-III, n (%)

	Paper I	Paper II		Paper III
		Primary analyses	Secondary analyses	
Covariate:	(n=22,271)	(n=6,864)	(n=10,732)	(n=6,834)
Occupational physical activity[c]	*N/A*	87 (1.3)	147 (1.4)	92 (1.4)
Accelerometry	16,486 (74)	*N/A*	*N/A*	*N/A*
Sex	0 (0)	0 (0)	0 (0)	0 (0)
Age	0 (0)	0 (0)	0 (0)	0 (0)
Education level	336 (2)	38 (0.5)	84 (0.8)	41 (0.6)
Smoking[a]	368 (2)	54 (0.8)	117 (1.0)	51 (0.8)
Alcohol consumption[b]	390 (2)	28 (0.4)	70 (0.7)	37 (0.5)
Waist-height-ratio	172 (1)	*N/A*	*N/A*	*N/A*
Self-reported health	170 (1)	49 (0.7)	70 (0.7)	*N/A*
Chronic pain	1,647 (7)	6 (0.1)	11 (0.1)	*N/A*
Household income	*N/A*	*N/A*	*N/A*	289 (4.2)

[a] In Paper I: combined daily smoking status and number of cigarettes; in Papers II-III: daily smoking status.
[b] In Paper I: combined alcohol consumption frequency and average units consumed; in Papers II-III: alcohol consumption frequency.
[c] Combined with categories for retirement, and disability or sick-leave.

3.7. Ethical considerations

Tromsø6 and Tromsø7 were approved by the Data Inspectorate of Norway, the Norwegian Data Protection Authority (reference 14/01463-4/CGN), and the Regional Committee of Medical and Health Research Ethics, North Norway. The Tromsø Study complies with the Declaration of Helsinki, International Ethical Guidelines for Biomedical Research Involving Human Subjects and the International Guidelines for Ethical Review of Epidemiological

Studies [43; 90].

During and after the surveys, data were stored in EUTRO, which is a University of Tromsø-developed and managed IT system allowing collection, storage and retrieval of sensitive data, along with an integrated biobank and project information. EUTRO functions to protect and manage data, metadata, and projects. It was evaluated and approved by the Norwegian Data Protection Authority [90].

The current project was approved by the Regional Ethics Committee of North-Norway (ref. REK North 2016/1794). All participants received information about the implications of participation in the Tromsø Study when the received their initial invitation. They were further provided with a written consent form, the signing of which was a requirement prior to participation (Appendices 4 and 5). Participants were also informed of the possibility to withdraw at any point during their participation, and of the opportunity to have their data excluded from the resulting datasets post-participation. Data from three such participants who later withdrew their consent were not used in any of the analyses of this thesis. Datasets extracted for use in this thesis were in secure locked storage, and kept on a hidden encrypted partition on a local, external, encrypted hard drive with the encryption key known only by me.

4. Summary of papers – main results

This section gives a brief overview of the findings published in each of the three papers included in this thesis. Key results are summarized in Figure 12.

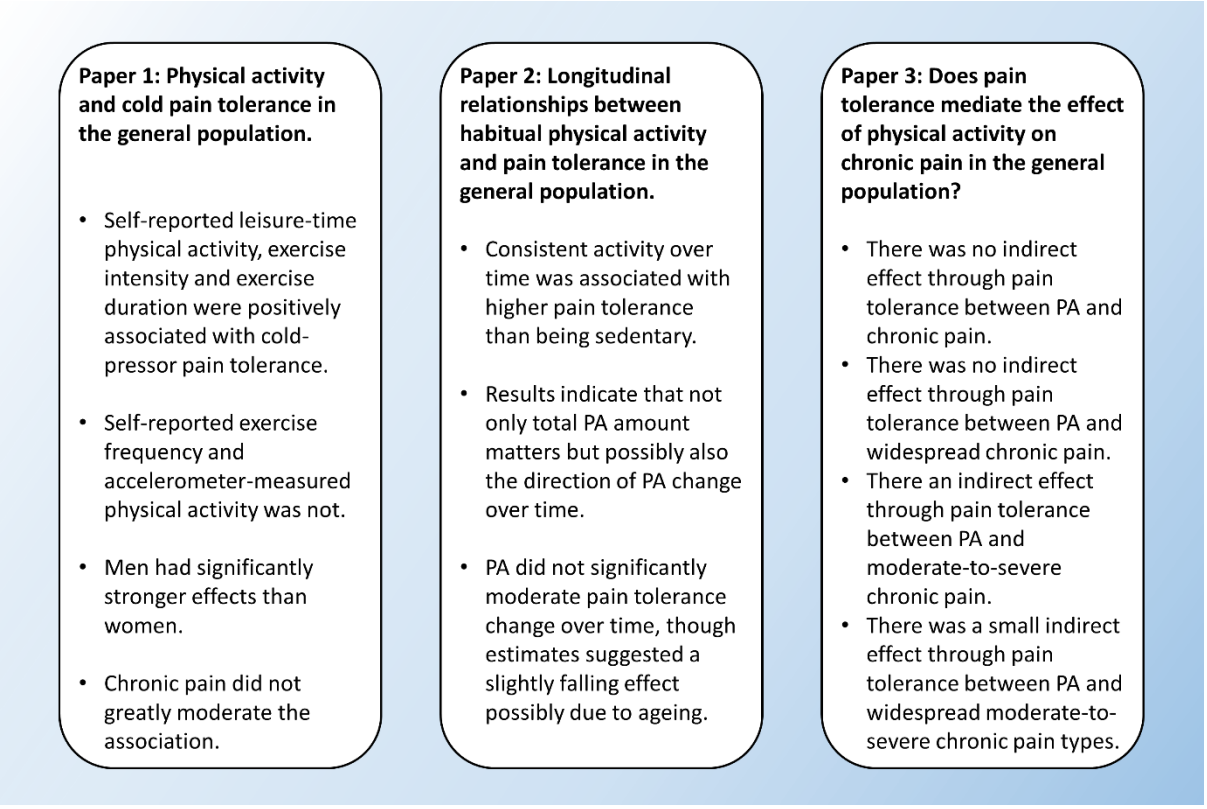


Figure 12: Results at a glance. PA=physical activity

4.1. Participant characteristics

Descriptive characteristics were almost similar across the three papers. Mean age varied between 55-57 years. There were 28% highly educated included participants in Paper I, 22% in paper II and 23% in Paper III. Respectively, 24% reported the lowest amount of education in Papers I-II vs. 22% in Paper III. There were 15% daily smokers included in Paper I, which changed to 20% in Paper II and 18% in Paper III. Alcohol consumption, self-reported health and occupational physical activity was apparent were distributed almost similarly across the three papers. Variations in LTPA across included in papers is shown in Table 6.

Table 6: Saltin-Grimby Physical Activity Level Scale (SGPALS) distribution Papers I-III (proportions).

LTPA Tromsø6:
"Exercise and physical exertion in leisure time. If your activity varies much, for example between summer and winter, then give an average. The question refers only to the last twelve months."

LTPA Tromsø7:
"Describe your exercise and physical exertion in leisure time over the last year. If your activity varies throughout the year, give an average."

	Paper I:	Paper II[a]:	Paper III:
Sedentary	15	19	17
Light	58	60	61
Moderate	24	19	20
Vigorous	3	2	2

[a]Paper II: baseline characteristics (Tromsø6).
LTPA=Leisure-time physical activity.

CPT tolerance was described using median and inter-quartile range in Paper I (62.5 (IQR 76.9)) and means and standard deviations in Papers II-III (approximately 90 seconds (SD 28)), which showed little variation and consistently approximately 10 seconds shorter duration for women versus men.

Chronic pain (Q1) prevalence ranged from 36% in Paper I to 32% in Paper II, with the GRIP-defined chronic pain ≥ 3 months of Paper III having a prevalence of 60%. GRIP-defined moderate-to-severe chronic pain prevalence was 18% in Paper I and 21% in Paper III. Conversely, widespread and widespread moderate-to-severe chronic pain in Paper III had a prevalence of 8.4% and 4.8% respectively.

4.2. Paper 1 – Physical activity and cold pain tolerance in the general population

In this paper, we used survival analyses on cross-sectional data to examine associations between self-reported and accelerometer-measured PA and CPT tolerance. We found that the proportions of participants withdrawing their hand from the CPT before reaching the maximum allowed time was higher in lower self-reported PA groups, and furthermore that those with higher self-reported levels of PA more frequently endured until the end of the test.

Comparing three LTPA groups with the sedentary group, the HR was 0.91 (95% CI:

0.86 – 0.96) for light LTPA, 0.85 (0.79 – 0.90) for moderate LTPA, and 0.71 (0.62 – 0.82) for vigorous LTPA. This association thus appeared to be dose-response shaped. There was significant moderation by sex, with effects being significantly larger for men compared to women in light and moderate LTPA. Given the size of the vigorous LTPA groups, these were likely not powered to accurately detect interaction effects.

Compared to habitual light exercise, moderate and vigorous intensity were associated with higher pain tolerance (HR 0.95 (0.92 – 0.99) and 0.94 (0.84 – 1.04) respectively). The lack of statistically significant association for the highest level must be seen in connection to the group number of 779 given the width and shape of the confidence interval. Men had significantly stronger effect estimates in moderate exercise than women, although absolute differences were modest.

There were significant associations between habitually exercising for a duration above 0-29 minutes, with effects for >60 minutes (HR 0.82 (0.77 – 0.87)) being even larger than those of 30-60 minutes (HR 0.86 (0.82 – 0.90)). There was no sex interaction for exercise duration.

There were no significant associations between exercise frequency and CPT tolerance, with HRs 0.99 (0.94 – 1.05) and 0.96 (0.90 – 1.02) for 1-3 times/week and approximately every day, respectively.

Those reporting chronic pain had significantly stronger, positive associations between vigorous exercise intensity and pain tolerance compared to those reporting no chronic pain. When imputing for missing, those reporting moderate-to-severe chronic pain had significantly stronger associations between habitually exercising >60 minutes compared to those without moderate-to-severe chronic pain. No other chronic pain interactions were seen using complete cases or imputed chronic pain ≥ 3 months, or moderate-to-severe chronic pain.

Accelerometer measurements of PA included 10-minute bouted moderate-to-vigorous PA as well as total activity counts, a measure of total activity amount. Neither models yielded significant associations with CPT, nor any significant interaction with sex or chronic pain.

Finally, associations between self-reported PA and CPT tolerance were of negligible difference in the accelerometry sub-sample compared to the total sample and were thus not reported.

4.3. Paper 2 – Longitudinal relationships between habitual physical activity and pain tolerance in the general population.

In Paper 2 we examined associations between self-reported LTPA change between Tromsø6 and Tromsø7 and CPT tolerance at Tromsø7. We also assessed the role of LTPA in longitudinal CPT tolerance change between the same two time points.

Maintaining light or moderate-to-vigorous habitual LTPA over time was associated with significantly higher CPT tolerance at follow-up compared to staying sedentary. Those who maintained a moderate-to-vigorous activity level had an estimated 20.4 seconds (95% CI 13.7, 27.1) more CPT tolerance than the consistently sedentary group's estimated average of 64.6 seconds (95% CI 59.4, 69.9). Results further showed that higher total amount of LTPA over time was associated with higher tolerance, with some signs that an LTPA change from low to high LTPA was better than an equally large change from high to low. Finally, any group containing sedentary LTPA at either time point was never significantly different from those who were sedentary at both times. There were no significant interactions with either sex or chronic pain.

Overall, in repeated measurements of individuals with data in both Tromsø6 and Tromsø7, CPT tolerance was 7%, 14%, and 16% higher respectively for light, moderate, and vigorous habitual LTPA compared to the sedentary group. The most active participants endured for an estimated average of 16.3 s. (95% CI 6.0, 26.5) longer compared to those who reported being sedentary.

Secondly, all participants displayed a decrease in CPT tolerance between surveys. This change in tolerance was significantly associated with time (i.e. survey occasion). LTPA did not interact in a statistically significant manner with this time effect, although testing the linear trend and effect estimates suggested a light, gradually increasing negative trend. That is, the higher effect of increasing LTPA levels was implied to diminish slightly over time.

There was no significant interaction with sex, although effect estimates appeared to be higher for males. There was no interaction with chronic pain ≥ 3 months.

In a sensitivity analysis using ordinary linear mixed models instead of the Tobit model, effect sizes were estimated to be up to 60% smaller than when using Tobit mixed models.

4.4. Paper 3 – Does pain tolerance mediate the effect of physical activity on chronic pain in the general population?

In Paper 3, we examined whether there was any indirect effect of baseline LTPA on chronic pain at follow-up through pain tolerance (i.e. mediation). There were negligible differences in estimates from model on complete study sample versus imputed study sample models. Combined with the generally small descriptive characteristics differences between these two samples, this suggests no extensive bias due to missing values, and complete study sample model results were primarily reported.

For the complete study sample, there were statistically significant total effects of increasing LTPA by one level on widespread chronic pain (RR: 0.84 (95% CI 0.73, 0.97)), moderate-to-severe chronic pain (RR 0.90 (95% CI 0.82, 0.98)), and widespread moderate-to-severe chronic pain (RR 0.76 (95% CI 0.63, 0.93)). At most, a one-level increase in LTPA decreased the risk of widespread moderate-to-severe chronic pain by 24%, versus a non-significant risk reduction of 4% for chronic pain ≥ 3 months.

Multivariable adjusted models showed no statistically significant indirect effects for chronic pain ≥ 3 months or widespread chronic pain. There was a small statistically significant indirect effect for moderate-to-severe chronic pain (RR 0.993 (95% CI 0.988, 0.999)) and widespread moderate-to-severe chronic pain (RR 0.988 (95% CI 0.977, 0.999)).

In a sensitivity analysis, we re-estimated models using a baseline sample with no reported chronic pain ≥ 3 months. These found negligible difference in indirect effects although all became statistically non-significant with decreased power of models. There was a significant total effect for moderate-to-severe chronic pain only (RR 0.83 (95% CI 0.72, 0.96)).

In stratified analyses, there were signs of gender differences in total effects, with men having slightly larger effect sizes for chronic pain than women. These differences increased from chronic pain ≥ 3 months (RR 0.94 for men, 0.97 for women) to widespread chronic pain (RR 0.74 for men, 0.93 for women), diminished somewhat for moderate-to-severe chronic pain only (RR 0.88 vs. 0.92), and were largest for widespread moderate-to-severe pain (RR 0.57 for men, 0.90 for women). Indirect effects were generally small and overlapping, with the exception of moderate-to-severe chronic pain in which men alone had a statistically significant indirect effect as opposed to women (RR 0.983 vs. 0.997).

5. Discussion

In this section I discuss methodological concerns before offering discussion that lies closer to the subject-matter of our findings, their interpretation and implications.

5.1. Methodology

Error in epidemiology is that which may cause us to draw the wrong conclusions [22]. In this thesis, that relates in particular to the representativeness of the Tromsø Study participants to the general population, and the internal validity of our data and analyses.

5.1.1. Study design

The papers of this thesis were hypothesis driven cohort studies in the sense that no intervention was performed on the participants. Paper I used a cross-sectional design, in which we could not fix exposures to temporally precede outcome, which is a requirement for allowing causal inference. The associations observed thus may reflect the effect of PA on CPT tolerance or vice versa. Paper II and III sought to improve the causal inference through looking at longitudinal changes.

5.1.2. Selection bias

Participation in health surveys is declining both in Norway and internationally [43; 56; 121]. Among reasons for this decline have been suggested an increasing burden on participants as surveys become increasingly comprehensive, time-consuming, and complicated [43]. If the non-responders are systematically different from the responders in factors critical to our study aims, such selection bias might impair the generalizability of our results and cause us to draw erroneous conclusions about the population as a whole.

In Tromsø6, and Tromsø7, invitation patterns were population-wide when possible, or included random samples of certain age groups in order to balance underlying distribution of health-related factors [43; 90]. Participation proportions were relatively high, compared to

population surveys in general, at >65%, but in absolute terms there is still a large proportion of unseen invitees that may differ systematically from those that did attend.

Participants of the Tromsø study have tended to be older, more frequently to be women, be in relationships, and have lower mortality rates, compared to non-attendees [96]. Tromsø6-attendees were reported to have a somewhat higher educational level than the general Norwegian and particular Tromsø population [43]. Furthermore, one comparable Norwegian population study found survey attendances to be marked by lower prevalence of select chronic diseases and higher socioeconomic status, but report more headache and musculoskeletal complaints than in the population at large [121]. This then would suggest at the same time that attendees have lower proportion of select risk factors for chronic pain (except for sex distribution), but at the same time report more pain-related health states. In our largest included sample (n=22,271), participants reported a chronic pain prevalence of 36%, and 18.4% for moderate-to-severe chronic pain. This is comparable to some other Norwegian population surveys (e.g. [120]), but as seen in the introduction there are broad discrepancies in reported prevalences. Other health surveys may experience the same non-participation bias as the Tromsø Study, and the variability in chronic pain definitions used makes comparison more challenging.

The inclusion of the Tromsø Pain Study in the past two surveys of the Tromsø Study, encompassing extensive questionnaires as well as QST of pain, could possibly have acted as an additional barrier for repeat participation in subsequent surveys.

However, both large questionnaires such as the Q2 as well as the GRIP enjoyed very high completion rates. The 28-page Q2 (17 questions with sub-tiers) was answered by 96% in Tromsø6 and the larger 47-page Q2 (38 questions with sub-tiers) was answered by 99% in Tromsø7; the completion proportion for GRIP in Tromsø7 was 96% [43; 90]. This suggests that the extensive questionnaires possibly did not hinder attendance.

It cannot be ruled out that pain-sensitive participants remembered their unpleasant experience from prior participation in the QST of Tromsø6 and therefore opted out of participation in Tromsø7. Such selection could skew participation towards more pain-tolerant individuals. However, participation proportion remained relatively stable between Tromsø6 and Tromsø7 [90]. The Tromsø7 participation proportion was also higher in previous attenders than first attenders, suggesting past attendance experiences to not be a greater barrier to future participation than factors not related to participation [90]. Finally, the papers

of this thesis found a generally lower pain tolerance level in Tromsø7 than Tromsø6. This altogether suggests that a skew towards pain-tolerant participants has not occurred.

Finally, a previous study from Tromsø2 suggested participants to not differ from non-respondents regarding leisure-time physical activity levels [97]. However, secular trends show an increase in physical activity occurring since the early 2000s [156], and we do not know whether that increase has been disproportionately distributed between responders and non-responders. If our samples exhibit higher PA levels than the underlying population, our results might over-estimate effects and thus diminish generalizability.

Thus, as in all population surveys, there are some differences between participants and non-responders on select variables which may resemble the typical healthy volunteer bias [28].

5.1.3. The effect of measurement error/misclassification on internal validity

All epidemiology is subject to error and bias, as measurement in humans is imperfect both in the act of measurement and in their face validity [22]. Bias and confounding can lead to misclassification of exposure and outcomes, which can skew results away from the true population estimates [220]. Bias impacts the internal, and hence external, validity of the results [33].

Response bias

We were primarily concerned with the effect of habitual PA on pain tolerance and chronic pain. Data on PA were primarily obtained from different questionnaires, and chronic pain status were exclusively questionnaire-derived. Such data are subject to response bias, where status on exposure and outcome is obtained by way of participant self-report [220]. One suggested amendment to help improve the properties of such self-report tools is to move away from simple definitions (e.g. dichotomous categories) towards more complex outcomes that utilize more information [220].

In Tromsø6 and Tromsø7, all chronic pain items included the 3-month duration requirement to be considered chronic. However, the GRIP questionnaire adds a condition for all pains that are reported in the questionnaire: the pain should have been experienced within the past 4 weeks. When comparing chronic pain ≥ 3 months based on Q1 in our Paper I sample to that constructed from GRIP in our Paper III sample, prevalences were around 36% versus 60%

respectively. This indicates that some conditions experienced as chronic pain by the participants might not fit the "past 4 weeks" criteria. Alternatively, individuals might respond differently to a simple pain question in a large and general questionnaire, as opposed to when filling in a questionnaire dedicated to the topic of pain alone.

When comparing several chronic pain definitions in Tromsø7, prevalences seem to match between "chronic pain for the past 4 weeks lasting for ≥ 3 months" from GRIP and another questionnaire asking "Have you during the last year suffered from pain and/or stiffness in muscles or joints in your neck/shoulders lasting for at least 3 consecutive months?". Furthermore, prevalences were also similar between the "chronic pain lasting for ≥ 3 months" from Q1 and GRIP-defined moderate-to-severe chronic pain (not published). This highlights the need for careful and consistent wording of chronic pain questionnaires, as well as the added benefit of comparing several chronic pain outcomes.

There is no gold standard to verify our chronic pain outcomes against. Therefore, in addition to knowledge of validity and reliability of similar tools, we compared chronic pain outcomes with higher versus lower degrees of complexion and requirements of participant reporting. Falling prevalences with increasing complexity thus probably express both actual reduction in prevalence combined with a degree of response bias in the simplest definitions. The magnitude of such bias is difficult to quantify but might imply that more stringent outcomes, though generalizable to a more highly selected population, possibly produce less biased associations than the 'simplest' chronic pain definitions.

In general, PAQs face known challenges in reliability and validity, and their sensitivity can suffer when recall periods increase in length or when measuring changes in PA patterns [125; 200; 219]. Despite the overall good validity and reliability of the PAQs used in this thesis, there can be misclassification of participants to adjacent PA levels. This could occur for example due to variations in interpretation of the physical activity category definition, e.g. that one participant interprets "How often do you exercise" to include a vigorous daily bike commute, whilst another does not. When such bias occurs in categorical exposures, misclassification to adjacent categories can change the shape of pattern of association [220]. Self-reported sedentary time in SGPALS and PAFID has been found to poorly reflect accelerometer-measured sedentary time [190]. Furthermore, the SGPALS might not be optimal for quantifying changes in PA pattern over time [68]. These issues might dilute the effect of some groups and inflate those of others, and could bias results of our papers towards the null.

PAQs can be influenced by the type of response bias called social desirability bias, which is the tendency to over-report responses which are perceived as more acceptable to the respondent [5]. Social desirability bias can be highly dependent on cultural context [221]. In Tromsø, as in Norway in general, secular trends in exercise (MVPA) have increased steadily for the past 20 years [156], implying that more people wish to engage in exercise and view higher MVPA levels as more desirable. If participants generally over-report their PA levels, as could be argued in Tromsø Study data [189], lower doses than those required are truly needed for our observed effects to appear. However, it is difficult to ascertain and interpret the potential impact of such bias.

PA measurement can be divided into three main components: volume (time×intensity×frequency), posture or activity type, and biological state or reactivity to the movement [62]. As no gold standard exists for measuring volume in free living, the accuracy of accelerometry and PAQs for doing so, and their inherent measurement errors, cannot be assessed [238; 247]. The true picture of physical activity is likely to lie in the intersection between measures of movement, activity type, energy expenditure, physiological fitness, and self-reported lifestyle habits. As it is not feasible to measure all these in large cohorts, the self-report proxies appear reasonably accurate and reasonably precise in categorizing participants relative to each other. SGPALS correlates moderately well with measures of physiological fitness, and at best moderately well to the total amounts of PA measured by accelerometry (which includes PA during work), and has been suggested to appropriately rank physical activity levels in large cohorts [190]. Possibly, SGPALS reporting expresses volume plus activity type, but at a very low resolution.

Accelerometry also suffers potential information bias in that it can be subject to the Hawthorne effect (also called reactivity), in which participants change their behaviour when conscious of being studied. Davis and Loprinzi compared day 1 monitoring estimates from two ActiGraph accelerometers with days 2 or 3 in 674 participants of all ages and concluded that no significant differences occurred [39]. Others have corroborated low levels of reactivity and recommend 5-7 days of monitoring [47]. Informal investigation of our own data supported this finding. Thus, although such reactivity to accelerometry is a possibility, it does not appear to exert extensive impact on results between days of measurement. We hence chose to include all days in our analyses. Reactivity lasting throughout the entire measurement period could occur, but this is more difficult to assess.

In theory, CPT could also be subject to the Hawthorne effect with regards to whether technician sex influences tolerance times. In Tromsø6, the majority of research technicians working with QST were female, and so for Tromsø7 the number of male technicians was intentionally increased in order to assess whether this significantly affected QST outcomes. Technician intra- and inter-rater performance was continuously monitored in order to facilitate early intervention should any skew arise. Preliminary analyses performed by the Tromsø Pain Study research group indicate negligible impact of technician gender on QST performance (unpublished). Possibly, participants perform better simply due to the presence of a technician, but there was no methodologically feasible way of testing for such an effect.

Classification bias - accelerometry

No wearable device provides valid results for all dimensions of 24-hour physical activity, and some will be better at capturing select dimensions, at the expense of other dimensions [62]. As accelerometry devices aimed at research are not suitable or feasible for long-term wear in large cohorts due to battery limitations, choices must be made by researchers in choosing the length of the data gathering interval and the sampling frequency of activity, sensor model and brand, measurement protocol, sampling and filtering of raw data, and the post-processing of such data [204; 239]. Epoch lengths must be defined, and wear-time and appropriate algorithms for classifying non-wear time must be chosen, followed by selection of valid day criteria and algorithms for classifying PA intensity. Finally, the researcher must aggregate the data into summary measurements of total PA or components of PA like given intensity volumes, and choose how these should be statistically analysed. These choices can have substantial impact on the data derived from accelerometry [12; 107; 147].

Our ActiGraph GT3X is among the best validated devices for movement intensity [62]. The sampling rate selected (100Hz) is seen as adequate to catch all human movement [11]. Nevertheless, it is likely our choice of requiring at least 10 minute bouts of MVPA to be valid underestimates the true exposure, as the proportion of adults in Tromsø7 reaching the PA recommendations (≥150 minutes of accumulated MVPA per week) was 22% when each MVPA bout had to last at least 10 minutes versus 70% if the criterion was removed [189]. The difference between bouted and non-bouted MVPA in Tromsø7 was large: 13.2 vs. 38.4 minutes/day [189] . Choosing bouted MVPA indicates that a large proportion of MVPA occurring in short bouts and potentially more frequently is excluded. This time is nevertheless

likely to affect the outcome in a similar manner as bouted MVPA, but could be unevenly distributed between those who perform much bouted MVPA and those who perform little bouted MVPA, and could thus dilute results. The low proportion of adults meeting the bouted requirement might also imply that this exposure is unlikely to extensively affect a pain sensitivity outcome to an extent that is easily detectable.

Accelerometry can underestimate some types of LTPA [81]. Furthermore, the accelerometry variables used in Paper I include all activity, including OPA. As suggested by the physical activity paradox, OPA was seen to associate very differently to CPT tolerance and chronic pain outcomes when included in models of self-reported PA in Paper II and III. This might also explain why self-reported but not accelerometer-estimated PA was significantly associated with CPT tolerance.

Classification bias – Cold-pressor test

In designing the CPT protocol, the researcher makes an a priori decision of where to set the upper test limit. This is done with regards to participant safety. The resulting data were shown to be varying degrees of right-censored, due to an accumulation of observations at the upper limit time point. As seen in Paper II, the analytical choices of such censored data can have large implications for the observed effects.

Water temperature and a reliable method of circulation and cooling must be chosen [110]. Treister et al. found that pain ratings in Tromsø6 did not increase substantially after the first 60 seconds, even decreasing for some participants [230]. In both Tromsø6 and compiled data from several cohorts in Haifa, Israel, most of those who withdraw do so before 60 seconds, even though the latter studies had a maximum allowed tolerance time of 180 seconds [230]. It therefore seems unlikely that increasing CPT duration will shift tolerance times distribution to the left.

However, the high proportion of right-censored should probably not be interpreted as an expression of absence of stimulus. Tromsø6, which had the highest proportion of right-censored, also showed mean VAS pain ratings of 7.84 and a mode of 10, which was very similar to the Haifa studies [230]. Thus, CPT appeared in both cohorts to represent a strong stimulus. One noticeable difference between Haifa and Tromsø was the use of 1°C vs. 3°C water. Although a temperature of as much as 20° is sufficient to induce pain [136], tolerance times in CPT generally increase with water temperature [149]. Indeed, the Haifa studies had a

far lower proportion right-censored than Tromsø6. Thus, the VAS ratings possibly express the high relative intensity of the stimulus, but the tolerance time distributions additionally show that the Haifa protocol provides the stronger stimulus of the two. A lack of non-right-censored people incurs a lack of power as there are fewer events (hand withdrawals) to detect group differences among. This impacts the precision of model estimates. Using 1°C water might counteract this through lowering proportion of censored measurements.

Furthermore, if proportion right censored was lower, there would be more opportunity for participants to increase their pain tolerance between Tromsø6 and Tromsø7 in a manner that would be detectable. This might have occurred in the large proportion of right-censored participants from Tromsø6 whose true tolerance change remains unobserved, and represents a possible bias towards the null in the included papers as it decreases the likelihood of a PA-induced increase in CPT tolerance over time.

Total sample QST tolerance decreased from Tromsø6 to Tromsø7. Concurrently, QST protocols differed between the two surveys. Other studies have suggested that the choice of combinations of QST procedures within a battery protocol is important for the reliability of the measurements [166]. There was also a difference in how participants rated the pain intensity during CPT in Tromsø6 and Tromsø7: reporting VAS to a technician or continuously imputing themselves through a digital VAS scale. These tasks might challenge the attention of participants differently. This was also the reason why participants in Tromsø7 were tested on their non-dominant hand as opposed to Tromsø6. One small study has found right-handed to have shorter CPT tolerances in their left hand [179]. As right-handedness is a dominant trait in the population, this could contribute to a downward shift in tolerance between Tromsø6 and Tromsø7. If the difference incurs bias, it should apply equally to all participants. It thus only represents a challenge for making statements on absolute CPT tolerance levels, and not for group comparisons which are the focus of the papers of this thesis.

5.1.4. Confounders, statistical modelling, and missing data

Confounding

Confounding variables pose serious threats to the veracity of findings from epidemiological studies if not handled appropriately [22]. Classically, confounders are related to both exposure and outcome, and are typically handled through adjustment in some statistical

model [220]. As seen in the introduction, both physical activity, pain sensitivity, and chronic pain are associated with a large number of covariates, with which causal patterns are complex and sometimes possibly bi-directional. It follows that fitting statistical models incurs a risk of both over- and under-fitting. Furthermore, model estimates and behaviour cannot reveal whether included covariates are truly confounders, mediators, or colliders. Adjustment should therefore be hypothesis-driven. All adjustment choices were made on basis of prior, subject-matter founded rationale, which are detailed in chapter 3. Additionally, Paper I also used a ±10% main effect coefficient change as an additional criterion. This criterion was dropped in subsequent papers as subject-matter rationale was thought to outweigh this criterion. In model building, explorative builds were frequently performed to see whether model estimates were volatile or particularly vulnerable to additional possible adjustments, but were not part of the decision-making process. In general, models were stable and once adjusted for the variables suggested by a priori hypotheses the rule of thumb was small incremental coefficient changes from additional adjustment and no large or unexpected shifts in the models overall.

Initially we included body composition (WHtR) as a confounder in Paper I. However, in Papers II and III, we had come to consider the possibility that body composition might mediate an effect of physical activity on pain sensitivity and chronic pain, and therefore elected not to include it as a confounder anymore.

Unmeasured confounding is particularly important in counterfactual mediation analyses [242], and so was explored further in Paper III through simulation of unmeasured confounding. These supported the impression of no substantial omitted adjustment: When the seemingly most important confounders were included in Paper III models, hypothetical dichotomous or continuous variables needed to have strong confounding effects in order to introduce significant bias to models. We thought it unlikely that such confounders should remain undiscovered.

In sum, we feel confident no large unexpected changes would be suddenly introduced by adding any single additional confounder to models. Whatever small incremental improvement in precision gained from adding more possible variables would to a certain extent be offset by the loss of statistical power due to additional parameters having to be estimated by models. Thus, we tried to follow the principle of finding the smallest viable model and avoid over-fitting [214].

We made no adjustment for mental health, sleep disorders/insomnia or specific comorbid conditions. This was discussed with co-authors and other colleagues whose speciality was generic and specific health-related quality of life measurement tools. From these discussions, we concluded that self-reported health as a surrogate [220] likely expressed much of the variance inherent in these factors and would incur little penalty to the models. It is possible that making a more thorough adjustment using such tools as the Hospital Anxiety and Depression Scale, sleep questionnaires, and the EuroQol-5 Dimensions, or selecting specific patient-reported co-morbidity might additionally improve confounding adjustment. It is also possible that additional number of estimated parameters and missing data might have penalized models to an extent that outweighed possible gains. Sensitivity analysis could possibly have explored this further, but was not performed.

Furthermore, we did not adjust for self-reported health in Paper III despite doing so in Papers I and II. This was due to the fear that both PA and chronic pain states impact general health in general. Knowledge of chronic pain and self-reported health associations are based on many associative studies, likely constituting cyclical relationships with possible feedback loops and it is difficult to know for certain how the components are expressed in modelling. Adjustment could thus induce collider bias in estimates [220]. Sensitivity analysis found such adjustment to have moderate impact on estimates when included in models using chronic pain as the dependent variable but negligible impact for pain tolerance (results not shown), and thus would probably not impact estimates of indirect effects from Paper III which were the focus of that paper.

We believe the most important adjustment that could have been made to improve confounding bias in this thesis was to adjust for OPA in accelerometry models in Paper I, as mentioned above. This could have partialled out some of the OPA effect of accelerometer MVPA measures and allowed for estimates that would be more commensurate with SGPALS LTPA. Thus, the accelerometry model should be understood as a summary MVPA measure of total PA, as discussed in Paper I.

Statistical modelling

The Tobit model used in Paper II assumes there is a distribution of pain tolerances to the right of the censoring limit. If the slight decline seen to occur prior to right-censoring for some participants is indicative of cold-induced hypoalgesia, values to the right of the censoring do

not represent potential hand withdrawals due to unbearable pain as the same participants would endure until the inevitable new upper limit. In that case, the latent distribution estimation of the Tobit model probably over-estimates the absolute values of latent (i.e. unobserved) tolerance times. On the other hand, if the Tobit model represents the more correct expression of the underlying latent distribution of CPT tolerance in the population, it follows that any modelling of CPT tolerance using ordinary linear regression underestimates associations with this variable. This again demonstrates the drawback of substantially right-censored variables, and why a lower proportion of right-censoring is desirable. In Paper III, the counterfactual mediation model was not able to accommodate Tobit modelling of the mediator pathway. We therefore had to use ordinary linear regression. As seen in Paper II, linear modelling underestimated latent effects by as much as 60% in comparison to Tobit modelling. It is likely that indirect effects in Paper III would be proportionally higher if estimated using Tobit regression, although they would probably remain modest in absolute terms. Considering possible causes of censoring, the absolute distribution is likely to lie somewhere between the two model estimates.

Concurrently, we faced some difficulties in assessing the particular Tobit model assumptions of distribution of residuals in Paper II [16; 17]. No statistical package was readily available in Stata to perform the required model diagnostics so a user-written package in R had to be used. As the package was not yet popularized and instructions on interpretation were not forthright, one of the package authors, adjunct prof. Santos-Neto (Department of Statistics, Federal University of Campina Grande, Brazil), was consulted. Interpreted output suggested some deviance was observed in residuals, which would suggest caution when interpreting borderline p-values. Significant results in Paper II had very low p-values. Combined with the high statistical power of Paper II analyses, it is unlikely any imprecision in calculation of p-values should have impacted our interpretation of results.

Levels of exposures, covariates, and outcomes are unobserved during the intercession between T6 and T7. In Paper III, the longitudinal aspect lay in exposure (and mediator) being measured prior in time to outcome. This aspect of mediation modelling is a requirement, as the model itself is causal by nature in that it assumes the roles of exposure, mediator, and outcome to be the true ordering of factors [241]. Nevertheless, the nature of these factors are dynamic and preceding changes in one may affect subsequent changes in the level, or risk, of another. It might be tempting then, to suggest that the solution lies in further adjustment; e.g. of baseline chronic pain for estimating the “true” risk of follow-up chronic pain in Paper III.

However, this does not eliminate the dynamic nature of chronic pain during the course of follow-up, but additionally introduces new interpretative challenges due to the phenomenon of Lord's paradox [173] as describe earlier in the thesis as well as below.

Missing data

In order to assess the impact of missing data, we performed MICE in both Papers I and III, as described in section 2.6.5. Resulting model estimates did not suggest substantial bias incurred by missing data. MICE was not performed on Paper II due to challenges with harmonizing the MICE software package with the Tobit model. As seen in section 3.1, the sample in Paper II had characteristics that were slightly different than those of Papers I and III, but likely not different enough to incur a change in generalizability. Furthermore, the repeated participation-samples of Paper II were the smallest samples in this thesis. Without having performed MICE, it is difficult to say whether the differences in characteristics and loss of power incurred bias or affected precision to a considerable degree. Certainly, the results of low power are seen in the precision of estimates for PA-change modelling in Paper II, but it is unknown how much it would have improved if missing data were imputed for all who participated in both surveys.

Table 7: Bias summarized

Issue	Type of bias	Assessed probability	Likely effect
Attendance proportions	Non-participation bias	Likely	Direction unknown
Pain data gathering	Non-participation bias	Unlikely	N/A
Population PA levels	Selection bias	Unknown	Direction unknown
Healthy volunteers	Participation bias	Likely	Bias towards the null
Pain questionnaires	Response bias	Possible	Possibly less bias with more stringent criteria
PA self-report	Misclassification bias	Likely	Unknown bias of associations, possibly towards the null
PA self-report	Social desirability bias	Likely	Unknown bias of associations
Acclereometry	Hawthorne/reactivity bias	Unlikely	N/A
CPT technicians	Hawthorne/reactivity bias	Unlikely	N/A
Accelerometry sensitivity	Classification bias	Possible	Bias towards the null
Bout requirement in accelerometry	Classification bias	Likely	Bias towards the null
Accelerometry not adjusted for OPA	Confounder bias	Likely	Bias towards the null (for LTPA)
CPT duration	Classification bias	Unlikely	N/A
CPT censoring proportion	Misclassification bias	Possible	Bias towards the null (for effect of LTPA change)
Model confounder adjustment	Confounder bias	Unlikely	N/A
Paper II missing data	Selection bias	Unlikely	N/A

PA=Physical activity; CPT=Cold-pressor test; OPA=Occupational physical activity

5.1.5. Generalizability

Beyond the impact of possible bias, the generalizability of our results depends on who they are claimed to be representative for. In the Tromsø6 and Tromsø7 surveys, no participant was younger than 30 years of age, and the participants were on average in their mid-fifties. The Tromsø Study mainly contains middle-class North-European Caucasian participants alongside a primarily Sami minority and our results are likely generalizable to such populations.

In summary, the differences between participants and non-participants tend to be small, and the Tromsø Study still enjoys relatively high participation proportions in comparison to other population surveys, which strengthen the representability of the survey. Furthermore, given the distribution of health and risk factors observed in non-responders, it seems likely that any effects observed in this thesis might be strengthened, not diminished, for the parent population as a whole. Future recruitment strategies should place importance on actively recruiting participants from groups perceived to have the lowest probability or possibility to participate in such surveys.

5.2. Discussion of findings

5.2.1. Associations of physical activity and pain tolerance in the general population

The first objective of this thesis was to estimate associations between types of PA and pain tolerance in the general population. Papers I and II looked at cross-sectional associations between SGPALS, PAFID, and accelerometry, as well as between baseline SGPALS LTPA and overall CPT tolerance for those who participated in both surveys. For self-reported exposures, the strength and consistencies of findings seem to lend strong support to the notion that habitual PA is associated with cold-pain tolerance, thus serving as a population-level corroboration of earlier findings. These findings represent long-term associations which potentially indicate the effect of regular PA on cold-pain tolerance.

When looking at repeated measures of the same individuals in Paper II, our longitudinal model confirmed the shape of associations seen for LTPA in our cross-sectional data in Paper I, suggesting associations to be stable over time. Given the caveats associated with our modelling in Paper II as discussed above, our model gave an estimate for the absolute average latent CPT distribution for the sample and the estimated difference in seconds for increasing PA levels, thus providing a population reference estimate of potential use to future studies. We are not aware of any other study which has estimated absolute CPT measures for population-based LTPA groups. The results reflected a dose-response shaped association between LTPA and CPT tolerance. Several EIH responses in pain detection thresholds are similarly reported to be dose-dependent (i.e. intensity-dependent) [161; 234],

although Zi-Han et al. reported a ceiling effect for high-intensity treadmill running in 66 healthy women [253].

Of the PAFID items, exercise intensity and duration appeared more important than frequency. In a review of animal studies by Lesnak and Sluka, greater intensity of exercise (10m/min versus 16m/min) was reported to result in greater amounts of analgesia in mice, although some animal studies found detrimental effects when exercise was always done to exhaustion, suggesting possible ceiling effects [129]. Stagg et al. have corroborated this finding in a 5-week exercise intervention on male rats, suggesting exercise intensity to be more important to analgesic effects than frequency [213]. Exercise was also found to reverse induced hyperalgesia in animal studies [129]. It is not intuitive that intensity and duration should be so disproportionately important relative to frequency, since exercise needs to be performed at a certain frequency for other effects (e.g. cardiovascular adaptations) to occur. Our findings might express how mechanisms governing effects on pain sensitivity adapt differently from those facilitating the cardiovascular effects of exercise. However, even a single performance of performing the 6-minute walking test was enough to significantly increase post-exercise pain tolerance in healthy adults [93], and there remains ambiguity to the required combinations of frequency, intensity, and duration to achieve certain inhibitory effects, both in the short and long-term.

Regarding the accelerometry findings of Paper I, past studies of accelerometer-estimated PA and pain sensitivity have reported small and/or inconsistent effects [26; 167; 245]. These studies used small samples, two of which included young participants only, did not adjust or account for OPA, and used pain thresholds which correlate less consistently with habitual LTPA [222]. Ohlman et al. found accelerometer-estimated MVPA but not bouted MVPA to predict EIH [167]. In a cohort of 22-year olds (n=714), Waller et al. measured associations between accelerometer-assessed PA and pressure or cold pain thresholds, stratified by the presence of single- or multi-site pain [245]. They reported the highest group of 10-minute bouted MVPA to be positively associated with cold-pain thresholds for those with no pain, and the highest level of unbouted vigorous PA to be positively associated with cold-pain thresholds in those with multisite pain. However, their study contained a very high number of comparison groups, as well as exposure and outcome parameters, and the clinical application of their significant findings versus the majority of non-significant ones is not clear.

If the effects of OPA and LTPA on pain tolerance diverge, the one might confound the effect of the other due to the physical activity paradox. Furthermore, triaxial accelerometry-estimated mean MVPA time in the Tromsø7 participants was over 290% higher if the bout requirement was not included (13.2 vs. 38.4 minutes/day) [189], comparable to another survey of physical activity and pain sensitivity [245]. As described in the discussion of accelerometry, we do not believe the contrast in results between self-reported and accelerometer-measured PA to reflect a true lack of association, but rather that accelerometry produces data according to the data processing and modelling criteria chosen [189]. Indeed, when estimating relationships between accelerometer-estimated unbouted MVPA and cuff-pressure algometry tolerance, associations appear quite different (to be published). Given the methodological particularities of our accelerometry model, it seems likely that results from Paper I would have harmonized if we had accounted for OPA and had used a more sensitive measurement of MVPA for these data.

5.2.2. Longitudinal associations – traces of causality?

Paper I established cross-sectional associations which appeared to be quite strong but had clear limitations with respect to causal inference. We therefore aimed to enhance causal inference further by looking at longitudinal relationships in Paper II, primarily looking at the effect of PA change over time on CPT tolerance, but also the effect of baseline LTPA on CPT tolerance change over time.

Paper II results were not conclusive regarding LTPA change over time. While higher total amounts of LPTA over time seemed to be associated with higher CPT tolerance, most of the group CIs overlapped. This was possibly in part due to due to poor questionnaire sensitivity to LTPA change, and also the low power in certain LTPA change index groups. Looking at effect size alone, there were signs that increasing PA levels were associated with higher CPT tolerance than a decrease, even though the "sum" of LTPA level combinations over time was equal. A decrease was always associated with lower estimates than maintaining or increasing LTPA from the starting point, possibly indicating that direction of change represented a small addition to effects beyond total LTPA amount alone. However, it is not possible to argue that our findings unequivocally demonstrate how a positive LTPA change over time is associated with higher pain tolerance than for those who did not change, or changed less.

In comparison, one seven-week military training intervention significantly increased

both EIH and pressure pain thresholds in 38 healthy young men and women [77]. Five other small, non-randomized studies of the effect of long-term PA are interventions on EIH have found inconsistent results [210]. In a 6-week moderate-to-vigorous aerobic cycling intervention in healthy adult nonathletes versus normally active controls (n=24), Jones et al. found significant increases in aerobic fitness and ischaemic pain tolerance despite seeing no differences in pressure pain thresholds or pain ratings [102]. In 28 overweight but pain-free men, 6 weeks of moderate-intensity continuous training improved PPTs in the lower, but not upper, extremities despite finding no acute effect of exercise on the same pain sensitivity parameters [74]. In addition to seeing dose-response increases in pain threshold for all subjects of an exercise intervention, Schmitt et al. found a cold pain tolerance increase that was dependent on physiological fitness increase [196]. They believed this demonstrated a functional adaptation of central neurological mechanisms in response to the intervention, with implications for why PA is an important treatment modality for chronic pain.

In contrast, O'Leary et al. found significant increases in ischaemic pain tolerance in 20 healthy adults (16 men) for high-intensity interval training but not moderate-intensity continuous training independently of pain sensitivity thresholds, despite both groups having significantly increasing their aerobic fitness to an equal extent [165]. They suggested high intensity exercise to induce enough metabolic disturbance to represent a noxious stimulus which induced familiarization and thus a shift in pain tolerance thresholds.

Such studies suggest long-term PA interventions to be effective at increasing pain tolerance. However, interventions are not easily comparable to cohort studies like ours, not least because they have a higher degree of control over levels of exposure. Furthermore, exposure dose might be considerably higher in interventions than what is represented by a one-level shift in our PAQ items for activity that is habitual. Nevertheless, we had expected stronger signs that PA change would affect subsequent tolerance level.

In Paper II, participants generally had less pain tolerance in Tromsø7 compared to Tromsø6. Baseline LTPA did not moderate this observed decline in CPT tolerance over time. We do not know whether the pain tolerance decrease occurred due to ageing of those who participated in repeated measurements, regression towards the null due to estimates that were high by chance in Tromsø6, differences in attention capacity or pain-modulatory effects due to the differences in batteries, or systematic errors in instruction of participants between the two surveys.

Due to censoring as discussed above, we would not have expected to see significant increases in CPT tolerance. Thus, causal inference would have been enhanced if LTPA interacted significantly and caused the decline to progress at a slower rate than for higher levels of LTPA. The absence of evidence in this case should not be interpreted as evidence of absence of causality. There is a possibility that the decline occurred due to age-dependent increases in pain sensitivity. Whether age has this effect on a population-based cohort should be explored in future studies.

5.2.3. Moderation: Physical activity, sex and chronic pain

Sex as a moderator

As summarized in the introduction, whether sex moderates how PA relates to pain sensitivity has not been extensively explored, especially for long-term physical activity. Like the field in general, available evidence is often low-powered, contains heterogeneity in choice of exercise exposure, and frequently uses pain thresholds. When sex differences have been seen, they more often suggest stronger effects for women, e.g. [113; 217; 234]. Paper I found support for a sex difference in the association between self-reported physical activity and pain tolerance. Here, as opposed to previous research, associations were between 3-15% stronger for men. Paper II found non-significant but similar patterns in repeated measurements effects, possibly lacking the statistical power to detect a difference. In Paper III, we found occasions of slightly stronger total effects for men, but fewer such differences in indirect effects. It is likely that the small indirect effect sizes of a 1-2% risk reduction as seen in Paper III were not sufficiently powered to detect such a modest moderation effect by sex. Hence, our data would indicate that if a so-called moderated mediation between PA, CPT tolerance, and chronic pain is present, it is more likely to appear as moderately stronger effect estimates for men. If pain sensitivity represents a mechanism for how PA affects clinical pain, this could be partially sex-dependent. However, an associated study by Fjeld et al. on the same population found no sex differences in the relationship of PA and chronic pain [54]. Indeed, given the size of the indirect component observed in Paper III, and the size of observed sex interactions throughout the thesis, this sex-difference would be unlikely to be clinically meaningful for any effect of PA on chronic pain.

As summarized in the introduction, there are several suggested sex-dependent mechanisms which affect both clinical pain and pain sensitivity. These include dimorph sex differences in

opioid receptors and descending pain-modulatory pathways (see review by Mogil: [152]), which are part of mechanisms implied to be active in a PA-dependent hypoalgesia [112; 160; 185]. As women tend to have lower experimental pain tolerance and higher risk of chronic pain, there might be such qualitative differences, or competing risks, which outweigh the benefits of PA to a greater extent in women than men. More research is needed to identify whether there are sex-dependent mechanisms for these relationships.

Chronic pain as a moderator

Several studies on effects of PA on QST parameters stratify, adjust, or select samples according to chronic pain status. Inconsistent associations have been seen between self-reported PA and several QST-parameters in musculoskeletal pain [138], and acute bouts of exercise and pain ratings, TS, and CPM in fibromyalgia and rheumatoid arthritis [143]. Another study found no association of self-reported PA on pain thresholds in chronic low back pain, but did find a lack of CPM [169]. EIH has further been found absent in localized musculoskeletal pain by one narrative review looking at isometric exercise conditioning and pain sensitivity thresholds. These studies had certain methodological drawbacks, and results could be dependent on exercise measurement, parameter estimated, participant gender, or the included chronic pain condition [27].

Evidence further suggests that exercise interventions in chronic pain conditions also cause decreases in pain sensitivity. In a meta-analysis of RCTs, Belavy et al. found medium effect sizes (hedge's g=0.55) for the effectiveness of 4-16 weeks of exercise interventions at increasing pressure pain thresholds [20]. This included conditions such as localized chronic pain, fibromyalgia, diabetes-related pain, and Achilles tendon pain, albeit the overall quality of included studies was low. In total, their primary meta-analysis included 926 participants, randomized to interventions or controls. One additional RCT (n=48) found significant increases of pressure-pain thresholds and temporal summation of pain for knee osteoarthritis patients adhering to 12 weeks of exercise therapy (n=25) [80]. Whilst these findings do not rule out a possible moderation of chronic pain, it would imply the size of such interaction not to be so great as to suppress the effect of PA on pain sensitivity.

The absence of interaction between chronic pain types and the associations between PA and CPT tolerance seen in the papers of this thesis imply the associations are the same for chronic pain-sufferers as for the pain-free. Whilst we cannot rule out that select clinical

subgroups in our sample might experience significant moderation to these associations, the fact that we found no interaction using both relaxed and stringent definitions of chronic pain in both cross-sectional and longitudinal designs seems to suggest that such subgroups would need to be quite specific. It could be argued that adjusting for chronic pain when modelling relationships of PA and pain sensitivity represents a specific way of conceptualizing how these three factors are related to one another, i.e. modelling with causal implications. I return to this below.

5.2.4. Why all this talk about endogenous pain modulation anyway? Causality and the implications of this thesis.

The underlying question of Paper III and the thesis in general was: if there is a relationship between PA and chronic pain, PA and experimental pain, and experimental pain and chronic pain, and given that these relationships are in fact causal, does experimental pain represent one of the mechanisms through which PA affects chronic pain? We are thus looking to make causal inference from the estimated relationships. Based on our findings in Paper III, and given all our caveats, it is possible that pain tolerance, as an expression of nervous system modulation of pain signalling, plays a small part in how PA affects the risk of chronic pain. Nevertheless, these findings are not exhaustive, as causal relationships cannot best be determined by such observational data as those used in this thesis due to the limitations inherent in both measurement occasion and methodology.

According to Hill's famous causal framework [83], causal inference in Paper III was challenged in particular by certain issues.

The size of effects, i.e. the indirect effects, were not large, and a very small proportion of the total risk difference could be ascribed to the indirect effect. A greater magnitude of findings would have increased our belief in the underlying causal reasoning. However, small effect sizes are not uncommon when attempting to predict chronic pain from experimental pain parameters [20].

We furthermore sought to support the temporality-criterion by using exposure estimated from the period before measurement of CPT, and comparing both exposure and mediator from Tromsø6 to chronic pain from Tromsø7. These surveys are separated by an average follow-up

time of approximately 7 years, showing “snapshots” of exposure, covariates, and outcomes which exist in complex causal patterns which are not visible in the data due to its low “temporal resolution”. Since we could not control how data varied during the follow-up period, our model estimates are likely to be biased towards the null with regards to effects we could have observed in more controlled settings. In this respect however, the data probably resemble the complexities of real life. However, it is difficult to assess how such classification bias could impact estimates.

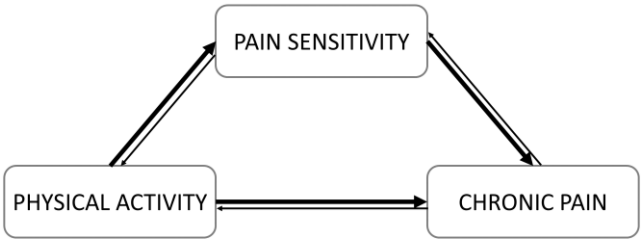
Judging whether the coherence-criterion is satisfied is challenging. Though the mediation model is causal in form, there is still a substantial gap of knowledge regarding how experimental pain relates to chronic pain. This relationship constitutes a necessary pathway for pain tolerance to be able to act as a mediator in our Paper III. However, the evidence for QST predicting future chronic pain or analgesia remains inconsistent, and is not easily summarized in meta-analysis due to high variability in the test paradigms and outcomes used [175]. Finnerup et al. further argue that central pain processing lacks a clearly predictive role in chronic pain and question whether pain sensitization leads to chronification at all [53]. Lacking more knowledge on how disrupted central pain processing could cause chronic pain in humans, there remains a chance that pain sensitivity could be more affected by PA and chronic pain than affecting them. I return to this possibility below.

The consistency criterion asks whether our observations corroborate other, similar observations. Just as clinicians like helping their patients, the field of pain research is ultimately centred on alleviating the suffering brought on by chronic pain conditions. In light of this, studies of how physical activity affects pain sensitivity have often been contextualized in some clinical usefulness, like how to provide effective relief of symptoms in pain patients [222]. Several of the reviews of this relationship have drawn parallels between the effect of physical activity on pain sensitivity or modulation of experimental pain in chronic pain conditions as compared to effect for pain-free and chronic pain populations, and the importance of such effects for management of clinical pain [20; 160; 185; 199; 236]. This provides much valuable insight into the workings of the endogenous pain modulatory system in pain free versus chronic pain conditions.

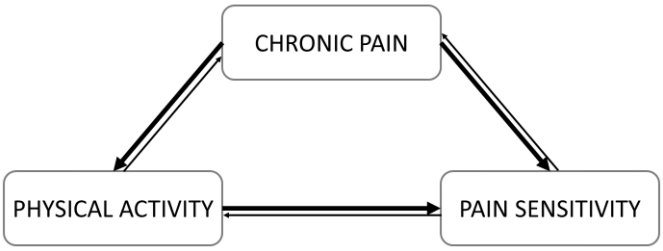
However as stated ad infinitum, experimental pain is not chronic pain. Though it is important to understand how phenomena like EIH manifests with and without chronic pain to better understand pain processing, we nevertheless cannot assess its clinical impact on chronic pain by using experimental pain sensitivity change as a proxy outcome whilst

stratifying according to, or assessing interaction with, chronic pain. Where questions of moderation mainly pertain to answer “when, where, in whom and under what conditions” and is closely related to the concept of confounding, mediation asks “why” [241]. Put differently, investigating the clinical implications of EIH on pain is not primarily a question of how chronic pain moderates or confounds EIH, but of how pain sensitivity mediates an effect of PA on chronic pain. Consistency is thus lacking since there are few comparable studies looking at such indirect effects, and so more research is needed to look for corroborating evidence.

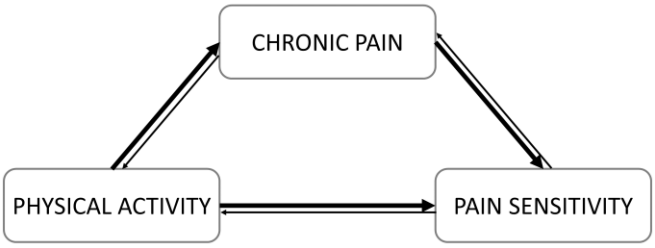
Are the small effect sizes, unresolved coherence, and a lack of comparative evidence expressing something else? There could be a possibility that a type of investigator bias is acting on the research regarding physical activity, endogenous pain modulation, and chronic pain. Although alluringly alike, Figure 13 illustrates how the three main relationships of this thesis can be conceptualized as three different causal models which each communicate different causal relationships:



a)



b)



c)

Figure 13: Pain sensitivity as mediator (a); chronic pain as confounder and potential moderator with pain sensitivity as collider (b); chronic pain as mediator and pain sensitivity as collider (c); allowing for some bi-directionality.

Whilst a) is the suggested model of this thesis, b) arguably shows how chronic pain should be modelled as a moderator, with c) suggesting that there could more plausibly be allowed a direct effect on chronic pain from PA. The latter two options entail a possibility which is not commonly discussed: pain sensitivity as assessed by QST could be a collider in the models.

The topics of interest for this thesis were explored based on the hypotheses that chronic pain is downstream of both endogenous pain modulatory capacity and physical activity. However, other studies have found that both chronic pain and physical activity are shown to alter expressions of endogenous pain modulation. They are both in turn affected by a multitude of factors. It may well be the case that endogenous pain modulation is primarily an expression of the state of the being and the forces or factors working upon it. In that case, pain sensitivity could be more affected by both physical activity and chronic pain than it would be affecting them. If this thesis assumes model a) whilst the true causal model is either b) or c), we risk drawing conclusions from data that are subject to collider bias. We should not be naïve to this possibility, and our research hypotheses, study designs, and the explicit description of our causal assumptions would do well to reflect this. If controlled experimental designs or mediation analyses of observational data cannot improve the causal claim that physical activity impacts chronic pain through an effect on endogenous pain modulation, future research should explore models b) or c).

5.3. Thoughts on future research

In future studies, researchers should be mindful to select measurements suitable to subject-matter requirements, and should also be aware of possible differences between LTPA and occupational PA. If using CPT, steps should be taken to minimize the amount of right-censoring in order to improve precision.

Future studies should also be mindful of possible sex-dependent effects and should account for such possible moderation and the power required to detect it in power calculations.

In order to better evaluate the mechanistic role of pain sensitivity for the effect of PA on chronic pain, interventions on PA should strive to independently observe effects on endogenous pain modulation and subsequent effects on chronic pain or risk of such, and the interplay between them. A higher temporal resolution and more rigorous control over the

dynamics of PA, pain tolerance, and chronic pain measurements might aid in this. We would expect that this would yield stronger indirect effects for pain tolerance on risk of chronic pain, and more so for more severe chronic pain types. It is possible that dynamic QST parameters would yield different estimates, although much care should be put into ascertaining the validity and repeatability of the chosen modality and methodology. It is a given, and clearly important, that care should be taken to appropriately identify the underlying causal model on which hypotheses are formed, for both researchers and readers.

6. Conclusions

Given the limitations inherent in observational designs of data collection and analyses, this thesis found evidence supporting higher self-reported habitual PA in leisure time, and higher exercise intensity and duration, to be associated with higher cold-pain tolerance. This association appeared to be dose-response shaped in leisure-time PA. Unlike previously reported, effect estimates appeared in general to be slightly larger for men than women. We found no effects for accelerometer-assessed PA, likely due to analytical choices and confounding by occupational PA. Leisure-time PA relationships appeared to be stable when measured at multiple time-points in the same individuals, and more PA over time was related to higher pain tolerance compared to being less active. There were weak signs that a positive change in PA levels was more strongly associated with higher pain tolerance than a negative change, even though the sum total PA level was the same over time. However, PA did not appear to counteract an overall drop in pain tolerance over time.

Higher PA levels were associated with lower risk of widespread and moderate-to-severe chronic pain types. For moderate-to-severe chronic pain types, a small part of this effect was mediated through an effect on pain tolerance, suggesting pain tolerance might have a mechanistic role in the effect of PA on chronic pain. Given the size of gender differences, these were unlikely to impact the effect of PA on chronic pain. The clinical significance of the small indirect effect observed in our study is unclear.

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Paper one

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ORIGINAL ARTICLE

Physical activity and cold pain tolerance in the general population

Anders P. Årnes[1,2] | **Christopher S. Nielsen**[3,4] | **Audun Stubhaug**[4,5] | **Mats K. Fjeld**[3] | **Laila A. Hopstock**[2] | **Alexander Horsch**[6] | **Aslak Johansen**[1] | **Bente Morseth**[7] | **Tom Wilsgaard**[2] | **Ólöf A. Steingrímsdóttir**[3]

[1]Department of Pain, Department of Community Medicine, University Hospital of North Norway, Tromsø, Norway

[2]Department of Community Medicine, UiT The Arctic University of Norway, Tromsø, Norway

[3]Division of Mental and Physical Health, Norwegian Institute of Public Health, Oslo, Norway

[4]Department of Pain Management and Research, Division of Emergencies and Critical Care, Oslo University Hospital, Oslo, Norway

[5]Institute of Clinical Medicine, University of Oslo, Oslo, Norway

[6]Department of Computer Science, UiT The Arctic University of Norway, Tromsø, Norway

[7]School of Sport Sciences, UiT The Arctic University of Norway, Tromsø, Norway

Correspondence
Anders P. Årnes, Department of Pain, University Hospital of North Norway, UNN Tromsø, 9038 Tromsø, Norway.
Email: anders.arnes@uit.no

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Abstract

Background: The relationship between habitual physical activity (PA) and experimental pain tolerance has been investigated in small samples of young, healthy and/or single-sex volunteers. We used a large, population-based sample to assess this relationship in men and women with and without chronic pain.

Methods: We used data from the sixth and seventh Tromsø Study surveys (2007–2008; 2015–2016), with assessed pain tolerance of participants with the cold pressor test (CPT: dominant hand in circulating cold water at 3°C, maximum test time 106 s), and self-reported total amount of habitual PA in leisure time ($n = 19{,}087$), exercise frequency ($n = 19{,}388$), exercise intensity ($n = 18{,}393$) and exercise duration ($n = 18{,}343$). A sub-sample had PA measured by accelerometers ($n = 4{,}922$). We used Cox regression to compare CPT tolerance times between self-reported PA levels. For accelerometer-measured PA, we estimated hazard ratios for average daily activity counts, and for average daily minutes of moderate-to-vigorous PA done in bouts lasting 10 min or more. Models were tested for PA-sex, and PA-chronic pain and PA-moderate-to-severe chronic pain interactions.

Results: Leisure-time PA, exercise intensity and exercise duration were positively associated with CPT tolerance ($p < .001$; $p = .011$; $p < .001$). More PA was associated with higher CPT tolerance. At high levels of leisure-time PA and exercise intensity, men had a significantly higher CPT tolerance than women. Accelerometer-measured PA was not associated with CPT tolerance.

Conclusions: This study is one of the first to show that higher self-reported habitual PA was connected to higher experimental pain tolerance in a population-based sample, especially for men. This was not found for accelerometer-measured PA.

Significance: This study finds that higher level of self-reported leisure-time physical activity is associated with increased cold pressor pain tolerance in a large population-based sample. Though present in both sexes, the association is strongest among men. Despite the robust dose–response relationship between pain tolerance and self-reported activity level, no such relationship was found for accelerometer-measured activity, reflecting a possible discrepancy in the aspect of physical activity measured. Though the study design does not permit causal conclusions, the findings suggest that increasing physical activity may increase pain tolerance in the general population.

1 | INTRODUCTION

Several reviews summarize how acute bouts of physical activity (PA) reduce sensitivity to experimental pain stimuli, manifested as temporary change in parameters such as sensitivity thresholds and tolerance thresholds (Koltyn, 2000; Naugle et al., 2012; Rice et al., 2019). This effect, called exercise-induced hypoalgesia, is seen using electrical, heat, cold, chemical and pressure pain modalities. A recent RCT found reduced pain sensitivity not to depend on intensity of acute exercise alone, but also on underlying fitness status (Schmitt et al., 2020). Indeed, a more enduring pain sensitivity reduction has been suggested as a feature associated with increased levels of *habitual* PA, a long-term counterpart to the transient exercise-induced hypoalgesia. This is seen using a prospective exercise intervention approach (Jones et al., 2014), comparing athletes to non-athletes (Geva & Defrin, 2013; Tesarz et al., 2012), or looking at self-reported (Lemming et al., 2015, 2017; Naugle & Riley, 2014) or device-measured PA (Ellingson et al., 2012; Naugle et al., 2017; Ohlman et al., 2018), with heat, cold, pressure or ischaemic pain modalities. The hypothesis of a long-term effect of PA on pain sensitivity was also supported by a meta-analysis of observational studies finding lower pain sensitivity in athletes compared to normally active controls (Tesarz et al., 2012).

Although an association with acute bouts of PA and even habitual PA seems to be well-founded, studies often examine single-sex samples despite well-established sex differences in clinical and experimental pain (Mogil, 2012; Racine et al., 2012). They are also often based on small, non-generalizable samples of young, healthy volunteers, and infrequently report accelerometer-measured PA.

Adverse change in central mechanisms of pain facilitation and inhibition appears to be a recurring component in several chronic pain conditions (Granovsky, 2013; Moana-Filho et al., 2018; O'Brien et al., 2018; Yarnitsky, 2010), and has accordingly been hypothesized to be an independent risk factor for developing chronic pain (Baert et al., 2016; Petersen et al., 2018; Staud, 2012; Treede, 2019; Yarnitsky et al., 2008). As habitual PA is an effective treatment modality and has been suggested to prevent chronic pain (Ambrose & Golightly, 2015; Holth et al., 2008), part of this effect is thought to occur through up-regulating pain-inhibiting mechanisms. However, if chronic pain is already present, this might, in some cases, sensitize individuals to pain in such a way as to act contrary to the benefits of PA on pain sensitivity. Indeed, the presence of chronic pain has been reported to coincide with a lacking, or even reversed, association between habitual PA and pain sensitivity (Mani et al., 2019; Orr et al., 2017), and identical acute exercise regimens can produce different central pain processing responses across different painful conditions (Meeus et al., 2015). It is therefore of interest to further assess how the presence of chronic pain might influence the relationship between levels of habitual PA and the experience of painful stimuli.

To improve our understanding of the relationship between habitual PA and pain sensitivity, studies combining heterogeneous study populations with large samples are warranted. The Tromsø Study has accumulated the hitherto largest population-based experimental pain data sample in the world. These data also contain self-reported and accelerometer-measured habitual PA. Thus, our objective was to model relationships between types and measurements of PA and experimental pain sensitivity in a population-based sample, including both sexes with and without chronic pain.

2 | METHODS

2.1 | Study population and sample

The Tromsø Study, conducted in the Tromsø municipality in Northern Norway, consists of seven repeated surveys from 1974 to 2016 (Tromsø 1-Tromsø 7). It has invited both total birth cohorts and random samples (Eggen et al., 2013; Jacobsen et al., 2012). Participants were recruited through mailed invitations and received no monetary reimbursement for attending. Data have been collected through questionnaires, biological samples and clinical examinations. Experimental pain testing using the cold pressor test (CPT) was included in Tromsø 6 (2007–2008) and Tromsø 7 (2015–2016). The participation proportion in Tromsø 6 was 66% (n = 12,984; age 30–87 years, 53% women), and 65% in Tromsø 7 (n = 21,083; age 40–99 years, 53% women).

For this cross-sectional study, we included individuals who participated in CPT in Tromsø 6 or 7 and had provided data on PA (Figure 1). For participants who had provided data in both Tromsø 6 and 7 (n = 6,500), we chose to use CPT, exposure and covariate data from Tromsø 7 only.

Second visit: Of all invitees to the first visit of Tromsø 7, a random sample was made of 20% of participants in age groups 40–59 (n = 4,008) and 50% of participants in age groups 60–84 (n = 6,142). In addition, the study invited all other participants of Tromsø 7 who had also participated in select clinical examinations in Tromsø 6 (n = 3,154). Of all these invitees to the second visit of Tromsø 7, 63% (n = 8,346) participated. The second visit contained more extensive examinations, including measurement of PA by accelerometry (Figure 1).

2.2 | Measurements

2.2.1 | Physical activity

This study used three different methods to assess PA. First, participants' self-reported level of leisure-time physical

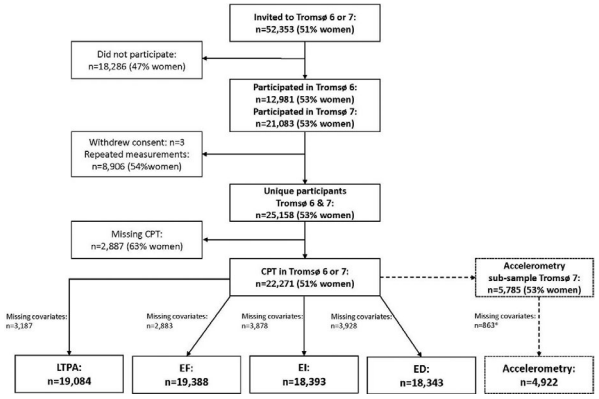

FIGURE 1 Flow of study participants. CPT: cold pressor test; LTPA: leisure-time physical activity; EF: exercise frequency; EI: exercise intensity; ED: exercise duration. The Tromsø Study 2007–2016. *644 participants had missing data on one or more PA questionnaires

activity (LTPA) using a modified version of the four-category Saltin and Grimby questionnaire (Grimby et al., 2015), which asks for average level of LTPA during the previous 12 months. Respondents can select from four mutually exclusive categories: Reading, watching TV or other sedentary activity; walking, cycling or other forms of exercise at least 4 hr a week (with examples); participation in recreational sports, heavy gardening, etc. at least 4 hr a week; or participation in hard training or sports competitions, regularly several times a week. Second, participants reported habitual exercise frequency (EF – 'How often do you exercise'); habitual exercise intensity (EI – 'If you exercise – how hard do you exercise'); and habitual exercise duration (ED – 'For how long do you exercise (give an average)'). Third, PA was measured by accelerometer in a sub-sample of participants.

Accelerometer recordings

PA was measured using an ActiGraph wGT3X (ActiGraph Corp, Pensacola, Florida). Participants were asked to wear the accelerometer on the hip for 7 consecutive days except during showering/bathing or swimming. Acceleration was measured in three axes at a sampling rate of 100 Hz and reduced to counts as a measure of PA. Non-wear time was defined using the Hecht 2009 algorithm (Hecht et al., 2009). According to this algorithm, at least two of the following conditions had to be met for any given minute to classify as valid wear time: (a) >5 counts per minute; (b) at least 2 min with counts >5 in the following 20 min; and (c) at least 2 min with counts >5 in the preceding 20 min. For processing of the count data into variables defining PA levels, we used Quality Control & Analysis Tool (QCAT), a custom-made software developed in MATLAB (The MathWorks, Inc., Natick, Massachusetts, USA). For the analyses, two PA variables were used: first, a variable showing the average daily number of accumulated activity counts; and second, a variable expressing moderate to very vigorous PA (MVPA) minutes per day occurring in bouts of activity lasting >10 min. This categorization of PA intensity was based on a combination of Sasaki et al. and Peterson et al. cut-offs for triaxial counts per minute (Peterson et al., 2015; Sasaki et al., 2011): sedentary <150; light 150–2689; moderate 2690–6166; vigorous 6167–9642; very vigorous >9,642. Counts per minute >2,690 were aggregated into MVPA.

Exclusion criteria from accelerometry were cognitive or physical impairments preventing participants from handling small devices. A total of 6,333 invited individuals consented to participate in accelerometry. We excluded 43 participants due to lost accelerometers and technical errors, 165 participants due to less than 4 days with at least 10 hr of wear time, and 340 participants due to missing CPT data. Thus, the final sub-sample with valid accelerometry included 5,785 individuals (Figure 1). Accelerometer data gathering and variable generation in the Tromsø Study have been extensively described elsewhere (Sagelv et al., 2019).

2.2.2 | Cold pressor test tolerance

The outcome of interest, pain tolerance threshold, was measured on-site as tolerance time during the CPT. Participants were asked to place their dominant hand and wrist in a 13-litres plexiglass vat containing continuously circulated 3.0°C water. Temperature control was provided by an attached cooling circulator (Julabo FP40HE, Julabo Labortechnik GmbH Germany, 22 l/min), and temperature in the external plexiglass chamber was calibrated with a precision thermometer. Participants were asked to keep their hand open and relaxed and hold it in the water for as long as possible, up to a maximum tolerance time of 106 s in Tromsø 6 and 120 s in Tromsø 7. Since maximum times differed for the two surveys, Tromsø Study tolerance times were censored at 106 s post hoc. Participants were informed of the possibility to abort the test at any time should the pain become unbearable. Reasons for exclusion from CPT included participant reluctance; bilateral loss of sensitivity in the hand; conditions causing a breach of the skin (open sores, painful eczema etc.) affecting both hands; Reynaud's syndrome or cold allergy where the participant believed this to be an obstacle for participation, and; inability to comprehend instructions. In instances where individuals were only able to participate with their non-dominant hand, this was allowed. At the CPT station at Tromsø 6, 1,831 participants were not seen due to capacity limitations of the station; in such cases, staff were requested to prioritize participants <60 years of age as that was the age group least sampled in the study (Stabell et al., 2013). Individuals not seen at the station were counted as not having participated in CPT (Figure 1).

2.2.3 | Covariates

Several covariates were assessed as possible confounders as described below. These were investigated based on a rationale that other works have found such factors to be associated with painful conditions, pain sensitivity or associated morbidity. We had questionnaire data on the following covariates: (a) education level (primary/secondary school up to 10 years, upper secondary up to 3 years, college/university less than 4 years and college/university for 4 years or more); (b) daily smoking (never, former or current daily smoker) and reporting of number of cigarettes smoked per day for present or former daily smokers, combined in a categorical variable (never smoked daily, smoked daily previously, smokes between 1 and 10 cigarettes daily and smokes more than 10 cigarettes daily); (c) self-reported health (very bad, bad, neither good or bad, good and excellent), combining 'very bad and bad'; and (d) alcohol consumption frequency (never, monthly or less, 2–4 times a month, 2–3 times a week and 4 or more times a week), combined with habitual number of units consumed when drinking alcohol (1–2, 3–4, 5–6, 7–9, 10 or more). The information about alcohol consumption frequency and units consumed was used to create a categorical variable of approximate tertiles indicating the average number of units consumed each week. Furthermore, we used waist-height-ratio (WHtR) as an alternative to body mass index (BMI), calculated by dividing in situ-measured waist circumference in centimetres on body height in centimetres in accordance to Swainson et al. (Swainson et al., 2017).

Information on chronic pain was obtained from a yes/no question: 'Do you have persistent or constantly recurring pain that has lasted for three months or more'. In Tromsø 7, 96% (N = 20,263) of participants reported on the absence/presence of chronic pain, as well as distribution and characteristics of all present pain, on an electronic body map, the Graphical Index of Pain (GRIP) (Steingrímsdóttir, 2020). Characteristics included pain location, onset, intensity, impact on activities of daily living and bothering, for each painful area. Characteristic items included a 'not applicable' option for those that had no chronic pain. Due to not participating in Tromsø 7, 2,987 participants of the present study sample had no GRIP data. For those participating, a technical error during a brief interval of the study period caused the loss of GRIP data for 642 of the participants in our sample.

2.3 | Statistical methods

Participant characteristics were described using means and standard deviations (*SD*) for continuous variables, and proportions for categorical variables. The distribution of CPT tolerance times was right-censored at a value corresponding to the upper time limit for the test. Additionally, 10-min bout MVPA was right-skewed. We therefore used median and interquartile range (IQR) to describe these data.

We assessed the association between PA and CPT tolerance using Cox proportional hazard regression models. This is a time-to-event model which estimates group differences in risk of experiencing an adverse event (in our case, the event of withdrawing the hand from the cold water prior to the maximum test time possible) at any given time during the test. Our group comparison was level of PA. Participants reaching the maximum test time of 106 s were right-censored, that is, they were counted by the model as having been at risk of but not having experienced the event of interest during the test time. As such, the model considers both the number of participants at risk of the event in each group at any given time of CPT, as well as the rates at which participants of each group are experiencing the adverse event during the test. The resulting 'hazard rates' of the groups can be compared across groups as 'hazard rate ratios' (HRs), which here serve as comparisons of how well participants in different PA groups tolerate the test stimulus. Thus, the HRs are the effect estimates of interest.

We used the Schoenfeld residuals test as well as visual inspection of log–log survival plots to ensure that the proportional hazards assumption was not violated—that is, that HRs were not dependent on the time of CPT.

Separate models were estimated for each PA exposure (Figure 1). Four models used questionnaire-derived PA as exposure. When estimating models for self-reported PA, we first included exposures as continuous variables to estimate significance of trend. Followingly, the lowest exposure categories were used as reference groups for group comparisons. For self-reported EF and ED, the lowest two exposure categories were combined into single categories to preserve statistical power. Two models were based on data from accelerometry as the main exposure, constituting sub-group analyses. The first of the accelerometry models was fitted using average amount of activity per valid day as the independent variable of interest, where the activity of a valid day was expressed as the average number of counts per minute per day. The other model was fitted using average daily minutes of MVPA done in bouts lasting 10 min or more as the independent variable of interest. Both accelerometer variables were included as continuous variables and HRs were reported per standard deviation increase.

All six models were adjusted for sex and age. Other listed covariates were assessed as possible confounders. Confounding was regarded as present if adding a covariate to any sex- and age-adjusted model changed the exposure-outcome coefficient by more than 10% in either direction. If confounding was regarded as present in any model, the confounder was included in all models.

To assess the impact that chronic pain might have on the PA-pain tolerance association, we tested for the presence of

a chronic pain•PA interaction by including a two-way cross product term in our regression models and assessing its statistical significance. We did the same for two-way cross product terms of sex•PA. We then used likelihood ratio tests to compare model fit with and without interaction terms. If interaction with chronic pain was present, models were presented stratified according to chronic pain status.

We performed a sensitivity analysis to assess the impact of different definitions of chronic pain when assessing interactions between PA and chronic pain. This was done by comparing a 'chronic pain yes/no' question from both Tromsø 6 and 7 to a 'moderate-to-severe chronic pain' item. To create this, we used a combination of the Tromsø 7 GRIP pain characteristics as an approximation of the ICD-11 criteria regarding intensity, bothering and impact of moderate-to-severe chronic pain (Treede et al., 2019): onset ≥3months, intensity >3, bothering >3, impact on ADL >3 (all on a 0–10 numeric rating scale). Some participants had missing information on some of these characteristics (not including participants responding 'not applicable'). Therefore, we compared the complete case model of moderate-to-severe chronic pain to a model which imputed missing GRIP data, as described below.

Another sensitivity analysis examined the associations between LTPA and CPT tolerance in the accelerometry sub-sample, to see whether the association differed in the sub-sample compared to the sample of the LTPA model.

All HRs are reported with 95% confidence intervals (CIs), and the significance level was set at 5%. Data analyses were performed using STATA 15.0 (StataCorp, College Station, TX, USA).

2.4 | Missing and multiple imputation

Appendix Table S1 shows frequencies and proportion of missing observations on covariates. Most of the missing information was attributable to item non-response of PA and chronic pain. To assess the impact of missing data on results, and to include observed data otherwise lost to analysis, we imputed missing covariable data for the models of LTPA, EF, EI and ED. When compared, results from imputation generally yielded small differences to our complete case models. The one notable difference was one level of one exposure for women changing from borderline non-significant to statistically significant (Appendix Table S2). Henceforth, we present results from complete case models only. Figure 1 shows the number of participants included in complete case model after excluding for all types of missing.

We also imputed GRIP values for those participants who reported pain in the GRIP of Tromsø 7 but were missing information on one or more of the pain characteristics required to compute the moderate-to-severe chronic pain variable. We then compared the model based on imputed values to that of the complete case model. Multiple imputation was performed using chained equations on 100 imputed datasets with predictive mean matching (known nearest neighbours = 10).

2.5 | Ethics

The current study was approved by the Regional Ethics Committee of North-Norway (ref. REK North 2016/1794). All participants gave written informed consent. Data from three participants who withdrew their consent were not used in the analysis.

3 | RESULTS

Baseline characteristics for study participants are given in Table 1. In total, 22,271 individuals participating in CPT in either Tromsø 6 or Tromsø 7 were included in the analyses. Of these, 12,881 (58%) of participants, of whom 57% were women, withdrew their hand before the maximum test time of 106 s. Total median CPT tolerance was 49 s for women and 95 s for men. Median CPT tolerance for only those participants who withdrew their hand was 32 s (IQR 27); 30 s for women (IQR 27) and 34 s for men (IQR 28).

According to accelerometry-measured PA, median daily amount of MVPA performed in bouts of 10 min or more was 7.6 min (IQR 19.7). Table 1 further shows mean valid wear-days and wear-time in hours per day. The sub-group with accelerometry measurements was on average 6 years older than the main study sample.

3.1 | Self-reported PA and CPT tolerance

Figure 2 shows the proportion of participants who aborted CPT before the maximum time or who were right-censored, by LTPA level at intervals of CPT tolerance time. Compared to the sedentary participants, all higher LTPA categories were significantly associated with higher CPT tolerance (Table 2). We observed a significant interaction between PA and sex, with an additional increase in pain tolerance with higher PA level for males. Only women who reported vigorous LTPA showed a significant increase in CPT tolerance compared to women reporting sedentary LTPA. In sex-specific analyses, associations were stronger with larger effects for men than women, although, in this one instance, the effect for women was larger than for men. Table 2 further shows that EF for both sexes combined was not significantly associated with CPT tolerance at any level of exposure, although the direction of the effect was consistent with that of other exposures. Moderate EI was significantly associated with higher CPT

TABLE 1 Descriptive characteristics of study participants (n = 22,271). The Tromsø Study 2007–2016

Covariate	All	Accelerometry, sub-sample	Withdrew hand in CPT (CPT <105.6 s.)	Endured CPT (CPT = 105.6 s.)
Number of participants (%)	22,271	5,785 (26)	12,881 (58)	9,390 (42)
% Female	51	53	57	43
CPT tolerance time (seconds), median (IQR)	62.5 (76.9)	57.1 (77.8)	31.9 (27.3)	–
Females	49.0 (8.5)	48.7 (80.6)	30.0 (26.9)	–
Males	95.3 (71.8)	71.3 (73.5)	34.3 (27.5)	–
Age, mean (*SD*)	57.0 (11.6)	63.0 (10.1)	57.0 (11.5)	57.0 (11.8)
WHtR, mean (*SD*)	0.56 (0.07)	0.56 (0.07)	0.56 (0.07)	0.56 (0.07)
Education level (%):				
Primary/secondary school, up to 10 years	24	28	25	22
Upper secondary, up to 3 years	29	29	30	29
College/university, less than 4 years	19	19	18	20
College/university, 4 years or more	28	24	27	30
Chronic pain (%)	36	35	38	33
GRIP[a]	16,620	5,021	10,001	6,619
GRIP moderate-to-severe chronic pain (%[b])	3,056 (18.4)	891 (17.8)	2,063 (20.6)	993 (15)
Smoking (%):				
Never	41	39	38	45
Smoked daily previously	44	49	46	41
Smokes 1–10 cigs a day	9.5	8	10	9
Smokes >10 cigs. a day	5.5	4	6	5
Average alcohol consumption (%):				
Never	8	8	9	8
0.375–0.875 units per week	23	23	24	22
1.125–2.5 units per week	24	25	23	24
>2.625 units per week	46	44	45	47
Self-reported health (%):				
Bad or very bad	5	4	6	4
Neither or	26	27	28	25
Good	54	56	53	55
Excellent	15	13	13	16
Physical activity leisure time (%):				
Sedentary	15	13	17	13
Light	58	62	60	56
Moderate	24	24	21	27
Vigorous	3	2	2	4
Exercise frequency (%):				
Never or less than once per week	17	16	17	16
1–3 times per week	57	56	57	56
Approximately every day	26	28	26	27

(Continues)

TABLE 1 (Continued)

Covariate	All	Accelerometry,	Withdrew hand in CPT	Endured CPT
Exercise intensity (%)[c]:				
Light	40	44	42	37
Moderate	56	53	54	58
Vigorous	4	3	4	5
Exercise duration (%)[c]:				
0–29 min	21	20	22	18
30–60 min	57	57	57	57
More than 60 min	22	23	21	25
Accelerometry [d]:				
Daily total counts (mean (*SD*))	–	536 (178)	530 (177)	543 (180)
Daily 10-min MVPA (median (IQR))	–	7.6 (19.7)	6.9 (18.7)	8.9 (21)
Valid wear-days (mean (*SD*))	–	6.8 (0.5)	6.8 (0.5)	6.8 (0.5)
Wear-time hours per day (mean (*SD*))	–	17.3 (1.8)	17.3 (1.8)	17.3 (1.9)

Abbrevations: CPT, Cold pressor test; IQR, interquartile range; *SD*, standard deviation; WHtR, waist-to-height ratio; MVPA, Moderate to very vigorous physical activity.

[a]Number of non-missing respondents to the Graphical Index of Pain characteristics of time of onset, pain intensity, pain distress and impact on activities of daily living; includes those without present chronic pain responding 'not applicable' to characteristics.

[b]3,056/ 16,620; 891/ 5,021

[c]Habitually, whenever exercising.

[d]$n = 5{,}785$

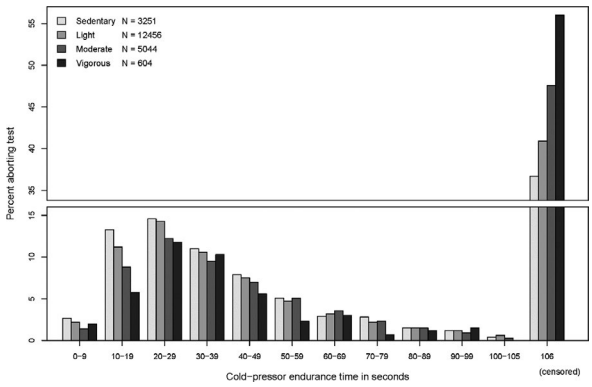

FIGURE 2 Proportions aborting cold pressor test and right-censoring over leisure-time physical activity groups; $n = 21{,}355$. The Tromsø Study 2007–2016

tolerance compared to light EI. Analysis showed a significant interaction between moderate EI and sex, and sex-specific analysis revealed that the association was significant for males only. The highest two levels of ED were significantly associated with higher CPT tolerance compared to the level of shortest duration. Analysis showed no significant interaction between ED and sex, and results were significant for both sexes when analysed separately.

All significant HRs were smaller than 1, with all directions of effect indicating increased CPT tolerance with higher PA.

3.1.1 | Chronic pain and CPT tolerance

Of the 18,642 participants of CPT who responded to GRIP, a total of 2,022 participants had missing data on either time of onset, intensity, bothering or impact on activities of daily living for any area they reported to be painful. This left 16,620 participants with complete GRIP information on chronic pain prevalence as well as chronic pain characteristics, including those responding 'not applicable', from which to construct the moderate-to-severe chronic pain item (Table 1). Using this definition of chronic pain, the prevalence of chronic pain among the respondents of GRIP was 18.4%.

Results from two-way interaction analyses between PA and chronic pain on CPT tolerance are presented in Table S3, and between PA and moderate-to-severe chronic pain on CPT tolerance in Table S4.

We found indication of an interaction with chronic pain on the relationship between EI and CPT tolerance. This was found using both the simple item no chronic pain versus chronic pain (pain duration ≥3 months), and moderate-to-severe chronic pain as defined according to the criteria suggested in ICD-11. Specifically, we found significant interaction effects for those who exercised at vigorous intensity. In individuals with chronic pain, we observed a stronger, positive association between EI and pain tolerance compared to those reporting no chronic pain. Despite no significant complete case interactions between ED and moderate-to-severe

TABLE 2 Hazard ratios of hand withdrawal on cold pressor test tolerance according to levels of physical activity by sex[a]. The Tromsø Study 2007–2016

PA type	*n* =	HR all (CI)	p, trend	HR women (CI)	HR men (CI)
Leisure-time PA, per unit	19,084	**0.91 (0.89–0.94)**	**<0.001**	**0.93 (0.89–0.97)**	**0.90 (0.86–0.94)**
Sedentary	2,872	1		1	1
Light	11,151	**0.91 (0.86–0.96)**		0.95 (0.89–1.03)	**0.86 (0.79–0.93)**
Moderate	4,509	**0.85 (0.79–0.90)**		0.91 (0.83–1.00)	**0.78 (0.71–0.86)**
Vigorous	552	**0.71 (0.62–0.82)**		**0.63 (0.51–0.78)**	**0.81 (0.67–0.97)**
Exercise frequency, per unit	19,388	0.98 (0.95–1.01)	0.146	**0.96 (0.92–0.997)**	1.00 (0.96–1.05)
< 1/week	3,187	1		1	1
1–3 times/week	11,094	0.99 (0.94–1.05)		0.99 (0.92–1.07)	0.99 (0.92–1.07)
Approximately every day	5,107	0.96 (0.90–1.02)		0.93 (0.85–1.01)	1.00 (0.91–1.10)
Exercise intensity, per unit	18,393	**0.95 (0.92–0.99)**	**0.011**	0.97 (0.92–1.02)	**0.94 (0.89–0.99)**
Light	7,212	1		1	1
Moderate	10,402	**0.95 (0.91–0.99)**		0.96 (0.91–1.02)	**0.92 (0.86–0.98)**
Vigorous	779	0.94 (0.84–1.04)		0.95 (0.81–1.11)	0.93 (0.81–1.08)
Exercise duration, per unit	18,343	**0.91 (0.88–0.93)**	**<0.001**	**0.92 (0.89–0.96)**	**0.89 (0.85–0.93)**
0–29 min.	3,681	1		1	1
30–60 min.	10,596	**0.86 (0.82–0.90)**		**0.87 (0.81–0.93)**	**0.85 (0.78–0.91)**
>60 min.	4,066	**0.82 (0.77–0.87)**		**0.85 (0.79–0.93)**	**0.79 (0.73–0.87)**
Accelerometry:	4,922				
Daily total counts[b]		0.99 (0.95–1.03)	0.734	1.02 (0.96–1.08)	0.96 (0.91–1.02)
Daily 10-min MVPA[b]		0.98 (0.94–1.02)	0.218	1.00 (0.94–1.05)	0.95 (0.90–1.01)

Note: Unstratified models are adjusted for: sex, age, waist-height-ratio, education, current smoker status, average weekly alcohol consumption, self-reported health and chronic pain. Statistically significant results denoted by **bold**. Disregarding sex, stratified models use identical adjustments.

Abbrevations: PA, physical activity; MVPA, moderate to very vigorous physical activity; HR, hazard ratio; CI, 95% confidence interval.

[a]Cox proportional hazards regression.

[b]Hazard ratio for 1 *SD* increase

chronic pain, the imputed model found a significantly stronger association with CPT tolerance for the highest level of ED for those without pain (Table S4).

3.2 | Accelerometer-measured PA and CPT tolerance

HRs for total counts and 10-min bout MVPA minutes are reported in Table 2. Associations between accelerometer-measured PA and CPT tolerance were not statistically significant. We found no interaction with sex or chronic pain.

Differences in associations of self-reported LTPA and CPT tolerance between the main sample and the sub-group with accelerometry data were found to be negligible (results not shown).

4 | DISCUSSION

In this study, self-reported LTPA, EI and ED were positively associated with CPT tolerance in a dose–response relationship while accelerometer-measured PA was not. Chronic or moderate-to-severe chronic pain did not moderate these relationships, suggesting the association between PA and pain tolerance to remain independent of either in this sample.

4.1 | PA and pain tolerance

Reviews have summarized possible mechanisms through which acute PA might affect pain sensitivity (Rice et al., 2019; Sluka et al., 2018), including activation of endogenous opioid

or non-opioid pain-inhibitory systems influencing central mechanisms of pain modulation, regulation of inflammatory mediators and autonomic nervous regulation of stress response systems. Others have further suggested cardiovascular interactions (Koltyn & Umeda, 2006; Ring et al., 2008). These mechanisms may plausibly be involved in long-term effects of PA on pain sensitivity, alongside select psychological factors that may beneficially modulate pain (Baker & Kirsch, 1991; Geva & Defrin, 2013; Jones et al., 2014). Regardless, the effect of long-term PA on pain sensitivity is surely multifaceted.

Previous studies suggest a link between habitual PA and experimental pain tolerance, both when comparing athletes to non-athletes (Geva & Defrin, 2013; Tesarz et al., 2012), when comparing self-reported PA levels (Lemming et al., 2015, 2017; Naugle & Riley, 2014) or measuring PA using accelerometry (Ellingson et al., 2012; Naugle et al., 2017; Ohlman et al., 2018). Jones et al. found increased pain tolerance in a controlled trial following a 6-week program of structured moderate to vigorous aerobic cycling (Jones et al., 2014), indicating that change in exercise at a certain level positively influences pain tolerance. Indeed, underlying level of physical fitness is found to affect pain sensitivity independently of acute exercise intensity (Schmitt et al., 2020), although most consistently when looking at pain tolerance thresholds (Tesarz et al., 2012). Schmitt et al. suggested that this reflects a functional adaptation of central neurological mechanisms, explaining why PA is a possible therapeutic avenue towards prevention and regulation of chronic pain conditions.

4.1.1 | Accelerometer-measured and self-reported PA

In addition to varying according to pain sensitivity parameter studied, correlations between PA and pain sensitivity vary considerably when PA is accelerometer-measured (Black et al., 2017; Ellingson et al., 2012; Ohlman et al., 2018; Waller et al., 2019). One large sample study found negative, and a lack of, associations between higher levels of accelerometer-measured PA and pain thresholds among 22 year olds (Waller et al., 2019). Comparing participants with varying distributions of current pain, they found ambiguous associations with pressure and cold pain threshold when measuring PA using an ActiGraph GT3X in a scheme much resembling that of our study. Others found significant prediction of pressure-pain threshold by accelerometer-measured MVPA, but no such effect for heat pain threshold (Ohlman et al., 2018).

Accelerometry is a feasible large-scale alternative to energy expenditure estimation using more expensive gold standard measures (Sylvia et al., 2014). Validating triaxial ActiGraph PA intensity cut points against indirect calorimetry, Santos-Lozano et al. found a moderate to high ability to correctly classify PA intensities (Santos-Lozano et al., 2013). Nevertheless, accelerometry might underestimate the volume of certain types of PA and their intensity, especially in free-living. For example, the uniaxial ActiGraph MTI seems prone to misclassification of activities such as carrying heavy loads, swimming or riding a bike, causing underestimation of total energy expenditure (Hagstromer et al., 2007). Also, accelerometer data rarely distinguish between occupational PA and LTPA. Although we are unaware of studies investigating the associations between occupational PA and pain tolerance, several have suggested high occupational PA as a risk factor for clinical pain (Bergmann et al., 2017; Heuch et al., 2017; Miranda et al., 2008; Shieh et al., 2016; Sim et al., 2006). Given a link between clinical and experimental pain, this could weaken associations in our study as a possibly detrimental effect of occupational PA counterbalances the effect of LTPA. Finally, there remains variability in accelerometer types, what output they provide and their corresponding validity in detecting PA correctly (Plasqui et al., 2013).

There is also a known discrepancy between self-reported and accelerometer-measured amount of PA in general (Skender et al., 2016) and in the Tromsø Study in particular (Sagelv et al., 2020). Known challenges to questionnaire reliability, validity and sensitivity include longer periods of recall, low sensitivity to change in patterns of activity or activity-related differences in health and large errors of absolute estimates of amount of activity (Lee et al., 2011; Shephard, 2003; Sylvia et al., 2014), with indications of significant overestimation of volume of PA, in particular higher intensities, with self-report compared to accelerometry (Dyrstad et al., 2014; Hagstromer et al., 2007). Our main analyses ranked and compared activity levels based on self-reported PA. Sagelv et al. found that associations between self-reported PA ranks and accelerometry measures were consistently and significantly positive, although correlations with accelerometer-measured steps, types of PA intensity counts and bouted MVPA were negligible to moderate. The Saltin-Grimby PA level scale correlates well with VO_2 max, resting heart rate (Emaus et al., 2010) and physical fitness as work capacity (Lochen & Rasmussen, 1992), and is significantly associated with the risk of myocardial infarction and death (Calais et al., 2014). Although volume of PA can be overestimated, the scale shows high predictive validity, with PA levels consistently inversely associated with 'different risk factors, morbidity and health as well as future mortality' (Grimby et al., 2015). While accelerometers seem suitable for measuring PA time•intensity, questionnaires appear useful in ranking and comparing participants' relative activity levels. In our self-report models, we observed a dose–response relationship of long-term PA rank and pain tolerance.

Utilizing accelerometer-measured PA, our sub-group analysis did not support findings from self-reported PA, despite similar associations of self-reported LTPA and CPT

tolerance in the primary sample and sub-groups. The cause of this discrepancy is unknown. It might reflect the difference inherent in assessing energy expenditure and fitness versus ranking PA habits and lifestyles. Although self-report results showed associations between habitual PA and pain tolerance, we cannot accurately state the inherent PA volume and intensity, and whether there is some other quality to an active lifestyle in our participants that mediates this association. No current measurement tool captures all components inherent to PA: intensity, duration, frequency, volume, domain and context (Sagelv et al., 2020). Rather, methodologies differ with regard to strengths and weaknesses. Future studies should be mindful to select measurements suitable to subject-matter requirements, and should also be aware of possible differences between LTPA and occupational PA. Thus, beyond adding towards confirming a relationship between PA and pain tolerance, our study found those reporting to habitually engage in PA with higher intensities and durations to be most tolerant to pain. This indicates a 'chronic' equivalent to the finding by Schmitt et al. of a similar response to both acute exercise and underlying fitness (Schmitt et al., 2020).

4.1.2 | Sex differences

Reviews and later studies find sex differences in experimental pain, with women generally being more pain sensitive (Bartley & Fillingim, 2013; Bulls et al., 2015; Defrin et al., 2009; Hashmi & Davis, 2014; Lemming et al., 2015, 2017; Mogil, 2012). In a review from 2012, 80% of studies looking at CPT found lower cold pain tolerance in women than men (Racine et al., 2012). In our study, men had almost twice the median tolerance time of women, with women more likely to abort the CPT before the maximum test time. Theories regarding underlying mechanisms of sex differences in pain have been summarized elsewhere (Bartley & Fillingim, 2013; Defrin et al., 2009; Mogil, 2012, 2018; Sorge & Totsch, 2017), and include sex-dependent differences in immunologic and inflammatory mediation of pain (Mapplebeck et al., 2016; Sorge et al., 2011). In our study, PA was more strongly associated with pain tolerance in men than women. Possible explanations for the sex-specific effect of PA include sex-dependent dimorphism of opioid receptors and descending pain-modulatory circuits (see review (Mogil, 2018); (Chakrabarti et al., 2010; Liu & Gintzler, 2000; Loyd & Murphy, 2014; Tershner et al., 2000)), both of which are mechanisms implicated in the hypoalgesic effect of PA (Koltyn et al., 2014; Naugle et al., 2012; Rice et al., 2019).

4.1.3 | Chronic pain

Only the level of most vigorous EI had any statistically significant interaction with chronic pain, suggesting even higher pain tolerance when exercising vigorously for those suffering from chronic pain compared to those who were pain-free. In general, we found that dose–response relationships between self-reported PA and pain sensitivity remained with and without chronic or moderate-to-severe chronic pain. Vaegter et al. found increased pain tolerance after acute exercise in subjects with and without, but other experimental pain measures were dependent on the underlying pain sensitivity of patients (Vaegter et al., 2016). Other studies have found inconsistent associations between exercise or self-reported PA and temporal summation of pain or conditioned pain modulation in chronic pain patients (Mani et al., 2019; Meeus et al., 2015; Orr et al., 2017). Similar to the findings of Vaegter et al. regarding acute exercise, our study found a positive relationship between habitual exercise and pain tolerance in pain-free subjects and subjects reporting various forms of chronic pain. The lack of moderating effect by chronic pain on the relationship between PA and pain tolerance indicates that this relationship remains the same for chronic pain sufferers as for the pain-free, suggesting that PA might still be able to positively influence habitual central modulation of pain despite the presence of chronic pain. However, the present study looks at two dichotomized types of chronic pain in sub-groups that are possibly quite heterogeneous. As the association between PA and clinical pain can differ between different types and severities of chronic pain conditions, we might therefore not be able to detect moderation at a more clinically meaningful level. To amend this, future population studies could group results on specific clinical pain states or could stratify analyses according to chronic pain characteristics such as distribution of painful sites. Finally, the link between experimental pain and clinical pain remains to be clarified. Future studies need to assess whether and to what extent pain sensitivity mediates a positive effect of PA on clinical pain states.

4.2 | Strengths and limitations

The main strength of this study is its unprecedented sample, enabling analysis of habitual PA and pain tolerance in a population-based sample of women and men, with a high participation proportion and with a heterogeneous combination of demography and health states, allowing a robust adjustment for possible confounders.

Analyses contained both self-reported and accelerometer-measured PA, both of which are methods with known methodological challenges. In addition, accelerometry was not able to distinguish between occupational and leisure-time PA. Another limitation is scarce evidence regarding the reliability of the CPT tolerance parameter. Looking at intraclass correlation coefficients for CPT duration (i.e. tolerance time), one reliability study including 19 pain-free students found fair coefficients for test–retest reliability and poor to

excellent coefficients for inter-examiner reliability (O'Neill & O'Neill, 2015). Koenig et al. reported an intraclass correlation of 0.92 for pain tolerance measured with 4°C CPT at two occasions separated by 2 weeks in, predominantly female, students (Koenig et al., 2014). Finally, our measure of chronic or moderate-to-severe chronic pain was of low resolution, possibly leading to a heterogeneous chronic pain sub-sample and diluted effects of the moderation analyses.

4.3 | Conclusion

In this population-based study, higher self-reported habitual PA was associated with higher experimental pain tolerance. This association was more evident for men than for women and was dose–response shaped. There were indications of higher tolerance with vigorous exercise for participants with chronic pain. Future studies could further investigate the possible relationships between accelerometer-measured LTPA, as well as occupational PA, and pain tolerance.

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CONFLICT OF INTEREST

All authors declare that they have no conflict of interests related to this study.

AUTHOR CONTRIBUTIONS

APÅ, CSN, AS, MKF, LAH, AH, BM and ÓAS all contributed to the collection of data. APÅ and ÓAS planned and outlined the manuscript. APÅ and TW were responsible for the statistical modelling, and APÅ performed all statistical analyses. All authors have contributed to the interpretation and discussion of results, and to the development of the manuscript through critical revision and comments. All authors have approved this paper.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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Table S1: Missing information on covariates (N=22,271). The Tromsø Study 2007-2016.

Covariate:	Missing, n (%)
Leisure-time physical activity	916 (4)
Exercise frequency	389 (2)
Exercise intensity	1,624 (7)
Exercise duration	1,676 (8)
Waist-height-ratio	172 (1)
Education level	336 (2)
Chronic pain	1,647 (7)
Present and past daily smoking	368 (2)
Average alcohol consumption	390 (2)
Self-reported health	170 (1)

Table S2: Hazard ratios of hand withdrawal on cold-pressor test tolerance according to levels of physical activity by sex[a], using imputed datasets[b]. The Tromsø Study 2007-2016.

PA type	HR all (CI)	p, trend	HR women (CI)	HR men (CI)
Leisure-time PA, per unit	**0.91 (0.88-0.93)**	**<0.001**	**0.93 (0.89-0.96)**	**0.89 (0.86-0.93)**
Sedentary	1		1	1
Light	**0.91 (0.86-0.95)**		0.95 (0.89-1.02)	**0.84 (0.78-0.90)**
Moderate	**0.83 (0.78-0.89)**		**0.90 (0.83-0.98)**	**0.76 (0.70-0.83)**
Vigorous	**0.70 (0.61-0.80)**		**0.61 (0.50-0.75)**	**0.78 (0.66-0.93)**
Exercise frequency, per unit	0.98 (0.96-1.01)	0.224	0.96 (0.93-1.00)	1.01 (0.97-1.05)
< 1/week	1		1	1
1-3 times/week	0.99 (0.94-1.04)		0.98 (0.92-1.06)	1.00 (0.93-1.07)
Approximately every day	0.97 (0.91-1.03)		0.93 (0.86-1.01)	1.02 (0.93-1.11)
Exercise intensity, per unit	**0.94 (0.91-0.97)**	**<0.001**	**0.94 (0.90-0.99)**	**0.92 (0.88-0.97)**
Light	1		1	1
Moderate	**0.93 (0.89-0.97)**		0.95 (0.90-1.00)	**0.90 (0.85-0.96)**
Vigorous	0.90 (0.82-1.00)		0.90 (0.78-1.04)	0.92 (0.80-1.06)
Exercise duration, per unit	**0.91 (0.88-0.93)**	**<0.001**	**0.92 (0.89-0.96)**	**0.89 (0.85-0.93)**
0-29 min.	1		1	1
30-60 min.	**0.86 (0.82-0.90)**		**0.86 (0.81-0.92)**	**0.87 (0.81-0.93)**
>60 min.	**0.82 (0.78-0.87)**		**0.86 (0.80-0.93)**	**0.79 (0.73-0.86)**

[a] Cox proportional hazards regression.

[b] Multiple imputation with chained equations; predictive mean matching (known nearest neighbours=10), 100 imputed datasets.

Stratified models are adjusted for: sex, age, waist-height-ratio, education, current smoker status, average weekly alcohol consumption, self-reported health and chronic pain. Statistically significant results denoted by **bold**. Disregarding sex, stratified models use identical adjustments.

PA: physical activity; HR: hazard ratio; CI: 95% confidence interval.

Table S3: Hazard ratios of hand withdrawal on cold-pressor pain tolerance test according to levels of physical activity by chronic pain (yes/no)[a]. The Tromsø Study 2007-2016.

		Chronic pain ≥ 3 months, yes/no		
PA type	**n**	**No**	**Yes**	***p*[b]**
		HR (95% CI)	HR (95% CI)	
PA Leisure, per level increase	19,084	**0.92 (0.89 - 0.96)**	**0.90 (0.85 – 0.94)**	0.33
Sedentary	2,872	1	1	
Light	11,151	**0.88 (0.82 - 0.95)**	0.95 (0.88 – 1.04)	0.16
Moderate	4,509	**0.86 (0.80 - 0.94)**	**0.79 (0.71 – 0.88)**	0.21
Vigorous	552	**0.69 (0.58 - 0.81)**	0.78 (0.61 – 1.00)	0.39
Exercise frequency, per level increase	19,388	0.99 (0.95 - 1.23)	0.96 (0.92 – 1.01)	0.45
< 1/wk	3,187	1	1	
1-3 times/wk	11,094	1.00 (0.93 - 1.07)	0.98 (0.90 – 1.06)	0.65
Aprox. every day	5,107	0.98 (0.90 - 1.06)	0.93 (0.85 – 1.03)	0.44
Exercise intensity, per level increase	18,393	0.98 (0.94 - 1.03)	**0.91 (0.86 – 0.96)**	**0.03**
Light	7,212	1	1	
Moderate	10,402	0.96 (0.91 - 1.02)	**0.92 (0.86 – 0.98)**	0.25
Vigorous	779	1.03 (0.91 - 1.16)	**0.78 (0.64 – 0.94)**	**0.02**
Exercise duration, per level increase	18,343	**0.92 (0.88 - 0.95)**	**0.89 (0.85 – 0.94)**	0.34
0-29 mins	3,681	1	1	
30-60 mins	10,596	**0.86 (0.81 - 0.92)**	**0.85 (0.79 – 0.92)**	0.87
>60 mins	4,066	**0.84 (0.78 - 0.90)**	**0.79 (0.72 – 0.88)**	0.39
Accelerometry[c]:	4922			
Total counts per day		1.00 (0.95 - 1.05)	0.99 (0.92 – 1.05)	0.79
10-minute MVPA minutes		0.97 (0.93 - 1.02)	0.98 (0.92 – 1.06)	0.76

[a] Cox proportional hazards regression including two-way interaction terms between chronic pain and physical activity levels.

[b] Statistical significance for physical activity*chronic pain interaction term. Significant results in **bold**.

[c] Hazard ratios for 1 standard deviation increase.

PA: physical activity; MVPA: moderate to very vigorous physical activity; HR: hazard ratio; CI: confidence interval.

Table S4: Hazard ratios of hand withdrawal on cold-pressor pain tolerance test according to levels of physical activity by moderate-to-severe chronic pain (yes/no)[a]. Multiple imputation and complete cases regression. The Tromsø Study 2007-2016.

	ICD11-based[b] moderate-to-severe chronic pain: imputed missing[c].				ICD11-based moderate-to-severe chronic pain: complete cases.			
PA type	**n[d]**	**No**	**Yes**	***p*[e]**	**n**	**No**	**Yes**	***p*[e]**
		HR (95% CI)	HR (95% CI)			HR (95% CI)	HR (95% CI)	
PA Leisure, per level	17,718	**0.87 (0.85 - 0.90)**	**0.91 (0.86 - 0.97)**	0.23	15,563	**0.88 (0.85 - 0.92)**	**0.91 (0.85 - 0.98)**	0.46
Sedentary	2,445	1	1	-	2,091	1	1	-
Light	10,273	**0.84 (0.79 - 0.90)**	0.92 (0.83 - 1.03)	0.09	9,011	**0.85 (0.79 - 0.91)**	0.93 (0.83 - 1.05)	0.17
Moderate	4,447	**0.76 (0.71 - 0.82)**	**0.83 (0.73 - 0.95)**	0.32	3,963	**0.78 (0.72 - 0.84)**	**0.82 (0.71 - 0.96)**	0.50
Vigorous	553	**0.63 (0.54 - 0.73)**	0.78 (0.55 - 1.10)	0.18	498	**0.66 (0.56 - 0.77)**	0.80 (0.53 - 1.22)	0.39
Exercise frequency, per level	17,718	**0.95 (0.92 - 0.99)**	**0.94 (0.88 - 0.99)**	0.67	15,807	**0.96 (0.92 - 0.99)**	0.95 (0.88 - 1.01)	0.73
< 1/wk	2,693	1	1	-	2,377	1	1	-
1-3 times/wk	10,105	0.95 (0.89 - 1.01)	0.97 (0.88 - 1.08)	0.55	9,059	0.96 (0.89 - 1.02)	0.96 (0.85 - 1.08)	0.95
Aprox. every day	4,920	**0.90 (0.84 - 0.97)**	**0.88 (0.78 - 0.99)**	0.74	4,371	**0.92 (0.85 - 0.99)**	0.90 (0.78 - 1.03)	0.76
Exercise intensity, per level	17,718	**0.90 (0.87 - 0.94)**	**0.87 (0.81 - 0.94)**	0.38	15,090	**0.93 (0.89 - 0.97)**	**0.89 (0.82 - 0.97)**	0.36
Light	6,842	1	1	-	5,588	1	1	-
Moderate	10,122	**0.88 (0.84 - 0.92)**	**0.89 (0.82 - 0.97)**	0.80	8,824	**0.90 (0.86 - 0.95)**	0.92 (0.83 - 1.01)	0.77
Vigorous	754	**0.90 (0.80 - 1.00)**	**0.67 (0.52 - 0.86)**	**0.03**	678	0.96 (0.85 - 1.08)	**0.67 (0.50 - 0.91)**	**0.03**
Exercise duration, per level	17,718	**0.90 (0.87 - 0.93)**	0.95 (0.89 - 1.01)	0.08	15,155	0.90 (0.83 - 1.16)	0.96 (0.89 - 1.03)	0.12
0-29 mins	3,895	1	1	-	3,046	1	1	-
30-60 mins	9,991	**0.87 (0.82 - 0.92)**	**0.90 (0.82 - 0.99)**	0.50	8,689	**0.86 (0.81 - 0.91)**	**0.89 (0.80 - 0.995)**	0.56
>60 mins	3,832	**0.81 (0.76 - 0.87)**	0.91 (0.81 - 1.02)	**0.05**	3,420	**0.81 (0.76 - 0.87)**	0.93 (0.81 - 1.07)	0.09
Accelerometry[f]:	n/a	-	-	-	5,463			
Total counts per day		-	-	-		0.97 (0.93 - 1.02)	1.03 (0.94 - 1.13)	0.22
10-minute MVPA minutes		-	-	-		0.97 (0.93 - 1.01)	0.97 (0.87 - 1.08)	0.96

[a] Cox proportional hazards regression including two-way interaction terms between moderate-to-severe chronic pain and physical activity levels.

[b] Moderate-to-severe chronic pain: onset ≥ 3months, intensity >3, impact on ADL >3, bothersomeness >3.

[c] Multiple imputation using chained equations with predictive mean matching, number of known nearest neighbours=10.

[d] Due to slight sampling variation in imputation, we report group numbers from first imputed dataset here.

[e] Statistical significance for physical activity*chronic pain interaction term. Significant results in **bold**.

[f] Hazard ratios for 1 standard deviation increase.

ICD: international classification of disease; PA: physical activity; MVPA: moderate to very vigorous physical activity; HR: hazard ratio; CI: confidence interval.

Paper two

Årnes AP, Nielsen CS, Stubhaug A, Fjeld MK, Johansen A, Morseth B, Strand BH, Wilsgaard T, Steingrimsdottir OA. Longitudinal relationships between habitual physical activity and pain tolerance in the general population. PLoS One 2023;18(5):e0285041.

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RESEARCH ARTICLE

Longitudinal relationships between habitual physical activity and pain tolerance in the general population

Anders Pedersen Årnes[1☯‡*], Christopher Sievert Nielsen[2,3☯], Audun Stubhaug[3,4☯], Mats Kirkeby Fjeld[2], Aslak Johansen[1], Bente Morseth[5☯], Bjørn Heine Strand[2,6‡], Tom Wilsgaard[7‡], Ólöf Anna Steingrímsdóttir[2☯]

1 Department of Pain, University Hospital of North Norway, Tromsø, Norway, **2** Division of Mental and Physical Health, Norwegian Institute of Public Health, Oslo, Norway, **3** Division of Emergencies and Critical Care, Department of Pain Management and Research, Oslo University Hospital, Oslo, Norway, **4** Institute of Clinical Medicine, University of Oslo, Oslo, Norway, **5** School of Sport Sciences, UiT The Arctic University of Norway, Tromsø, Norway, **6** The Norwegian National Centre for Ageing and Health, Vestfold Hospital Trust Norway, Tønsberg, Norway, **7** Department of Community Medicine, UiT The Arctic University of Norway, Tromsø, Norway

☯ These authors contributed equally to this work.
‡ APÅ, BHS and TW also contributed equally to this work.
* anders.arnes@uit.no

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Abstract

Physical activity (PA) might influence the risk or progression of chronic pain through pain tolerance. Hence, we aimed to assess whether habitual leisure-time PA level and PA change affects pain tolerance longitudinally in the population. Our sample (n = 10,732; 51% women) was gathered from the sixth (Tromsø6, 2007–08) and seventh (Tromsø7, 2015–16) waves of the prospective population-based Tromsø Study, Norway. Level of leisure-time PA (sedentary, light, moderate, or vigorous) was derived from questionnaires; experimental pain tolerance was measured by the cold-pressor test (CPT). We used ordinary, and multiple-adjusted mixed, Tobit regression to assess 1) the effect of longitudinal PA change on CPT tolerance at follow-up, and 2) whether a change in pain tolerance over time varied with level of LTPA. We found that participants with high consistent PA levels over the two surveys (Tromsø6 and Tromsø7) had significantly higher tolerance than those staying sedentary (20.4 s. (95% CI: 13.7, 27.1)). Repeated measurements show that light (6.7 s. (CI 3.4, 10.0)), moderate (CI 14.1 s. (9.9, 18.3)), and vigorous (16.3 s. (CI 6.0, 26.5)) PA groups had higher pain tolerance than sedentary, with non-significant interaction showed slightly falling effects of PA over time. In conclusion, being physically active at either of two time points measured 7–8 years apart was associated with higher pain tolerance compared to being sedentary at both time-points. Pain tolerance increased with higher total activity levels, and more for those who increased their activity level during follow-up. This indicates that not only total PA amount matters but also the direction of change. PA did not significantly moderate pain tolerance change over time, though estimates suggested a slightly falling effect possibly due to ageing. These results support increased PA levels as a possible non-pharmacological pathway towards reducing or preventing chronic pain.

Community Medicine, UiT The Arctic University of Norway). Ethical and legal restrictions prevent data from being made publicly available. These revolve around the protection of potentially sensitive data that cannot be shared publicly without being in risk of breaching data protection laws. Bona fide researchers can apply for data from the Tromsø Study. Guidelines on how to access the data are available at the website https://uit.no/research/tromsostudy. All inquiries about the Tromsø Study should be sent by e-mail to tromsous@uit.no. Similar reasoning has been given for previous publications of Tromsø Study-based studies in PLOS ONE.

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Introduction

Physical activity (PA) is a commonly recommended non-pharmacological intervention for preventing and treating a range of chronic pain conditions [1–7]. Concurrently, the prevalence of chronic pain and musculoskeletal complaints is seen to decrease with higher levels of PA in cohort studies [8–11]. There is some evidence regarding a pain-inhibitory response immediately following an acute bout of exercise. This phenomenon is referred to as exercise-induced hypoalgesia (EIH), and was reviewed with regards to exercise protocols, possible mechanisms, and behaviour in sub-populations by Rice et al. in 2019 [12]. Although evidence is sparse, results from experimental studies indicate that the presence of chronic pain can lower the efficacy of EIH [12, 13]; i.e. reducing potential effects of exercise on pain sensitivity. As in acute exercise, higher levels of *habitual* PA are also associated with lower sensitivity to experimental pain [14–17]. Some studies have suggested that individual sensitivity to some quantitative sensory tests of pain has predictive value for subsequent development and progression of chronic pain, often post-operatively [18–22], but the evidence is conflicted and frequently suffers methodological challenges regarding quality of studies and choices of exposures and outcomes. In summary, the sparse literature in this field indicates that a reduction in pain sensitivity might be a possible mechanism through which higher habitual PA levels might modify the risk, or progression, of chronic pain.

Previous studies of PA and pain sensitivity commonly employ small, homogenous samples of young, healthy, or single-sex subjects. In a review by Tesarz et al. including 15 studies of between 6 to 67 participants, athletes had significantly higher pain tolerance than normally active controls, but data were less uniform regarding pain detection thresholds [16]. Several of the studies were single-sex samples and most were on students <30 years of age. Two later studies (n = 53 and n = 36) further supported such an association to pain tolerance in athletes in particular [23, 24]. However, little basic research exists to describe the relationship between habitual PA and pain tolerance in the general population. Our recent cross-sectional study on approximately 19,000 participants was the first study with a sample size of this magnitude to find that higher population-based levels of habitual PA were similarly associated with higher cold-pressor pain tolerance in the general population as that seen in smaller observational and experimental studies [25]. However, causal direction cannot be ascertained by cross-sectional studies. Interestingly, two experimental studies on 24 and 20 healthy participants found increases in pain tolerance following a 6-week moderate to high exercise intervention [14, 26], indicating an effect on pain tolerance by leisure-time types of PA. However, these were of low power and unable to investigate conditional effects for sex and clinical pain. As large studies on PA interventions are lacking, a population-based approach to assessing whether a population change of PA is related to subsequent pain tolerance could provide important basic knowledge.

Furthermore, it would be relevant to examine whether PA influences any potential change in pain tolerance when measured repeatedly in the same individuals over time, and also how these longitudinal relationships are affected by moderating factors such as sex and clinical pain.

Using population data from the Tromsø Study, our current objectives were thus 1) to assess the relationship between longitudinal habitual PA change and subsequent pain tolerance, and 2) to estimate the longitudinal relationship between habitual PA and pain tolerance in repeated measurements of individuals and assessing whether PA moderated any change in tolerance over time. We also assessed whether these relationships changed over sex or chronic pain status.

Materials and methods

Ethics

This study was approved by the Regional Ethics Committee of North-Norway (case number REK North, 2016/1794). Written informed consent was acquired for all participants.

Study population and sample

The present study used data from the sixth and seventh surveys of the Tromsø Study: Tromsø6 (baseline, years 2007–08) and Tromsø7 (follow-up, years 2015–16). The Tromsø Study is a prospective population-based health study conducted in the municipality of Tromsø, Northern Norway. It has gathered population-wide data on PA and experimental pain tolerance in two surveys separated by 7–8 years. This includes data on potentially confounding or moderating factors, including sex, chronic pain, and socio-demographic covariates, and is the largest source of repeated measurements of quantitative sensory test data in the world. Such data can be used to assess relationships with temporal ordering of events. Total birth cohorts and random samples of the local populace have been invited to participate through mailed invitations. No payment is offered for participation. The study collects data through questionnaires, biological samples, and clinical examinations. Further information about recruitment and participation proportions for the entire study has been given elsewhere [27–29].

In Tromsø6, 66% of invitees participated (n = 12,984; mean age 57.5 years; 53% women), while participation proportion for Tromsø7 was 65% (n = 21,083; mean age 57.3 years; 53% women). Of all participants in Tromsø6, 11,284 were especially invited to a follow-up visit in Tromsø7, which 79% attended (n = 8,906; mean Tromsø6 age 55.8 years; 54% women). Both Tromsø6 and Tromsø7 included questionnaires on physical activity and quantitative sensory testing of pain using several types of modalities. The current study sample included individuals participating in both Tromsø6 and Tromsø7 who had information on PA and cold-pressor test (CPT) tolerance at baseline and follow-up (Fig 1; n = 10,732).

Measurements and variables

Leisure-time physical activity. Participants self-reported LTPA level in both surveys using a modified version of the four-level "Saltin and Grimby LTPA Physical Activity Level Scale" (SGPALS [30, 31]). SGPALS asks participants to recall the past 12-month-average level of LTPA specifying four mutually exclusive categories: "Reading, watching TV, or other sedentary activity"; "walking, cycling, or other forms of exercise at least four hours a week (with examples)"; "participation in recreational sports, heavy gardening, etc. at least four hours a week"; or "participation in hard training or sports competitions, regularly several times a week". Categories correspond to sedentary, light, moderate, or vigorous LTPA.

The cold-pressor test. CPT pain tolerance was measured on-site at baseline and follow-up as maximum tolerance time during the CPT. Participants placed their dominant (Tromsø6) or non-dominant (Tromsø7) hand and wrist in a 13-litres Plexiglass vat containing water maintained at 3.0˚C by a cooling circulator (Julabo FP40HE, Julabo Labortechnik GmbH). The difference in test-methodology was due to the addition of an electronic VAS rating mechanism in Tromsø7 which had to be operated using the dominant hand.

During testing, participants were asked to keep their hand open and relaxed with the hand and wrist submerged in the water for as long as possible, up to a maximum tolerance time of 106 seconds for Tromsø6 and 120 seconds for Tromsø7. Participants were informed of the possibility to abort the test at any time during testing.

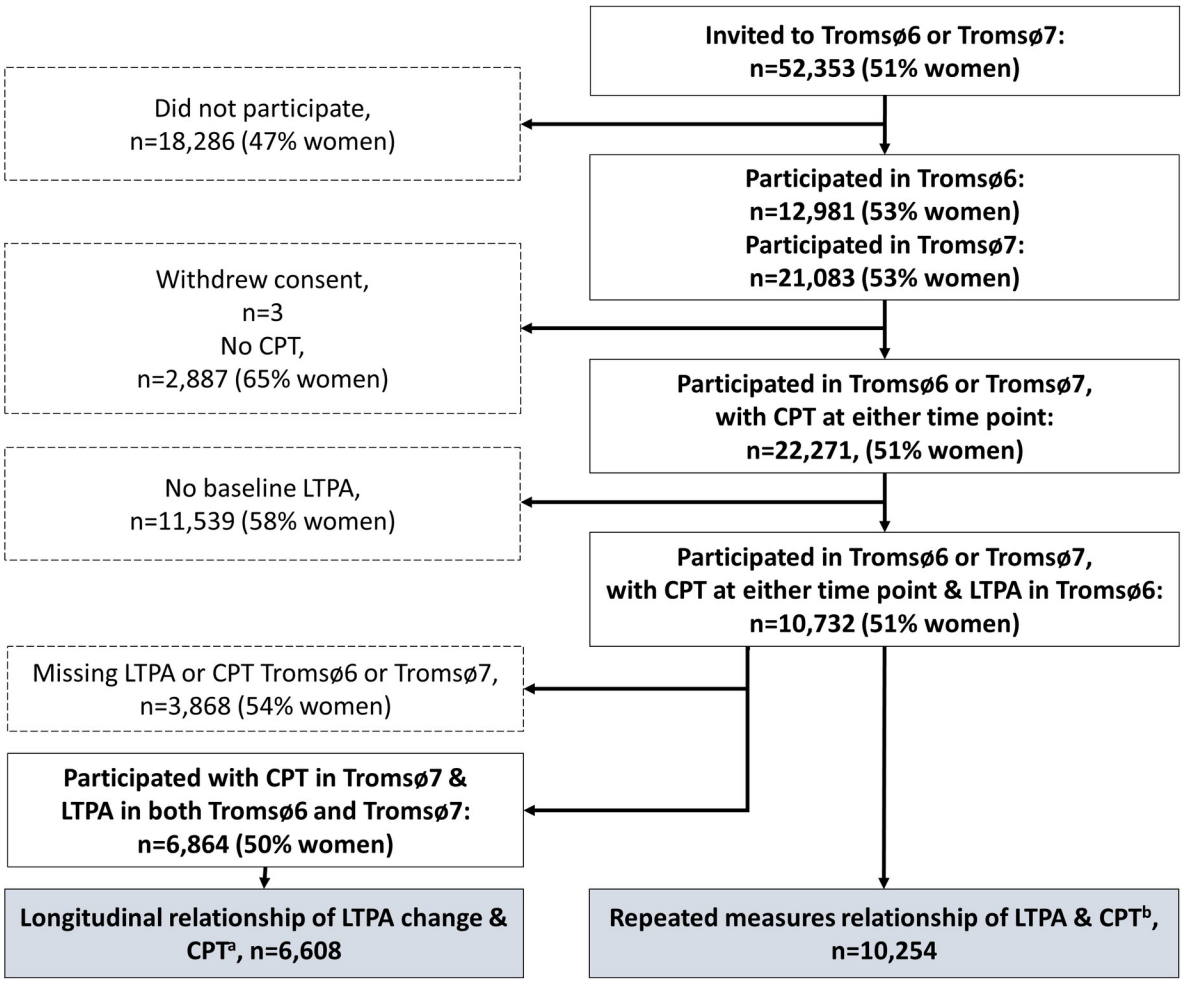

Fig 1. Flow of study participants. [a] Linear Tobit regression; n missing covariates = 256. [b] Mixed model Tobit regression; missing on covariates = 478. LTPA = leisure-time physical activity; CPT = cold-pressor test.

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Participants were excluded from CPT in Tromsø6 or Tromsø7 according to the following criteria: unwilling to participate; cognitive or language problems making them unable to comprehend and follow instructions; Reynaud's syndrome, cold allergy or other conditions that in participants' experience affects their response to cold; bilateral loss of sensitivity in the hand; breached skin on both hands (e.g. caused by eczema, open sores).

We recoded maximum tolerance times for CPT in Tromsø7 to 106 s. post hoc to make the censoring time identical for both surveys. This recoded the right-censored values of 120 s. to 106 s. for 2,499 participants of Tromsø7. Of these, 142 participants had CPT values ranging between 107 and 119 sec.

Baseline covariates. Covariates included self-reported level of education (primary or secondary school up to 10 years, technical/vocational/high school up to three years, college/university less than four years, college or university for four years or more); daily smoking (present, previous, or never); alcohol consumption (never, monthly or less frequently, 2–4 times a month, 2–3 times a week, 4 or more times a week); and self-reported health (very bad, bad, neither good nor bad, good, excellent). We also included occupational PA as a covariate as reported by participants on the Saltin and Grimby occupational PA questionnaire: "If you

have paid or unpaid work, which statement describes your work best?". Participants could choose among "Mostly sedentary", "Work that requires a lot of walking", "Work that requires a lot of walking and lifting", and "Heavy manual labour". Participants who did not respond to this but who elsewhere reported being retired or on disability pensions, unemployment benefits, or sick leave were assigned to the categories "retired" or "disability/sick leave", respectively. We also included chronic pain (constant or recurring pain for three months or longer) as a covariate to be able to assess its importance as a possible effect moderator.

These covariates were defined as potential confounders rather than colliders or mediators, based on their previously known or suspected association to physical activity and/or pain sensitivity [32–38]. On the other hand, research regarding occupational PA and pain tolerance is generally lacking; occupational PA was nevertheless expected to be a confounder based on the reported paradoxical relationship between LTPA and occupational pain, and chronic pain and disability [39].

Statistical analyses

In our primary analysis, we computed an index of LTPA change between baseline and follow-up by computing combinations of LTPA levels across Tromsø6 and Tromsø7. The index was computed as an ordinal variable we assessed the relationship between this index of LTPA change from baseline to follow-up and CPT tolerance at follow-up, using ordinary Tobit regression with right-censored values. We used Tobit regression because the CPT data contained a substantial number of right-censored values (maximum test-time = 106 s.). Such data will bias ordinary linear regression-based estimates of effect. Tobit-class regression models account for the expected distribution of values for the unobserved (here; the right-censored) outcome distribution. Regression parameters can therefore be interpreted as estimates for the true underlying (unbiased) effect on the latent but censored dependent variable, i.e. the expected distribution of the outcome had CPT not been stopped at 106 seconds.

To assess whether a change in pain tolerance over time varied with level of LTPA, our secondary analysis used mixed Tobit regression. Here we estimated the association at both survey occasions, adjusting for survey occasion [40, 41]. Adding a cross-product of LTPA×survey occasion allowed using interaction analysis to assess whether LTPA moderated change of pain tolerance over time. We also added a random intercept for individual subjects to adjust for multiple observations of the same individual due to the repeated measurements of two surveys. In this analysis, we also included participants with only one outcome measurement, as the mixed model used in the secondary analysis makes use of participants with incomplete data to improve the accuracy of estimates. Comparing the model with and without the random intercept for subjects using likelihood-ratio test, we found a significantly better fit ($p<0.05$) for the random effects model. To evaluate the estimation of the random effects model, we examined the accuracy of the quadrature calculation by doubling the default number of integration points used (14 vs. 7), finding negligible differences in estimates. This suggests high accuracy and thus adequately estimated random effects.

As a sensitivity analysis, we specified an identical model using an ordinary linear mixed model with random intercept to observe the impact on effect estimates of using censored values as they were.

The Tobit model is more vulnerable to assumptions of normality than ordinary least squares regression. We used R [42] package tobitdiag to estimate normal distribution Martingale-type residuals which we plotted and inspected for potential deviations, as suggested by Barros et al. [43, 44]. Results showed some deviation from normality in residuals; we discuss the implications of this under strengths and limitations.

Interactions for LTPA and survey, sex, and chronic pain were assessed by adding cross-products of these variables to separate models and testing their model contribution with likelihood-ratio tests. We also assessed the statistical significance of coefficients of each interaction group.

In both primary and secondary analyses, we adjusted for sex, baseline age, education level, alcohol frequency consumption, self-reported health status, daily smoker status, occupational PA level, and chronic pain to account for their possible confounding effect.

Effect sizes were reported with 95% confidence intervals (CI); significance level was set at 5%. Data analyses were performed using Stata 15 and Stata 16.1 (StataCorp, College Station, TX, USA), and R (R Foundation for Statistical Computing, Vienna, Austria; 42).)

Missing data

Causes of missing CPT data included program or technician error, as well as 1,831 participants in Tromsø6 who were not tested due to capacity limitations. Whenever this occurred, staff were told to prioritize participants below 60 years of age as that was the age-group under-sampled in the study (Stabell et al., 2013). Individuals not seen at the testing station were regarded as not having participated in CPT.

Of the 6,864 who participated in CPT in Tromsø7 and had two measurements of LTPA, 256 were lost to primary analysis due to missing information on one or more covariates (S1 Table).

Of the 10,752 with baseline LTPA, and CPT in either Tromsø6 or Tromsø7, 478 were lost to analysis due to missing information on one or more covariates (S2 Table).

Results

The 6,864 participants that reported LTPA in both Tromsø6 and Tromsø7 as well as CPT tolerance in Tromsø7 (50% women; mean age 54.2 (SD 10.8)) were included in primary analyses of LTPA change on subsequent CPT. Furthermore, the 10,732 that participants reported LTPA in Tromsø6 and completed CPT in Tromsø6 and/or Tromsø7 (51% women; mean age 55.8 (SD 11.8)) were included in the overall longitudinal analyses (Fig 1). There was some difference in covariate distributions between men and women (Table 1). Men had a higher age and CPT mean, higher proportion censored in CPT, and proportion engaging in MVPA. Women had the highest proportions of light LTPA, longest education, most chronic pain sufferers, and current retirees. Sample mean CPT outcome over levels of LTPA, sex, and survey occasion is shown in Table 2. There was a general decline in tolerance times across surveys. In both surveys, CPT tolerance was somewhat higher for men vs. women, and higher for higher levels of LTPA.

LTPA and pain tolerance

In the primary analysis, when using longitudinal LTPA change as exposure and CPT tolerance at follow-up as outcome, we found a statistically significant, positive association for those who remained active over time as compared to those who remained sedentary (Table 3; Fig 2). Effect sizes show increased CPT tolerance primarily for those with the highest total amount of PA; secondly more frequently for those with high vs. low PA level at follow-up; and thirdly to a limited extent for those with a positive vs. a negative change in PA over time. Despite these tendencies in effect estimates, no combination containing sedentary LTPA at any time point was significantly different from those who were sedentary in both surveys. Groups containing combinations of light and moderate-to-vigorous LTPA were statistically similar to each other, with 8–12 s. higher CPT tolerance than those who were sedentary in both surveys. Those

Table 1. Baseline characteristics of study samples over main analyses models; mixed model by gender. The Tromsø Study 2007–2016.

Baseline Characteristic:	Total sample			PA-change model
	Total sample *n = 10,732*	Women *n = 5,505 (51%)*	Men *n = 5,227*	Total sample *n = 6,864*
Age, mean (SD)	55.8 (11.8)	55.3 (12.0)	56.2 (11.7)	54.2 (10.8)
CPT, mean (SD)	88.4 (28.3)	83.4 (30.8)	93.6 (24.3)	91.1 (26.5)
Censored CPT[a], n; %	6,718 (62.6)	3,005 (54.6)	3,713 (71.0)	4,369 (63.7)
LTPA, n; %	10,732 (100)	5,505 (51)	5,227 (49)	6,864 (100)
Sedentary	19.3	18.3	20.3	17.2
Light	60.2	67.7	52.3	60.3
Moderate	18.8	13.1	24.8	20.4
Vigorous	1.7	0.9	2.6	2.1
Education level, n; %	10,648 (99.2)	5,467 (99.3)	5,181 (99.1)	6,826 (99.5)
Primary/secondary school	24.6	26.6	22.5	20.8
Technical/vocational/high school	34.5	33.1	35.9	35.0
College less than 4 years	18.8	16.7	21.0	20.4
College 4 years or more	22.1	23.6	20.6	23.8
Alcohol consumption, n; %	10,662 (99.4)	5,459 (99.2)	5,203 (99.5)	6,836 (99.6)
Never	8.7	10.9	6.4	6.4
Monthly or less frequently	27.7	30.3	24.7	25.3
2–4 times a month	40.4	37.6	43.2	42.8
2–3 times a week	18.1	16.6	19.7	19.9
4 or more times a week	5.3	4.6	6.0	5.6
Self-reported health, n; %	10,662 (99.4)	5,464 (99.3)	5,198 (99.5)	6,815 (99.3)
Bad or very bad	4.4	4.8	3.9	3.3
Neither or	30.8	26.3	26.5	22.2
Good	83.9	51.6	54.6	55.9
Excellent	16.1	17.3	14.9	18.6
Daily smoker, n; %	10,615 (98.9)	5,432 (98.7)	5,183 (99.2)	6,810 (99.2)
Yes, now	20.2	21.7	18.6	17.5
Yes, previously	42.5	39.0	46.1	43.1
Never	37.3	39.3	35.2	39.4
Chronic pain, n; %	10,721 (99.9)	5,499 (99.9)	5,222 (99.9)	6,858 (99.9)
Yes	31.7	37.1	26.0	29.9
Occupational PA, n; %	10,585 (98.6)	5,430 (98.6)	5,155 (98.6)	6,777 (98.7)
Sedentary	39.1	35.6	42.8	43.5
Light	18.3	20.3	16.2	19.5
Moderate	13.1	13.2	12.9	13.8
Heavy	2.3	0.8	4.0	2.3
Retired	26.4	29.3	23.4	20.2
Disability/sick leave/unemployed	0.7	0.9	0.7	0.7

[a] Censored: Cold-pressor test tolerance = 106 s.

PA = physical activity; SD = standard deviation; CPT = cold-pressor test; LTPA = leisure-time physical activity.

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maintaining MVPA across surveys had the highest tolerance time, enduring an estimated 20.4 s. longer than the consistently sedentary reference group.

Weak and overall non-significant interactions were found for sex (Table 3). There was no interaction with chronic pain (results not shown).

In the secondary analyses of CPT change over time, CPT in Tromsø6 and Tromsø7 varied according to level of baseline LTPA (Fig 3). CPT tolerance declined by an estimated average of

Table 2. Participant mean CPT endurance time (seconds) at both occasions over baseline physical activity levels and sex[a]. The Tromsø Study 2007–2016.

	n (%)	Leisure-time physical activity			
		Sedentary	*Light*	*Moderate*	*Vigorous*
Tromsø 6	9,773	84.9 (30.2)	87.7 (28.7)	93.6 (24.3)	96.1 (21.2)
Women	4,956 (50.7)	80.0 (31.9)	83.6 (30.7)	86.5 (29.5)	90.2 (25.2)
Men	4,817 (49.3)	89.3 (27.9)	93.2 (24.5)	97.5 (20.0)	98.3 (19.0)
Tromsø 7	7,136	56.6 (37.2)	60.7 (37.7)	68.0 (37.2)	69.0 (37.9)
Women	3,605 (50.5)	52.8 (37.2)	56.3 (37.6)	61.6 (38.3)	60.5 (37.3)
Men	3,531 (49.5)	60.0 (37.0)	66.7 (37.0)	71.4 (36.1)	72.3 (37.9)

[a]Values are mean CPT tolerance times in seconds with standard deviations in parentheses

CPT = cold-pressor test.

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-54.7 seconds from Tromsø6 to Tromsø7 (at means of covariates). For those who were sedentary, this was estimated to be a decline from 122.5 seconds on average in Tromsø6, to 67.8 seconds in Tromsø7.

Overall tolerance time was significantly and positively associated with higher levels of baseline LTPA (Table 4). CPT tolerance was 7%, 14%, and 16% higher respectively for light, moderate, and vigorous habitual LTPA across the two surveys, compared to the sedentary group. The most active participants endured for an estimated average of 16.3 s. (95% CI 6.0, 26.5) longer compared to those who reported being sedentary. There was no statistically significant interaction between LTPA and survey occasion, indicating that the change in pain tolerance over time did not differ according to level of baseline LTPA (Table 4). However, the

Table 3. Regression coefficients with 95% confidence limits for the association between leisure-time physical activity change over time and cold-pressor tolerance time (seconds) overall and by sex. The Tromsø study 2007–2016.

LTPA change index[a]	n = 6,608	Overall	Women	Men
Reference group CPT tolerance[c]	477	64.6 (59.4, 69.9)	63.2 (55.7, 70.8)	66.7 (59.6, 73.9)
Sedentary-Sedentary	477	0 (reference)	0 (reference)	0 (reference)
Light-Sedentary	366	4.4 (-3.5, 12.3)	3.2 (-8.0, 14.5)	5.1 (-5.8, 16.0)
Sedentary-Light	532	6.1 (-1.0, 13.2)	1.4 (-8.8, 11.5)	**10.1 (0.2, 20.1)**
Sedentary-MVPA	114	9.0 (-2.9, 20.8)	0.1 (-19.4, 19.6)	**15.9 (0.9, 30.1)**
MVPA-Light	545	**10.8 (3.6, 18.1)**	3.8 (-7.2, 14.7)	**16.8 (7.2, 26.4)**
Light-Light	2,868	**11.3 (5.7, 17.0)**	4.9 (-3.2, 12.9)	**17.1 (9.2, 25.1)**
Light-MVPA	759	**11.9 (5.2, 18.7)**	0.7 (-8.8, 10.3)	**22.7 (13.4, 32.0)**
MVPA-Sedentary	52	15.6 (-1.3, 32.5)	14.3 (-15.2, 43.8)	18.8 (-2.0, 39.5)
MVPA-MVPA	895	**20.4 (13.7, 27.1)**	**13.1 (2.8, 23.5)**	**26.2 (17.5, 34.9)**
p-value for equality[d]		**<0.001**		
p-value for equality[e] men vs. women				0.0732

[a] Linear Tobit regression with upper limit (censoring) = 106 s.

[b] Significant interaction levels in **bold**.

[c] Model-predicted mean of CPT tolerance for reference group at means of covariates.

[d] Global Wald test of equality between all coefficients.

[e] Test of interaction between LTPA and sex using likelihood ratio test.

Models adjusted for baseline sex, age, education, alcohol consumption frequency, smoking status, self-reported health, occupational physical activity, chronic pain.

Significant results in **bold**.

Abbreviations: LTPA = leisure-time physical activity; CPT = cold-pressor test; CI = confidence interval; MVPA = moderate-to-vigorous physical activity.

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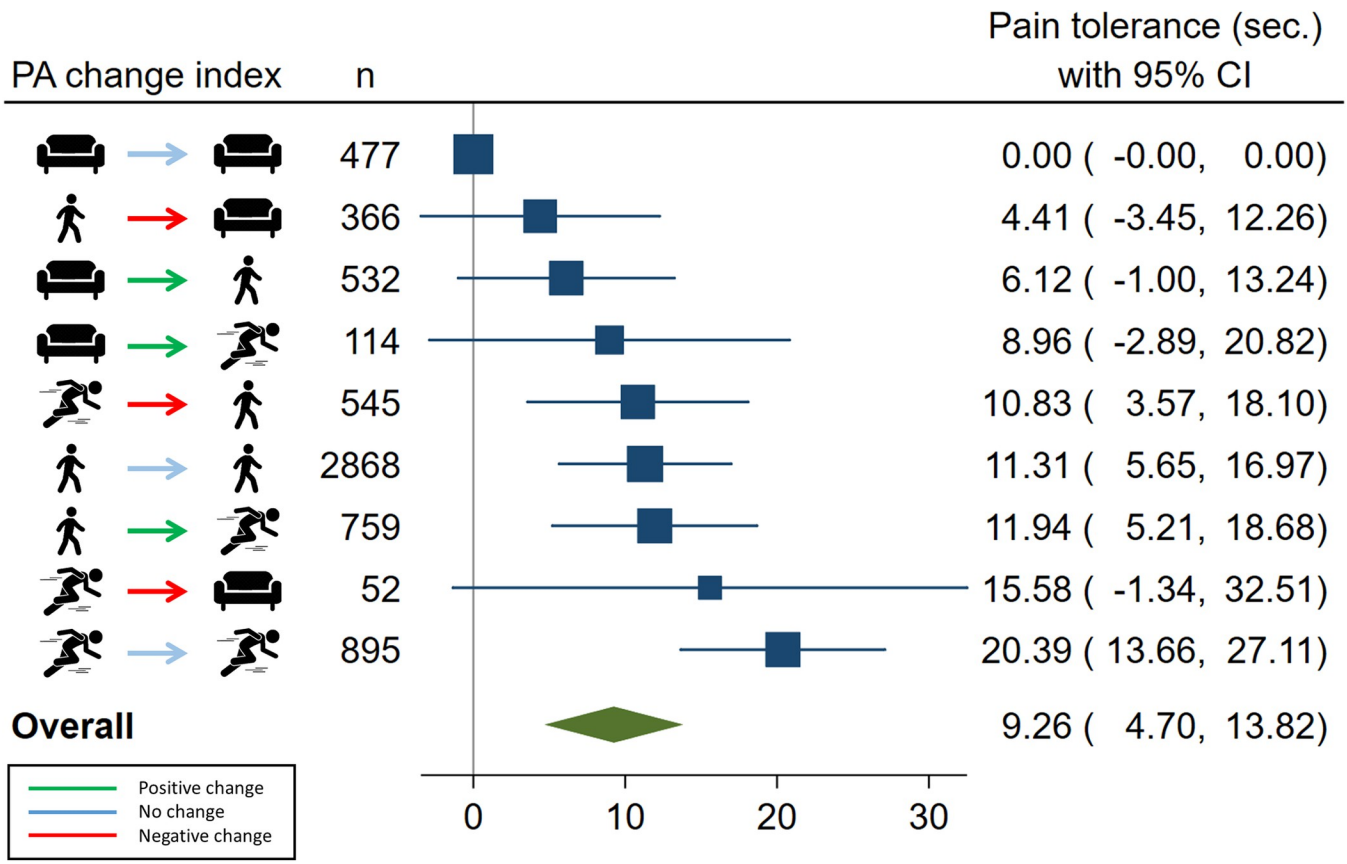

Fig 2. Relationship between groups of physical activity change from Tromsø6 to Tromsø7 and seconds of cold pain tolerance. Ordered by effect size. PA = physical activity; CI = confidence interval.

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interaction was borderline significant when modelling LTPA as a continuous rather than a categorical variable, and subsequently testing the linear trend and effect estimates suggested a gradually increasing negative trend.

There was no significant interaction with sex, although tolerance appeared to be higher for males, and no interaction with chronic pain (S3 Table).

Using ordinary linear, rather than Tobit, mixed regression appeared to substantially underestimate effect sizes, although results remained statistically significant. E.g.: linear models would underestimate the effect estimate of vigorous LTPA by almost 60% (6.7 vs. 16.3 s.; S4 Table).

Discussion

In this study, pain tolerance increased with level of PA. Being physically active at either of two time points measured at a 7-8-year interval was associated with higher pain tolerance compared to being sedentary at both time-points. Pain tolerance increased with higher total activity levels, and more for those who increased their activity level at follow-up. Overall, higher LTPA was associated with a significantly higher pain tolerance when measured repeatedly in the same individuals. A general decline in pain tolerance over the two time points was not significantly moderated by the level of LTPA, although the benefit of higher levels of LTPA on pain tolerance seemed to be gradually decreasing over time.

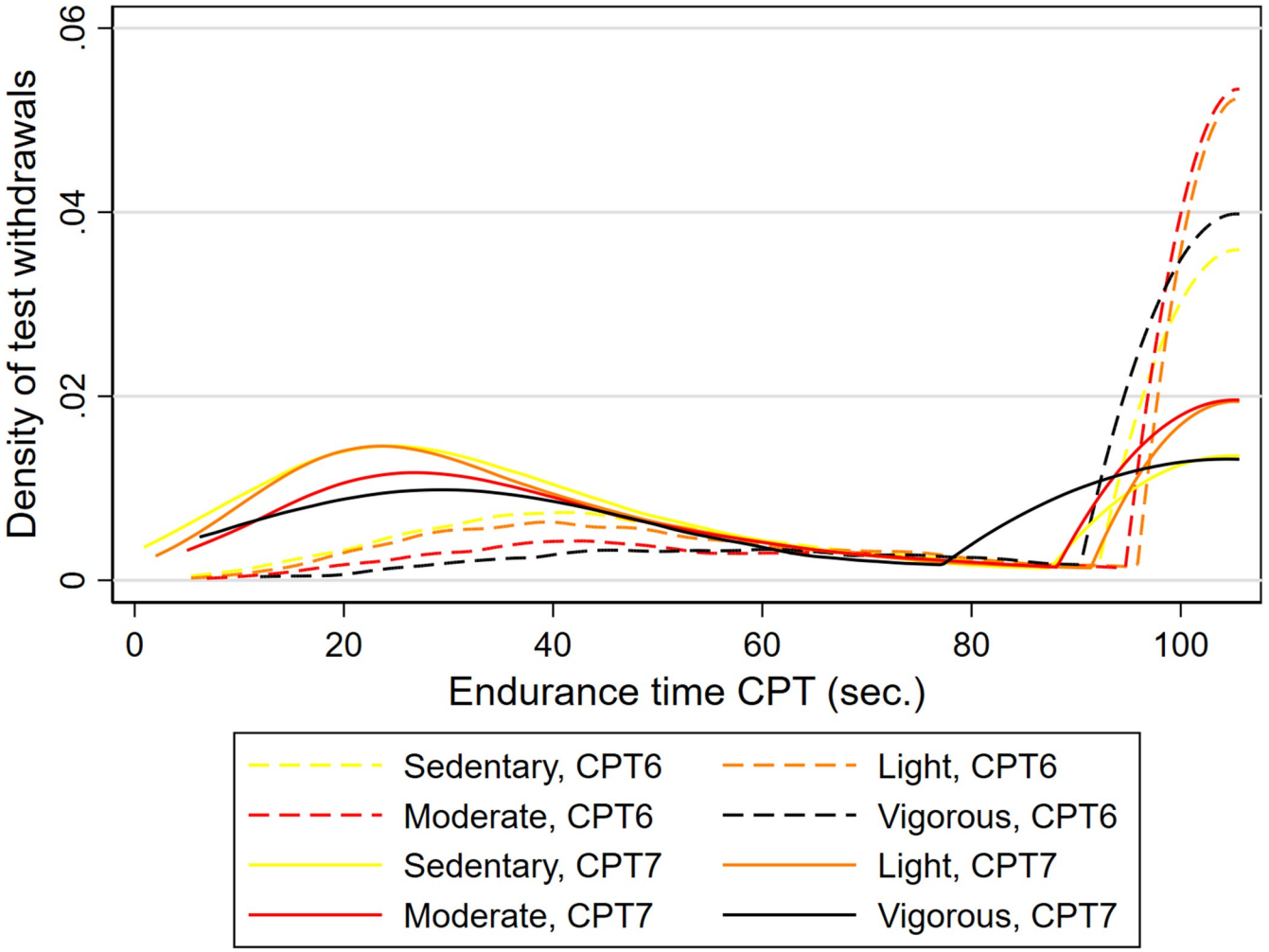

Fig 3. Withdrawals from the cold-pressor test according to leisure-time physical activity groups. Tromsø6 and Tromsø7. CPT = cold-pressor test; LTPA = leisure-time physical activity (6 or 7 for respective Tromsø Study survey).

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Physical activity and cold-pressor test tolerance

Physical activity changes and pain tolerance. In comparison to the present results, two small clinical studies have indicated that inducing PA change in humans over time may increase pain tolerance: Exposing 24 healthy participants to a high-intensity cycle ergometer program for 6 weeks caused ischemic pain tolerance to increase by 20%, with no increase in the normally active controls [14]. O'Leary et al. corroborated this in 6 weeks for high-intensity interval training only [26]. They theorized that the intensity required could be because the noxious stimulus produced by the metabolic disturbance inherent in high-intensity exercise causes a familiarization and subsequent shift in pain tolerance levels. They further found no evidence of this being linked to an improvement in physical fitness levels. A meta-analysis of 15 randomized controlled trials likewise found adaptations of pain sensitivity thresholds to occur over time in exercise interventions in both healthy individuals and individuals with chronic pain [45].

Mechanisms through which such PA change might influence pain sensitivity in humans are poorly understood. As most studies have investigated acute exercise-induced hypoalgesia

Table 4. Regression coefficients with 95% confidence intervals for the association between baseline levels of leisure-time physical activity and cold-pressor tolerance time (seconds) without and with time interaction. The Tromsø Study 2007–2016.

		Model 1[a]:	Model 2[b]:	
	n = 10,254	**Overall**	**Baseline CPT**	**CPT change**
Reference group CPT tolerance[c]	1,962	99.4 (96.5, 102.3)	122.5 (119.1, 125.9)	-54.7 (-58.2, -51.2)
Baseline LTPA				
Sedentary	1,962	0 (reference)	0 (reference)	0 (reference)
Light	6,178	**6.7 (3.4, 10.0)**	**6.7 (2.9, 10.5)**	-0.01 (-4.1, 4.1)
Moderate	1,933	**14.1 (9.9, 18.3)**	**16.6 (11.6, 21.6)**	-4.6 (-9.8, 0.6)
Vigorous	181	**16.3 (6.0, 26.5)**	**20.0 (7.3, 32.8)**	-6.6 (-19.5, 6.3)
p for trend		**<0.001**		0.054
p for equality[d]				0.13

[a] Mixed model Tobit regression with upper limit (censoring) = 106 s. for latent distribution of CPT outcome. Models were adjusted for measurement occasion, as well as baseline sex, age, and self-reported occupational PA level, education, alcohol consumption frequency, smoking status, health status, and chronic pain. Significant results in **bold**.

[b] Mixed model with LTPA×survey interaction.

[c] Model-predicted sedentary CPT tolerance at means of covariates.

[d] Test of interaction between LTPA and time using the likelihood ratio test.

Abbreviations: LTPA = leisure-time physical activity; CI = confidence interval; CPT = cold pressor test.

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(EIH), the underlying mechanistic hypotheses mostly relate to this phenomenon. These include PA-induced activation of endogenous opioid and endocannabinoid modulation of pain, and genetic, immunological and psychological mechanisms [12]. On the other hand, the 'chronic' effect of habitual PA level on pain sensitivity has garnered less attention, perhaps mainly through animal models of EIH. In a recent review of animal studies, regular physical activity appeared consistently effective at reducing, or preventing, hyperalgesia in neuropathic, and inflammatory and non-inflammatory muscle pain models [46]. Some of these mechanisms observed in animal studies appear to overlap those proposed in humans, like the mediation by mu-opioid receptors of analgesia induced by habitual wheel running in mice [47].

It is important to assess whether these patterns primarily express the pain tolerance required to tolerate physical activity at certain levels, or if a PA change in humans can lead to a change in pain tolerance. Contrary to O'Leary et al. [26], our modelling of PA change and pain tolerance at follow-up primarily found the greatest effect in avoiding a persistently sedentary lifestyle. This resonates with the idea that a sedentary lifestyle has a detrimental impact on health in general [48, 49]. The results further indicate that a change to or away from being sedentary yielded higher effect estimates than remaining sedentary. Also, higher total, as well as consistent, amounts of PA reported over time appeared to be positively associated with pain tolerance compared to remaining sedentary. These effect estimates were dose-response shaped for consistent light PA and moderate-to-vigorous PA in a way similar to that reported in a previous cross-sectional study [25]. Notably, participants changing one PA level over time were not significantly different from those that kept a consistent level. This similarity could be due to sensitivity issues with the questionnaire, a lack of statistical power in the model, or possibly that the change had not yet had the time to impact pain tolerance. Finally, though levels of change did not have unequivocal patterns of association to pain tolerance, increasing PA level appeared to predict stronger associations to pain tolerance than a decrease. The latter was always associated with a smaller effect estimate than maintaining or increasing PA beyond the original level. This might indicate that the direction of change matters in addition to total amount of activity.

In summary, these findings suggest that becoming or remaining active at a level above being sedentary, or making a positive change in activity level, over time is associated with higher pain tolerance as opposed to being sedentary or making a negative change.

The stability of the relationship over time. The secondary analyses of this study aimed at assessing whether pain tolerance changed for the included individuals over time, and whether any such change was moderated by their level of LTPA. This is the first population-based study to estimate the repeated association of LTPA level and pain tolerance, and to assess how a change in pain tolerance over time was moderated by habitual LTPA. The repeated measurements-association between PA and CPT tolerance was similar to results from our recent cross-sectional study using total samples drawn from Tromsø6 and Tromsø7 [25].

The lack of significant interaction between LTPA and time indicates that baseline PA level did not significantly influence the general drop in pain tolerance across the two measurements of individuals over time. However, though this interaction was not significant, the linear trend of moderation, as well as effect estimates, might suggest that the positive association of LTPA and pain tolerance diminishes in size over time, and more so for higher activity groups. This interaction between LTPA and time might have gained significance with higher power in the highest PA groups.

Our study sample consisted of individuals aged 30–87 years at baseline, with approximately eight years separating the two survey occasions. Thus, it is possible that ageing interferes with the association of LTPA and pain tolerance, potentially diminishing a positive effect over time. Whether ageing interferes with the effect of LTPA on pain tolerance, especially in older age groups, is something which should be further explored in future studies. Alternative explanations to this time-effect could be methodological differences between Tromsø6 and Tromsø7 of which effect we are not aware.

Potential moderators. Several studies of both humans and animal models have identified sex as one of the determinants of pain sensitivity or modulation [32, 33, 50, 51]. In our previous cross-sectional study we also found that sex moderated the PA-tolerance relationship [25]. Despite some signs of sex differences in the effect estimates of our PA-change model, no overall significant interaction was seen in our current study.

There is inconsistent evidence regarding EIH in patients with chronic pain, in part due to a lack of high-quality studies [12, 13]. A narrative review suggested no EIH in patients with localized musculoskeletal pain, however only reviewing isometric exercise and sensitivity thresholds [52]. Nevertheless, using both the standard 3-month cut-off for chronic pain as in the present study, and a stricter 'moderate-to-severe chronic pain' definition previously, chronic pain has not influenced the association of habitual PA and pain tolerance in a general population either in cross-sectional designs, longitudinally, or when looking at PA change over time. This suggests that the present epidemiologically defined chronic pain does not significantly interfere with the relationship between PA and pain tolerance in large heterogeneous samples. Naturally, this might look different in more highly selected diagnostic groups or if using different definitions of chronic pain.

Possible limitations

The observational and temporal nature of these data obscure how the exposure, covariates, and outcome vary prior to baseline, and between baseline and follow-up. As we did not adjust for baseline CPT in our model in order to avoid the bias expressed as Lord's paradox [53], part of the associations observed in our PA-change model might theoretically express some dynamic of pain tolerance during follow-up. However, sensitivity analysis with adjustment (results not shown) found negligible change in associations and only slightly diminished effect estimates.

Exploratory analyses found a significant interaction between CPT tolerance and survey. As our models look at relative group difference rather than absolute tolerance levels, this difference is not likely to impact results.

Whilst self-report tools like the SGPALS may over- or under-report absolute amount of PA undertaken, they have consistently proven to adequately rank respondents according to health outcomes, thus being suitable for group comparisons [31, 54]. Furthermore, the SGPALS aims to capture physical activity over a 12-month period rather than the relatively short time span used by other questionnaires or methodologies. This may give more accurate grouping of participants in longitudinal data. However, the similar effect estimates of several PA change categories might indicate that the SGPALS is inaccurate when measuring amounts of PA change over time; some participants might define themselves as bordering two categories. Their change score might reflect this more than any actual PA change.

Our use of Tobit regression on quantitative sensory test data suggests how high proportions of censored data may bias effect estimates of pain tolerance means. Since we discovered some deviations from normally distributed residuals, borderline p-values have to be interpreted with care. However, most of the current significant results had very low p-values, and high statistical power in analyses further diminishes the risk of miscalculated p-values impacting significance.

Conclusion

In this study of a general population sample, being physically active across two measurements was associated with higher pain tolerance at follow-up as compared to being sedentary at both time-points. Furthermore, changing PA from lower to higher levels might be associated with a higher pain tolerance than an equally large change going from higher to lower PA. This might indicate that it is not only the total PA amount that matters but also the direction of change. Repeated measurements of this association in the same individuals over two time points found a negative change in pain tolerance over time that was not significantly moderated by LTPA. This indicates a strong positive association between physical activity and pain tolerance which was independent of time passing. Nevertheless, some findings indicated that LTPA might have a diminishing positive association over time, possibly due to ageing. As pain tolerance has been suggested to impact risk, or severity, of chronic pain, these results might suggest increasing PA levels as a possible non-pharmacological pathway towards reducing or preventing chronic pain.

Supporting information

S1 Table. Primary analysis sample missing data on baseline covariates (N = 6,864). The Tromsø Study 2007–2016.
(DOCX)

S2 Table. Secondary analysis sample missing data on baseline covariates (N = 10,732). The Tromsø Study 2007–2016.
(DOCX)

S3 Table. Regression coefficients with 95% confidence limits for the association between baseline levels of leisure-time physical activity and cold-pressor tolerance time (seconds) by sex or chronic pain[a]. The Tromsø Study 2007–2016. Mixed model Tobit regression with upper limit (censoring) = 106 s. for latent distribution of CPT outcome. Models were adjusted for measurement occasion, as well as baseline sex, age, and self-reported occupational PA level, education, alcohol consumption frequency, smoking status, health status, and chronic

pain. Significant results in bold.
(DOCX)

S4 Table. Regression coefficients with 95% confidence limits for the association between baseline levels of leisure-time physical activity and cold-pressor tolerance time (seconds) according to sensitivity analyses. The Tromsø Study 2007–2016. Censored estimates (all censored values included as is) by linear mixed models with random intercept. Models were adjusted for measurement occasion, as well as baseline sex, age, and self-reported occupational PA level, education, alcohol consumption frequency, smoking status, health status, and chronic pain. Significant results in bold.
(DOCX)

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Author Contributions

Conceptualization: Anders Pedersen Årnes, Christopher Sievert Nielsen, Audun Stubhaug, Aslak Johansen, Bente Morseth, Tom Wilsgaard, Ólöf Anna Steingrímsdóttir.

Data curation: Anders Pedersen Årnes, Christopher Sievert Nielsen, Audun Stubhaug, Bente Morseth, Ólöf Anna Steingrímsdóttir.

Formal analysis: Anders Pedersen Årnes, Bjørn Heine Strand, Tom Wilsgaard, Ólöf Anna Steingrímsdóttir.

Funding acquisition: Anders Pedersen Årnes, Christopher Sievert Nielsen, Audun Stubhaug, Aslak Johansen, Ólöf Anna Steingrímsdóttir.

Investigation: Anders Pedersen Årnes, Mats Kirkeby Fjeld, Ólöf Anna Steingrímsdóttir.

Methodology: Anders Pedersen Årnes, Mats Kirkeby Fjeld, Bente Morseth, Bjørn Heine Strand, Tom Wilsgaard, Ólöf Anna Steingrímsdóttir.

Project administration: Anders Pedersen Årnes, Aslak Johansen, Ólöf Anna Steingrímsdóttir.

Supervision: Bente Morseth, Tom Wilsgaard, Ólöf Anna Steingrímsdóttir.

Visualization: Anders Pedersen Årnes.

Writing – original draft: Anders Pedersen Årnes.

Writing – review & editing: Anders Pedersen Årnes, Christopher Sievert Nielsen, Audun Stubhaug, Mats Kirkeby Fjeld, Aslak Johansen, Bente Morseth, Bjørn Heine Strand, Tom Wilsgaard, Ólöf Anna Steingrímsdóttir.

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Table S1: Primary analysis sample missing data on baseline covariates (N=6,864). The Tromsø Study 2007-2016.

Covariable:	n (%)
Sex	0 (0)
Age	0 (0)
Education level	38 (0.5)
Alcohol consumption frequency	28 (0.4)
Self-reported health	49 (0.7)
Daily smoking status	54 (0.8)
Chronic pain	6 (0.1)
Occupational PA/retired/sick leave/disability	87 (1.3)

PA= physical activity.

Table S2: Secondary analysis sample missing data on baseline covariates (N=10,732). The Tromsø Study 2007-2016.

Covariable:	Missing, n (%)
Sex	0 (0)
Age	0 (0)
Education level	84 (0.8)
Alcohol consumption frequency	70 (0.7)
Self-reported health	70 (0.7)
Daily smoking status	117 (1.0)
Chronic pain	11 (0.1)
Occupational PA/retired/sick leave/disability	147 (1.4)

Abbreviations: LTPA=leisure-time physical activity; CPT= cold-pressor test

Table S3: Regression coefficients with 95% confidence limits for the association between baseline levels of leisure-time physical activity and cold-pressor tolerance time (seconds) by sex or chronic pain[a]. The Tromsø Study 2007-2016.

LTPA	**n=10,254**	**Sub-groups [b]**	
Reference group	1,962	Female	Male
CPT tolerance[c]		*90.4 (86.4, 94.5)*	*116.9 (114.3, 119.6)*
LTPA			
Sedentary	1,962	0 (reference)	0 (reference)
Light	6,178	**5.0 (0.5, 9.4**)	**8.5 (3.7, 13.2)**
Moderate	1,933	**10.1 (3.9, 16.4)**	**17.2 (11.7, 22.7)**
Vigorous	181	11.4 (-6.1, 29.0)	**19.4 (6.9, 31.8)**
p for equality[d]			0.38
Reference group	1,962	No chronic pain	Chronic pain
CPT tolerance[c]		*99.2 (95.6, 102.8)*	*99.6 (94.7, 104.5)*
LTPA[e]			
Sedentary	1,962	0 (reference)	0 (reference)
Light	6,178	**7.7 (3.7, 11.8)**	4.8 (-0.7, 10.2)
Moderate	1,933	**13.3 (8.3, 18.2)**	**17.1 (9.6, 24.5)**
Vigorous	181	**14.2 (2.8, 25.6)**	**26.2 (3.5, 49.0)**
p for equality[d]			0.21

[a] Mixed model Tobit regression with upper limit (censoring)=106 s. for latent distribution of CPT outcome. Models were adjusted for measurement occasion, as well as baseline sex, age, and self-reported occupational PA level, education, alcohol consumption frequency, smoking status, health status, and chronic pain. Significant results in **bold**.

[b] Modelling with interactions LTPA·sex or LTPA·chronic pain.

[c] Model-predicted sedentary CPT tolerance at means of covariates.

[d] Test of interaction between LTPA and sex or chronic pain using the likelihood ratio test.

[e] Model additionally adjusted for chronic pain.

Abbreviations: LTPA=leisure-time physical activity; CPT=cold pressor test.

Table S4: Regression coefficients with 95% confidence limits for the association between baseline levels of leisure-time physical activity and cold-pressor tolerance time (seconds) according to sensitivity analyses. The Tromsø Study 2007-2016.

LTPA	n=10,254	Overall effect
Censored CPT[a]		
Sedentary		*0 (reference)*
Light		***3.1 (1.6, 4.6)***
Moderate		***6.4 (4.5, 8.3)***
Vigorous		***6.7 (2.2, 11.1)***

[a] Censored estimates (all censored values included as is) by linear mixed models with random intercept.

Models were adjusted for measurement occasion, as well as baseline sex, age, and self-reported occupational PA level, education, alcohol consumption frequency, smoking status, health status, and chronic pain. Significant results in **bold**.

CPT=cold pressor test.

Paper three

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Does pain tolerance mediate the effect of physical activity on chronic pain in the general population? The Tromsø Study.

Anders Pedersen Årnes[1,2], Mats Kirkeby Fjeld[3,4], Hein Stigum[5], Christopher Sivert Nielsen[3,6], Audun Stubhaug[4,6], Aslak Johansen[1,7], Laila Arnesdatter Hopstock[8], Bente Morseth[9], Tom Wilsgaard[2], Ólöf Anna Steingrímsdóttir[3].

1. Department of Pain, University Hospital of North Norway, Tromsø. Norway
2. Department of Community Medicine, UiT The Arctic University of Norway, Tromsø, Norway
3. Division of Mental and Physical Health, Norwegian Institute of Public Health, Oslo, Norway.
4. Institute of Clinical Medicine, University of Oslo, Oslo, Norway.
5. Institute of Health and Society, University of Oslo, Norway
6. Department of Pain Management and Research, Oslo University Hospital, Oslo, Norway
7. Department of Clinical Medicine, UiT The Arctic University of Norway, Tromsø, Norway
8. Department of Health and Care Sciences, UiT The Arctic University of Norway, Tromsø, Norway
9. School of Sport Sciences, UiT The Arctic University of Norway, Tromsø, Norway

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* Corresponding author:

Anders P. Årnes, Department of Pain, University Hospital of North Norway.
UNN Tromsø, 9038 Tromsø, Norway.
Tel: +47 48 15 56 04
Email: anders.arnes@uit.no / anders.pedersen.arnes@unn.no

Previously presented as abstract on 2021 annual meeting of the Norwegian Epidemiological Association.

Data availability statement:
The data for this study cannot be shared publicly because the current study is based on data owned by a third party (The Tromsø Study, Department of Community Medicine, UiT The Arctic University of Norway). Ethical and legal restrictions prevent data from being made publicly available. These revolve around the protection of potentially sensitive data that cannot be shared publicly without being in risk of breaching data protection laws. Bona fide researchers can apply for data from the Tromsø Study. Guidelines on how to access the data are available at the website https://uit.no/research/tromsostudy - All inquiries about the Tromsø Study should be sent by e-mail to tromsous@uit.no.

Abstract

Knowledge is needed regarding mechanisms acting between physical activity (PA) and chronic pain. We investigated whether cold-pain tolerance mediates an effect of leisure-time physical activity on risk of chronic pain 7-8 years later using consecutive surveys of the population-based Tromsø Study. We included participants with information on baseline leisure-time PA (LTPA) and level of cold-pressor assessed cold-pain tolerance, who reported chronic pain status at follow-up as: chronic pain for ≥3 months, widespread chronic pain, moderate-to-severe chronic pain, or widespread moderate-to-severe chronic pain. We included 6,834 participants (52% women; mean age 55 years) in counterfactual mediation analyses. Prevalence decreased with severity, e.g. 60% for chronic pain versus 5% for widespread moderate-to-severe chronic pain. People with one level higher LTPA rating (light to moderate or moderate to vigorous) at baseline had lower relative risk (RR) of four chronic pain states 7-8 years later. Total RR effect of a one-level LTPA increase was 0.95 (0.91, 1.00), i.e. -5% decreased risk. Total effect RR for widespread chronic pain was 0.84 (0.73, 0.97). Indirect effect for moderate-to-severe chronic pain was statistically significant at RR 0.993 (0.988, 0.999); total effect RR 0.91 (0.83, 0.98). Statistically significantly mediated RR for widespread moderate-to-severe chronic pain was 0.988 (0.977, 0.999); total effect RR 0.77 (0.64, 0.94). This shows small mediation of the effect of LTPA through pain tolerance on two moderate-to-severe chronic pain types. This suggests pain tolerance to be one possible mechanism through which PA modifies risk of moderate-to-severe chronic pain types with and without widespread pain.

1. Introduction

Chronic pain is responsible for considerable direct and indirect societal and personal costs [55; 63; 77]. It is associated with excess mortality [50], remains one of the leading causes of disability in the world [10; 18; 64], and is also a key defining feature of many of the most common somatic and mental health conditions [64]. In some populations, widespread use of dependency-inducing prescription pharmaceuticals for chronic pain has inadvertently contributed to substantial human and economic harm, whilst producing pain sufferers dissatisfied with their pain treatments [11; 63; 64]. Thus there is a need to promote treatment modalities integrating self-management and non-pharmaceutical care [3].

Large population studies have commonly found falling prevalence of chronic pain with higher level of physical activity (PA) in both young and older adults [16; 20; 43; 82]. An overview of Cochrane reviews from 2017 found small to moderate effects of PA interventions on average pain intensity and physical function across a broad range of chronic pain conditions [17]. Included studies were characterized by high heterogeneity and risk of bias, highlighting a need for high quality studies. Higher PA has also been associated with lower use of opioids in a range of painful conditions [9]. This supports PA as an effective treatment modality for lowering pain severity and improving physical function, whilst being unlikely to cause harm in persons with chronic pain [17].

Concurrently, several studies find associations between PA and quantitative sensory test (QST) parameters of pain sensitivity [65; 76]. Similarly, increasing habitual PA can improve the capacity for endogenous pain inhibition in humans over time [8; 23; 24; 36; 58]. Similar effects of PA on pain and pain sensitivity are seen in mice, where regular PA produces analgesia in induced neuropathic and noninflammatory muscle pain, as well as some other pain models [46]. Experimental pain tolerance, assessed through QST, has shown a strong correlation with habitual physical activity levels and is responsive to physical activity interventions. [36; 58; 76]. Cold-pain tolerance in particular is strongly associated with leisure-time physical activity levels in the general population [6; 89].

There is also evidence to suggest that some chronic pain conditions (e.g. low back pain, knee osteoarthritis, and fibromyalgia) exhibit increased pain sensitivity [57; 62; 71], and that testing sensory profiles on pain free individuals in some cases can predict a propensity to develop chronic pain [61; 79]. However, the evidence for QST predicting future chronic pain or analgesia is not easily summarized in meta-analysis due to high variability in the test paradigms and outcomes used [61].

The influence of PA on experimental pain in chronic pain conditions is thought to have implications for the management of clinical pain [65; 69; 83]. Potentially then, pain tolerance could represent one mechanism amongst many determining how PA affects chronic pain. We are not aware of any studies using population-based samples to examine whether cold-pain tolerance acts as a mediating mechanism through which PA affects the risk of chronic pain.

The longitudinal Tromsø Study contains measurements of PA and QST, and follow-up information on chronic pain gathered 7-8 years later from a large, representative population-based sample. Our objectives were to assess whether cold-pain tolerance mediates the association between PA and risk of future chronic pain, widespread pain, moderate-to-severe chronic pain, and widespread moderate-to-severe chronic pain. Secondary objectives were assessing effects for newly incident chronic pain only, and sex differences in effects.

2. Materials and methods

2.1 Study population and sample

This study used data from two consecutive surveys of the Tromsø Study (baseline: Tromsø6 2007-2008; follow-up: Tromsø7 2015-2016). The Tromsø Study is an ongoing prospective population-based health survey conducted in the municipality of Tromsø, Norway, since 1974. It gathers various clinical, biological, experimental, and self-reported data online and on-site, and contains a high number of repeat participations by the same individuals. The study mailed invitations to total birth cohorts as well as random samples of the municipality's populace for participation. Participants receive no monetary reimbursement. More information regarding recruitment and participation proportions for The Tromsø Study has been published elsewhere [2; 12; 29; 31].

A total of 19,765 municipal inhabitants aged 30-87 years were invited to participate in Tromsø6, resulting in a participation proportion of 66% (n=12,981; mean age 57.5 years; 53% women). In Tromsø7, all 32,591 inhabitants aged 40 years or above were invited, yielding a participation proportion of 65% (n=21,083; mean age 57.3 years; 53% women). Of participants in Tromsø6, 79% also attended Tromsø7 (n=8,906; mean Tromsø6 age 55.8 years; 54% women).

In Tromsø6 and Tromsø7, all participants were asked to report their average yearly habitual leisure-time physical activity (LTPA) level, and to complete testing of cold-pain

tolerance with the cold-pressor test (CPT). In Tromsø7, all participants were asked to self-report pain and pain characteristics using a hierarchical digital body map questionnaire called the Graphical Index of Pain (GRIP) [74].

This study used LTPA reported in Tromsø6 as exposure, cold-pain tolerance measured in Tromsø6 as mediator, and types of chronic pain from GRIP self-reported in Tromsø7 as outcomes (Figure 1). In total, 6,834 participants had complete data on exposure, mediator, and outcome, and were included for analyses.

***** Insert Fig. 1 approx. here *****

2.2 Measurements and variables

2.2.1 Leisure-time physical activity

Self-reported habitual leisure-time and occupational PA in Tromsø6 was obtained through a modified version of the "Saltin-Grimby Physical Activity Level Scale" (SGPALS) [22; 68]. SGPALS includes a recall of LTPA level; "How much do you move and exert yourself physically during leisure time? If your activity varies greatly between, for example summer and winter, try to estimate an average. The question concerns the last year", with four mutually exclusive categories: "*Reading, watching TV/screen, or other sedentary activity*; *walking, cycling, or other forms of exercise at least four hours a week (including walking or cycling to place of work, Sunday-walking, etc.)*; *participation in recreational sports, heavy gardening, snow shovelling etc. at least four hours a week*; or *participation in hard training or sports competitions, regularly several times a week*". These categories are then substituted for sedentary, light, moderate, or vigorous LTPA. In the Tromsø Study, the SGPALS has been modified by introducing a duration requirement of at least four hours for level three "moderate" LTPA [22]. The item was coded into a corresponding four-level categorical variable which was used as the exposure of this study.

In the Tromsø Study population, SGPALS LTPA shows significant moderate correlations to VO2max, and weak-to-moderate correlation to resting heart rate and accelerometer-assessed moderate-to-vigorous PA, with all accelerometer measures of PA increasing with levels of LTPA [15; 67]. Intra-class correlation coefficient reliability to accelerometer-assessed PA indicate moderate to good reliability [15]. It correlates strongly with the long International Physical Activity Questionnaire [19] and shows strong predictive validity for several health-related conditions [28; 30; 34; 78]. It has been deemed found to produce appropriate relative ranking of physical activity levels in large cohorts [67].

SGPALS also includes an occupational PA level item: "If you have paid or unpaid work, which statement describes your work best?", with four mutually exclusive categories: "*Mostly sedentary work (e.g. office work, mounting); Work that requires a lot of walking (e.g. shop assistant, light industrial work, teaching); Work that requires a lot of walking and lifting (e.g. nursing, construction); Heavy manual labour*".

2.2.2 Cold-pain tolerance

Tromsø6 included the static QST measure of cold-pain tolerance , assessed as maximum tolerance time in the cold-pressor test with an upper limit of 106 seconds. Participants submerged their dominant hand and wrist in a 13-litres cold-water plexiglass vat kept at 3°C by a cooling circulator (Julabo FP40HE, Julabo Labortechnik GmbH) (Figure S1). Participants were requested to maintain an open and relaxed hand throughout the test. They were informed of the possibility to abort the test at any time but asked to keep their hand submerged for as long as they were able to or until the test was ended.

Exclusion criteria from the CPT included unwillingness to participate; cognitive or language problems disabling participants from comprehending and following instructions; conditions such as Reynaud's syndrome, cold allergy, or other if participants themselves believed the condition would affect their response to cold; bilateral sensitivity loss in the hand; breached skin on both hands caused by conditions such as eczema, open sores, etc.

Static cold-pain sensitivity in general shows good-to-excellent long-time test-retest reliability [52]. In our data, CPT produced a continuous variable with an upper limit further described elsewhere [90]. Distribution of tolerance times shows some resemblance to those of the only other comparable datasets in the world, from Haifa, Israel, and a home-administered CPT-study from the US [53]. CPT shows excellent test-retest reliability, with tolerance thresholds showing higher reliability than sensitivity thresholds [41].

2.2.3 Chronic pain

All participants of Tromsø7 were asked to complete the GRIP pain questionnaire [74]. This is a hierarchical body map divided into 10 first-tier regions (head, neck, left and right arm, upper and lower back, left and right leg, chest, abdomen, genitals/pelvic floor/urethra/anus) followed by a second tier of multiple pain loci for each first-tier region (Figures S2, S3). Participants were requested to report on all pain experienced during the last four weeks, except for pain which had been transient or brief. Women were requested not to include menstrual pain. The participants reported on the following pain characteristics for each of the 10 first-tier regions: Pain onset, episode frequency, episode duration, depth of pain, pain intensity, and level of bother caused by pain. Intensity and bother were measured on 11-point numerical rating scales (anchors: "No pain" / "The strongest imaginable pain" and "No bother" / "The greatest imaginable bother"). Participants further reported on the total effects of pain on sleep quality, and impact on daily activities. Chronic pain was defined as persistent or recurring pain experienced within the past four weeks in at least one of the 10 first-tier regions that had an onset more than three months prior to participation, as suggested in the ICD-11 definition [80].

Physical activity behaviours have been suggested to be related to central nervous system regulation of widespread chronic pain types [14]. In accordance with the proposed 2019 criterion for widespread pain as suggested by Wolfe et al. [88], we used GRIP-reported pain areas and duration to construct a binary chronic widespread pain variable. Chronic widespread pain was regarded as present if the following criteria were fulfilled: total number of pain sites ≥7 (0-19 possible sites), pain in four or five body regions (axial, left upper, right upper, left lower, or right lower possible regions), and present for ≥ 3 months. Information from chest, abdomen, right jaw and left jaw were not included in the body regions but did count towards body sites.

The ICD-11 classification includes a 'moderate-to-severe' form of chronic pain as pain persisting or recurring for longer than 3 months with further requirements for severity of usual pain intensity, pain-related distress, and task interference [81]. We thus constructed a chronic pain outcome in which we regarded such moderate-to-severe chronic pain to be present if participants reported chronic pain in at least one of the first-tier areas that scored 4 or more on an 11-point numeric rating scale for both pain intensity, pain bothering, and impact on activities of daily living.

Finally, as it is possible for both widespread and moderate-to-severe chronic pain to be present simultaneously, we constructed a fourth chronic pain outcome termed 'widespread moderate-to-severe chronic pain', hypothesizing that this would be a more severe outcome than the previous three.

The GRIP as a relatively novel tool has not been tested for reliability or validity. However, its design goal was to provide an improved, standardized high-resolution pain measurement tool alternative to the types of questionnaires that for decades have been used to gather data on clinical pain [74]. It has proven to be highly feasible for large population studies with 96% of Tromsø7 adult participants of all ages filling it in, suggesting its design does not constitute a barrier for respondents. In general, pain questionnaire completeness and adherence appears to be better when delivered digitally through apps than through pen and paper [51], and using body manikins or digital applications appears to be no worse for capturing pain location than using written or questions delivered on paper [35; 84].

2.2.4 Baseline covariates

Included covariates were selected a priori based on theory-based assumptions of their roles as confounders. Afterwards, a directed acyclic graph (DAG) was drawn in DAGitty (www.dagitty.net) to illustrate the assumed roles of included variables and our explicit choices in the analyses (Figure 2). As shown, we included age and sex in our analyses as potential confounders, alongside several markers of socio-economic status: self-reported alcohol consumption frequency (never, monthly or less frequently, 2-4 times a month, 2-3 times a week, 4 or more times a week); daily smoking status (present, previous, never); level of achieved education (primary/secondary school, technical/vocational/high school/university or university college less than 4 years/university or university college 4 years or more); and total taxable household income the previous year (including social benefits and similar). These have been found to predict general health, chronic pain, and pain sensitivity [38; 40; 42; 45; 72]. We also included the occupational PA item from SGPALS, as this can influence both LTPA level and chronic pain prevalence [27; 54]. Participants not currently employed who elsewhere reported being retired or on disability pensions, unemployment benefits, or sick leave were assigned to categories "retired" or "disability/sick leave", respectively.

The DAG of Figure 2 also shows how we consider the possibility for relevant but

unmeasured confounders for this study. It further shows how we believe both body-mass index (BMI) and disturbed sleep/insomnia would act as mediators in this model. Several reviews find that PA interventions may causally impact body composition [26; 32; 37; 70] although some newer studies suggest a possible bi-directionality in this association [13; 66]. Similarly, though there is conflicting evidence regarding the causal relationship between PA and sleep disturbance/insomnia, we nevertheless found the evidence sufficient to believe PA may substantially affect symptoms of insomnia [39; 49; 85]. Since adjusting for mediators would detract their indirect effects from the total effect of PA on chronic pain, we chose to adjust for neither BMI nor insomnia.

We regarded blood pressure, as well as mental health and the subsequently associated self-reported health to be probable colliders in the data. This is due to their likelihood of being significantly influenced by both physical activity and chronic pain. Adjusting for such variables introduces bias to model estimates. Consequently, we refrained from adjusting for these in analyses.

***** Insert Fig. 2 approx. here *****

2.3 Statistical analyses

Descriptive statistics were presented for all baseline (Tromsø6) variables included in modelling. Means with SD or frequencies and percentages were used as appropriate. The four chronic pain outcomes were tabulated to assess prevalence at follow-up.

We used mediation analysis to investigate cold-pain tolerance mediated the risk-ratio effect of PA on chronic pain (Figure 3). A mediator represents a pathway, or mechanism, through which an exposure is affecting an outcome in the form of an indirect effect on this outcome [87]. Classical mediation analysis techniques such as the difference- [87] or product [7] methods are not feasible with models using the "noncollapsible" odds ratio [21], as this measure fails to approximate the risk ratio and will be biased as outcome prevalence and number of covariates in the model increase [87]. The counterfactual mediation framework with natural effects is able to accommodate the dichotomous, common (>10% prevalence) chronic pain outcomes of this study without incurring such biases of effect estimates [86]. Using the Stata package `paramed`, we modelled the effect of LTPA (X) on CPT tolerance (M) using ordinary linear regression. The effect of X and M on chronic pain (Y) was modelled using log-linear (log-risk) regression. Counterfactual mediation then produces natural direct (X on Y) and natural indirect (X on Y via M), as well as marginal total (X on Y

+ X on Y via M) effects. We estimated four models according to the four outcomes: chronic pain, widespread chronic pain, moderate-to-severe chronic pain, and widespread moderate-to-severe chronic pain. In order to preserve statistical power, LTPA was added as a linear exposure and effects estimated for a one-level change in the variable. LTPA has previously shown dose-response associations to both CPT tolerance and GRIP-estimated chronic pain in the current study population [5; 16].

For all models, we examined whether adding an interaction term between the exposure and mediator produced either substantial alterations in the model or a statistically significant interaction term. As this had negligible impact on all models, the interaction term was left out of the final analyses.

Counterfactual mediation analysis requires there to be no substantial unmeasured confounders between exposure, mediator, or outcome to give reasonably unbiased estimates [86]. There is a possibility for some unmeasured confounding in our model (Figure S4). To assess how this unmeasured confounding would have to influence X, M, and Y to significantly alter the observed effects of our models, we performed an exploratory simulation. Here, we simulated a dataset of N=10,000,000 observations and used it to model the presently observed relationship between X, M, and Y. We inserted first a normally distributed, then a binary, unmeasured confounder. These were given hypothetical, large confounding associations with X, M, and Y (see supplementary). We then simulated how much bias such confounders would introduce to the direct, indirect, and total effect of the mediation model. This allowed us to assess the likelihood of there being such an unmeasured confounder, as well as its potential impact on effect estimates.

Our main analyses included persons with and without baseline chronic pain. Such pain is a possible mediator for the effect of PA on chronic pain at follow-up, and adjusting for it would remove this indirect effect component from the total effect (Lord's paradox: [60]). These models were compared to models excluding all participants reporting chronic pain at baseline.

Final models were stratified according to sex to visually compare estimates for men and women. All analyses were performed, and the simulation package written, in Stata 17 (StataCorp, College Station, TX, USA).

***** Insert Fig. 3 approx. here *****

2.4 Missing data

Of the 8,906 participants who participated in both Tromsø6 and Tromsø7 with GRIP data,

CPT data were missing for 1,407 participants. This was principally due to capacity limitations in Tromsø6, mainly during the influenza season when study technicians were sick-leaved. At such times of low station capacity, participants below 60 years of age were prioritized by staff to increase participation in this under-sampled age-group [73]. Individuals not examined were assigned missing values in CPT. In total, 2,072 of the 8,906 participants of Tromsø6 and Tromsø7 had missing on either exposure, mediator, or outcome, leaving 6,834 participants for inclusion.

The four chronic pain outcomes were constructed using different pain characteristics items from the GRIP. Therefore, outcomes constructed from several GRIP items had a proportion of missing information on one or more items. Thus, of the 6,834 included, 6,625 had information on chronic pain (3% missing), 6,459 on chronic widespread pain (6% missing), 6,259 on moderate-to-severe chronic pain (8% missing), and 6,052 on widespread moderate-to-severe chronic pain (11% missing). Table S1 details missing data for covariates in the final sample. Household income the previous year had the highest proportion missing in the final sample (n=289 (4.2%)). In total, 84% of the included participants had no missing on any covariates or on any GRIP variables.

To investigate possible bias in complete-cases models caused by missing data, we performed multiple imputation with chained equations using predictive mean matching with known nearest neighbours=20, a burn-in of 10, and 10 iterations on 30 imputed datasets.

2.5 Ethics

This study was approved by the Regional Committee for Medical and Health Research Ethics of North-Norway (reference REK North, 2016/1794). Written informed consent was acquired for all participants.

3. Results

Table 1 presents descriptive statistics for sample baseline characteristics for all who participated in Tromsø6 and Tromsø7, and those who had information on exposure, mediator, and outcome. Baseline descriptive characteristics are also shown for all those who reported having either of the four chronic pain outcome types at follow-up. The final complete study sample contained 51.5% women and had a baseline mean age 54.8 years (standard deviation (SD) 10.9). Average endurance time in the CPT for complete study sample was 89.7 (SD

27.5) seconds. Proportion of women increased in all chronic pain outcomes, with every three out of four participants reporting widespread moderate-to-severe chronic pain being women.

Descriptive characteristics of imputed sample showed complete study sample to be slightly younger, more affluent, educated, and active in leisure (Table S1). Chronic pain prevalences were comparable. Descriptive characteristics for imputed sample generally fell between the limits set by the complete study sample and the total population of Tromsø6. The 6,834 participants who met complete-case inclusion criteria were at baseline approximately 2.5 years younger, smoked slightly less, consumed more alcohol, and had higher income, education, and slightly higher PA-level than all participants of Tromsø6. Differences in baseline characteristics between complete study sample, imputed sample, and the complete survey population of Tromsø6 were generally small.

3.1. Chronic pain outcomes

For complete study sample with information on chronic pain for more than three months (n=6,625) reported prevalence was 60% (n=3,953). For widespread chronic pain (n=6,459) the prevalence was 8% (n=540). For moderate-to-severe chronic pain (n=6,259) the prevalence was 21% (n=1,297). Finally, for chronic pain that was both widespread and moderate-to-severe (n=6,052) reported prevalence was 5% (n=289) (Figure 4; Table 1). Proportion of missing on covariates for complete study sample are shown in table S2.

***** Insert Fig. 4 approx. here *****

3.2 Direct, indirect, and total effects

Differences between model estimates for complete study sample and imputed study sample models were negligible (Table S3). Together with the small differences in descriptive characteristics, these suggest no extensive bias imposed by missing values. We therefore report model results from complete-case models below.

Unadjusted and sex- and age adjusted models of the chronic pain outcome showed statistically significant protective direct and total but not indirect effects, implying no mediation by cold-

pain tolerance (Table 2, Figure 5). Significant effects became non-significant when adjusting for covariates, although the effect estimates remained very similar. Effects estimates were slightly stronger but remained not statistically significant when looking at those without chronic pain at baseline only (Table 3). Sex-stratified models showed no large differences in multivariable-adjusted complete study sample models (Table S4).

Unadjusted models for widespread chronic pain estimated statistically significant direct, indirect, and total effects, than seen for chronic pain only, implying a small mediated effect by cold-pain tolerance towards lower risk (Table 2, Figure 5). The indirect effect became non-significant when adjusting for sex, age, and other covariates, again with relatively small changes in effect estimates. These effects were attenuated to no statistically significant effects when using a baseline without chronic pain (Table 3). In sex-stratified models, direct and total effects were stronger and hence showed lower risk for men than women (Table S4).

In unadjusted models of moderate-to-severe chronic pain, we found slightly smaller, statistically significant risk-reducing direct, indirect, and total effects, than seen for widespread chronic pain (Table 2, Figure 5). The mediated indirect effect remained significant when adjusting for sex, age, and other covariates, as before with relatively small changes in effect estimates. Estimates on a baseline sample without chronic pain showed markedly stronger direct and total effects for LTPA, but a not statistically significant indirect effect (Table 3). In stratified models, there were moderate signs of stronger direct, indirect, and total effects in men than women (Table S4).

In unadjusted models of widespread moderate-to-severe chronic pain, we found statistically significant direct, indirect, and total effects, implying a small mediated indirect effect by cold-pain tolerance (Table 2, Figure 5). Effects remained significant when adjusting for sex, age, and other covariates, again with small changes in effect estimates. Modelling on a baseline sample without chronic pain showed negligible differences in all effect estimates although all effects became not statistically significant (Table 3). In sex-stratified models, there were clear signs of stronger direct and total effects in men than women, but small indications of the opposite regarding the mediated effect (Table S4).

The effect of increasing LTPA by one level indicated a 24% reduced risk of widespread moderate-to-severe chronic pain, as compared to the non-significant 4% reduction in risk seen in the model of chronic pain only. Approximately 1% of this risk reduction in widespread moderate-to-severe chronic pain appeared to stem from the effect of a one-level increase in LTPA on cold-pain tolerance.

Figure S5 shows the amount of estimated bias in direct, indirect, and total effects given strength of unmeasured confounding for continuous and binary confounders, respectively. Maximum hypothesized confounding (1 on x-axes) never caused more than approximately 5% bias to direct, indirect, or total effects.

***** Insert Fig. 5 approx. here *****

4. Discussion

The results of this study indicate lower relative risk of four chronic pain states at follow-up with higher levels of LTPA at baseline. In the main analyses, cold-pain tolerance was not an important indirect pathway between PA and the simplest definition of chronic pain (pain for three months or more). However, the mediated indirect effects of PA via cold-pain tolerance were statistically significant for chronic pain outcomes that included the moderate-to-severe characteristics. Higher severity of chronic pain and whether it was widespread were indicators of larger direct effect sizes, with the largest effects found for both conditions combined.

4.1. Cold-pain tolerance as mediator

The present study investigated whether the effect of PA on risk of chronic pain was driven by its impact on pain sensitivity. We have previously established strong associations between PA and chronic pain [16], and PA and cold-pressor tolerance in the same population [89], and have found some evidence suggesting that increasing PA over time can be beneficial to pain tolerance [90]. Whilst the present study found that cold-pain tolerance was an indirect pathway through which PA affects the risk of some chronic pain types, it also suggests that this component can be limited in size.

To detect this effect in a heterogeneous population-based sample, a large sample size

was needed. Even though the sample size required to demonstrate such an effect might be reduced in a more clinically homogenous group, Löfgren et al. did not find any effect of long-term PA on pressure-pain thresholds or EIH in 30 participants with rheumatoid arthritis [48]. However, they did find significant effect on reported clinical pain levels. It is possible that a pain sensitivity component might have been detected with higher statistical power, but simultaneously likely that additional mechanisms related to the PA intervention played an important role in changing participants' evaluation of their own experience.

Indeed, besides its effect on endogenous pain modulation, PA has been suggested to beneficially impact inflammatory markers in mice and humans [47; 59] and psychosocial and behavioural components resulting in improved tolerance of painful stimuli [36]. Such mechanisms may also represent possible indirect pathways between PA and clinical pain.

4.2. Cold-pain tolerance and chronic pain

Previously, the role of the effect of PA on pain sensitivity in clinical pain has often been examined in the context of the phenomenon of exercise-induced hypoalgesia (EIH) and whether this is conditional on chronic pain being present. Since disruption in endogenous pain modulation is a frequent feature of chronic pain, a PA-derived effect on pain sensitivity amongst chronic pain patients is deemed to hold much clinical promise. Consequently, the rationale behind several published reviews of EIH in individuals with and without chronic pain imply close connections between ratings of experimentally induced pain and symptoms experienced in clinical pain states, or the utility of exercise to those symptoms [8; 56; 65; 69; 83]. This implies that a change in experimentally induced pain sensitivity among those with chronic pain states could translate to possible pain relief for clinical manifestations of pain.

Similarly, a review by Treede concluded that QST-parameters had potential in predicting propensity to develop chronic pain [79]. Doubtlessly, altered central processing of pain can be a feature in many chronic pain states. The present study found some limited signs of a possibly causal pathway for PA on chronic pain through cold-pain tolerance. Such indirect effects were small and thus probably do not represent the principal mechanisms behind the effect of PA on risk of chronic pain. This might in part be due to the use of a static QST-parameter. As dynamic parameters like exercise-induced hypoalgesia and conditioned pain modulation are suggested to more closely represent endogenous pain-inhibitory capacity [4; 61], their use might produce different results.

Furthermore, the observed significance of the mediated pathway and the total effect of

PA in the present study depended on which outcome definition was used. The International Classification of Disease (11th ed.) classifies chronic pain as pain that persists or recurs for three months or more [1], which is also a widely used criteria in epidemiological studies [75]. With an estimated prevalence of 60%, this group likely contains a high degree of variance. However, pain can also be assessed according to how widespread [88] and severe it is [80]. Increased responsiveness in central neuronal pain pathways as well as peripheral and central neuroinflammation have been suggested to be drivers of widespread chronic pain [33]. Furthermore, Hattori et al. found higher pain severity and increased pain sensitivity to be associated with lack of effect from PA on persistent osteoarthritis pain [25]. In a review, Geneen et al. hypothesized that findings of inconsistent effect of PA on chronic pain might be partially attributable to the fact that the included studies only investigated mild-to-moderate chronic pain [17], suggesting the effect might be different for other types of chronic pain. Presently, the mediated effect through cold-pain tolerance was strongest for moderate-to-severe pain combined with widespread pain. Thus, these findings might suggest that the indirect effect of PA through pain sensitivity acts more strongly on risk of chronic pain types exhibiting these characteristics. However, widespread chronic pain types had low prevalences, indicating selected groups. More research is needed to further explore the importance of QST-related mechanisms for such clinical sub-groups.

4.3. Sex and individuals without chronic pain

Earlier studies on this population have found sex to moderate a relationship between LTPA and CPT tolerance [89] and between LTPA and chronic pain [16]. Women were found to have lower CPT tolerance and higher prevalence of chronic pain compared to men. We were therefore not surprised to find the same patterns in our sex-stratified models. Interestingly, we found indications of differences in direct effects between men and women for both types of widespread chronic pain, whereas the differences in indirect effects via cold-pain tolerance were mainly found in models of moderate-to-severe chronic pain.

Looking at only individuals without baseline chronic pain, it could appear that total effects of PA are strengthened with regards to preventing future moderate-to-severe chronic pain types, and diminished for widespread chronic pain only. Such results might suggest PA is a stronger preventive agent for the chronic pain types that exhibit the strongest indirect pathways when modelling includes individuals with chronic pain at baseline. However, excluding individuals with baseline chronic pain represents stratification, and thus an

adjustment, according to previous chronic pain. Therefore, results possibly represent only the direct effect of PA on later chronic pain as well as incomplete information on indirect effects, because the indirect effect of PA through baseline chronic pain has been removed.

4.4. Potential limitations

Sample selection is caused by selective attendance to the Tromsø Study, and by who has missing information on exposure, mediator, and outcome. Our sample follows a trend seen in large health surveys where participants are more often female, have less chronic illness, and higher socioeconomic status than non-participants [31; 44]. Compared to all participants of Tromsø7, our sample had lower prevalences of several chronic pain types [16]. This likely underestimates the current findings.

All observational models can be influenced by unmeasured confounding. Sensitivity analysis by simulated data showed negligible impact from hypothesized unmeasured confounders, with bias of estimates being at maximum approximately 5%. Unmeasured confounders might have other distributions than those modelled here but given the relatively strong confounding effects that were assumed in the analysis, we believe it improbable that other combinations would introduce significantly stronger bias. Using estimates of PA gained through other methodologies (such as accelerometry) could complement the current results as these might relate differently to cold-pain tolerance [89].

Effects were modelled as continuous due to the counterfactual models used. PA and chronic pain may have associative patterns that are non-linear. However, previous studies on both PA and CPT, and PA and chronic pain in this population support a linear trend [16; 89]. It is possible that the direct or indirect effects have different slopes for the higher levels of PA than for the lower ones, and future studies should be mindful of this. Furthermore, we have identified CPT tolerance to be highly right-censored and better modelled using Tobit regression [90]. This was not possible with the current statistical approach. We expect that accounting for this would strengthen effect estimates. Also, we did not adjust for baseline chronic pain since this is a possible mediator for the effect of PA on chronic pain at follow-up. Adjusting for it would bias effect estimates (Lord's paradox: [60]). Sensitivity analyses showed high loss of power from adjusting for baseline due to the high prevalence of all outcomes. Furthermore, our baseline sample without chronic pain is not easily comparable to the general population, in which chronic pain is frequent. Such a sample might have considerable differences in underlying risk factors which are not immediately apparent. These models are thus not directly comparable and must be interpreted accordingly.

Finally, mediation implies a causal relationship and mediation analysis seeks to disentangle the components of this relationship. We cannot rule out possible bidirectional or reversed causation. However, we have sought to strengthen causal inference by using an exposure measured prior to mediator which was measured prior to outcome. Effects are nevertheless on a group level and do not make individual prediction.

4.5. Conclusion

We estimate that higher PA levels predict lower risk of chronic pain, with indications of a small mediated effect on this risk through cold-pain tolerance for moderate-to-severe chronic pain states. There was no significant mediation when measuring chronic pain using the simplest definition (pain for more than three months). These findings suggest cold-pain tolerance to be a mechanism through which PA modifies the risk of moderate-to-severe chronic pain types with and without widespread pain.

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Figure legends:

Figure 1: Flow of participants in the study.

Figure 2: Directed acyclic graph of study. Graph details choices and modelling of covariates in the present study. Red indicates confounders, blue indicates mediators and outcome, green indicates exposure, grey indicates colliders, white indicates unmeasured potential confounders. Note: the full variable set of the graph does not equate to the variables included for modelling. T6 and T7 denote surveys Tromsø6 or Tromsø7. BMI = body mass index.

Figure 3: Schematic representation of mediation model.

Figure 4: Sample prevalence of chronic pain types.

Figure 5: Forest plot of effect estimates. Direct effects are for one level increase in leisure-time physical activity when cold-pressor test score is kept constant. Indirect effects are for increasing cold-pressor test scores with what they would change with a 1-level increase in leisure-time physical activity, but keeping the leisure-time physical activity level constant. Marginal total effects are the combined direct and indirect effects.

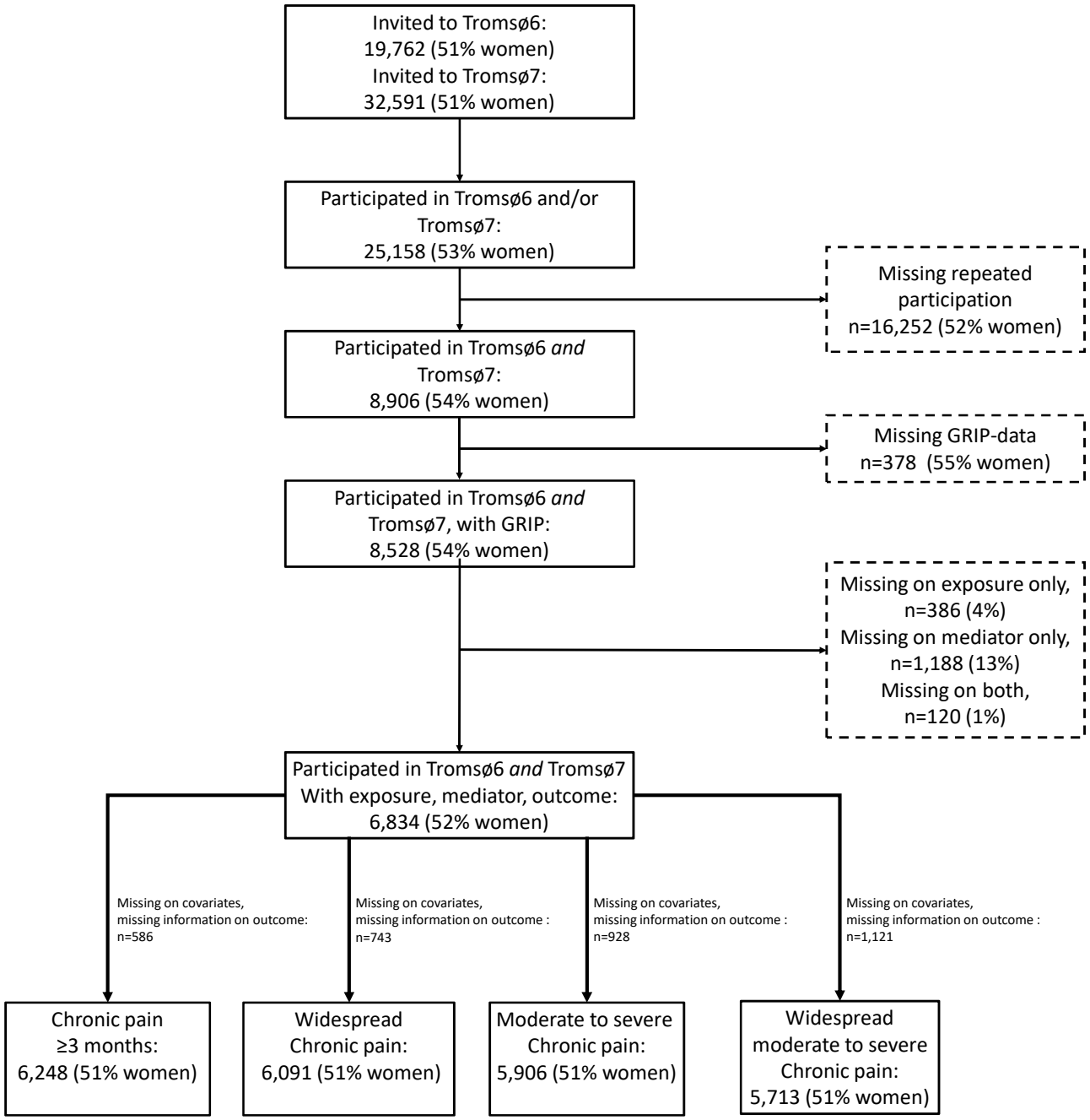
Figure S1: Hand placement in cold-water vat during cold-pressor test.

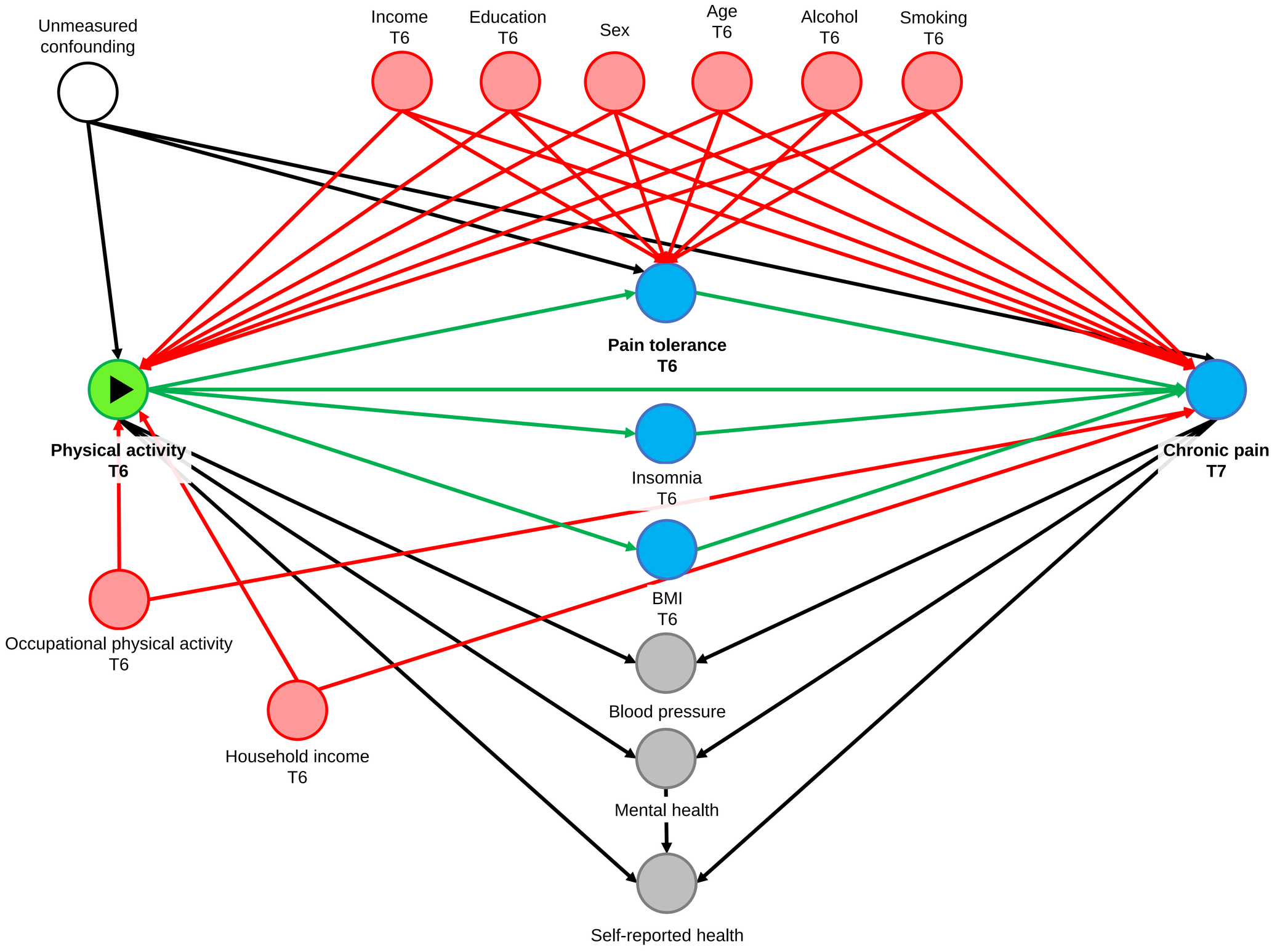
Figure S2: Graphical index of pain, tier 1.

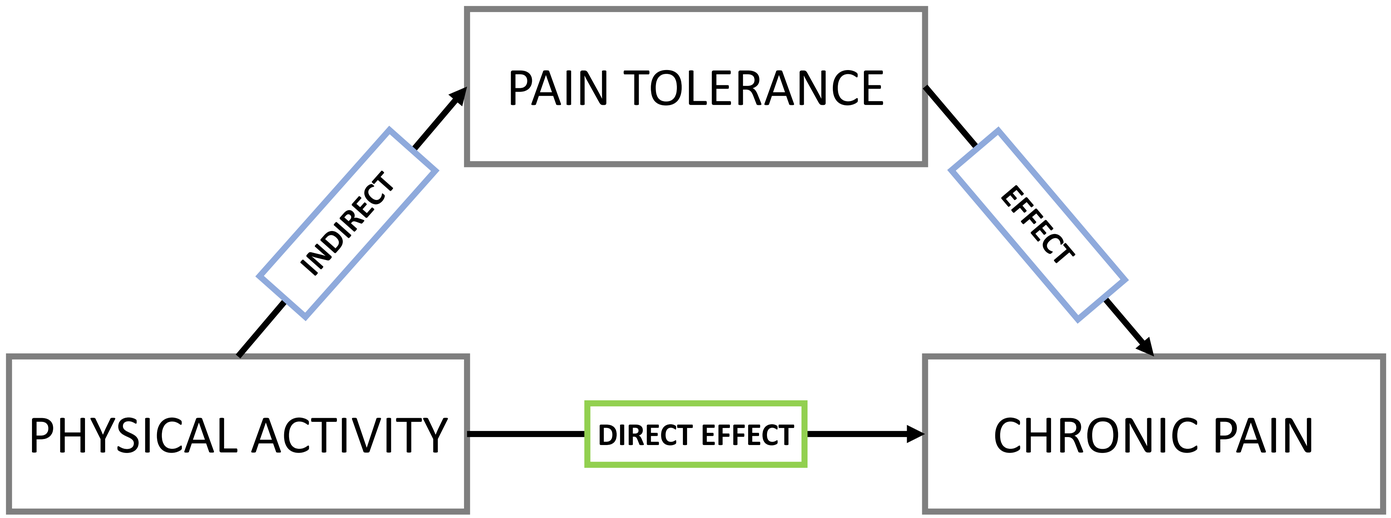
Figure S3: Graphical index of pain, tier 2.

Figure S4: Simple schematic representation of simulated model.

Figure S5: Simulated confounding for direct, indirect, and total estimated effects using a continuous or a dichotomous unmeasured confounder. X-axes: Confounding load factor on a scale of 0% - 100% unmeasured confounding. Y-axes: Proportion bias introduced to model estimates by simulated unmeasured confounders according to load factor. For simulation of a continuous confounder, “D”, with mean=10, SD=2, a load factor of 1 equals: DX=OR 0.9 (logistic regression); DM=-0.5 sec. (linear regression); DY=OR 1.1 (logistic regression), for a one-step increase in D. For simulation of a dichotomous confounder, “D”, 0,1 with 50% probability distribution, a load factor of 1 equals: DX=OR 0.5 (logistic regression); DM=-20 sec. (linear regression); DY=OR 2 (logistic regression), for going from 0 to 1 on D. Note: N=10,000,000 simulated observations; “XY”, “XM”, and “MY” represent associations from the mediation model of the present study which are used in the simulation.


Invited to Tromsø6:
19,762 (51% women)
Invited to Tromsø7:
32,591 (51% women)
Participated in Tromsø6 and/or Tromsø7:
25,158 (53% women)
Missing repeated participation
n=16,252 (52% women)
Participated in Tromsø6 *and* Tromsø7:
8,906 (54% women)
Missing GRIP-data
n=378 (55% women)
Participated in Tromsø6 *and* Tromsø7, with GRIP:
8,528 (54% women)
Missing on exposure only,
n=386 (4%)
Missing on mediator only,
n=1,188 (13%)
Missing on both,
n=120 (1%)
Participated in Tromsø6 *and* Tromsø7
With exposure, mediator, outcome:
6,834 (52% women)
Missing on covariates, missing information on outcome: n=586
Missing on covariates, missing information on outcome : n=743
Missing on covariates, missing information on outcome : n=928
Missing on covariates, missing information on outcome : n=1,121
Chronic pain ≥3 months:
6,248 (51% women)
Widespread Chronic pain:
6,091 (51% women)
Moderate to severe Chronic pain:
5,906 (51% women)
Widespread moderate to severe Chronic pain:
5,713 (51% women)


Unmeasured confounding
Income T6
Education T6
Sex
Age T6
Alcohol T6
Smoking T6
Pain tolerance T6
Physical activity T6
Chronic pain T7
Insomnia T6
BMI T6
Occupational physical activity T6
Household income T6
Blood pressure
Mental health
Self-reported health


PAIN TOLERANCE
INDIRECT
EFFECT
PHYSICAL ACTIVITY
DIRECT EFFECT
CHRONIC PAIN

TOTAL SAMPLE
n=6,834

n=6,625

CHRONIC PAIN
>3 MONTHS
3,953/6,625
(60%)

n=6,459

WIDESPREAD
CHRONIC PAIN
540/6,459
(8%)

n=6,259

MODERATE-
TO-SEVERE
CHRONIC PAIN
1,297/6,259
(21%)

n=6,052

WIDESPREAD
MODERATE-
TO-SEVERE
CHRONIC PAIN
289/6,052
(5%)

Chronic pain type	n	Relative risk with 95% CI
Chronic pain	6248	
Direct effect		0.95 (0.91, 1.00)
Indirect effect		1.00 (0.997, 1.003)
Total effect		0.96 (0.91, 1.00)
Widespread chronic pain	6091	
Direct effect		0.84 (0.73, 0.97)
Indirect effect		0.993 (0.984, 1.001)
Total effect		0.84 (0.73, 0.97)
Moderate-to-severe chronic pain	5906	
Direct effect		0.91 (0.83, 0.99)
Indirect effect		0.993 (0.988, 0.999)
Total effect		0.90 (0.82, 0.98)
Widespread moderate-to-severe chronic pain	5713	
Direct effect		0.77 (0.64, 0.94)
Indirect effect		0.988 (0.977, 0.999)
Total effect		0.76 (0.63, 0.93)

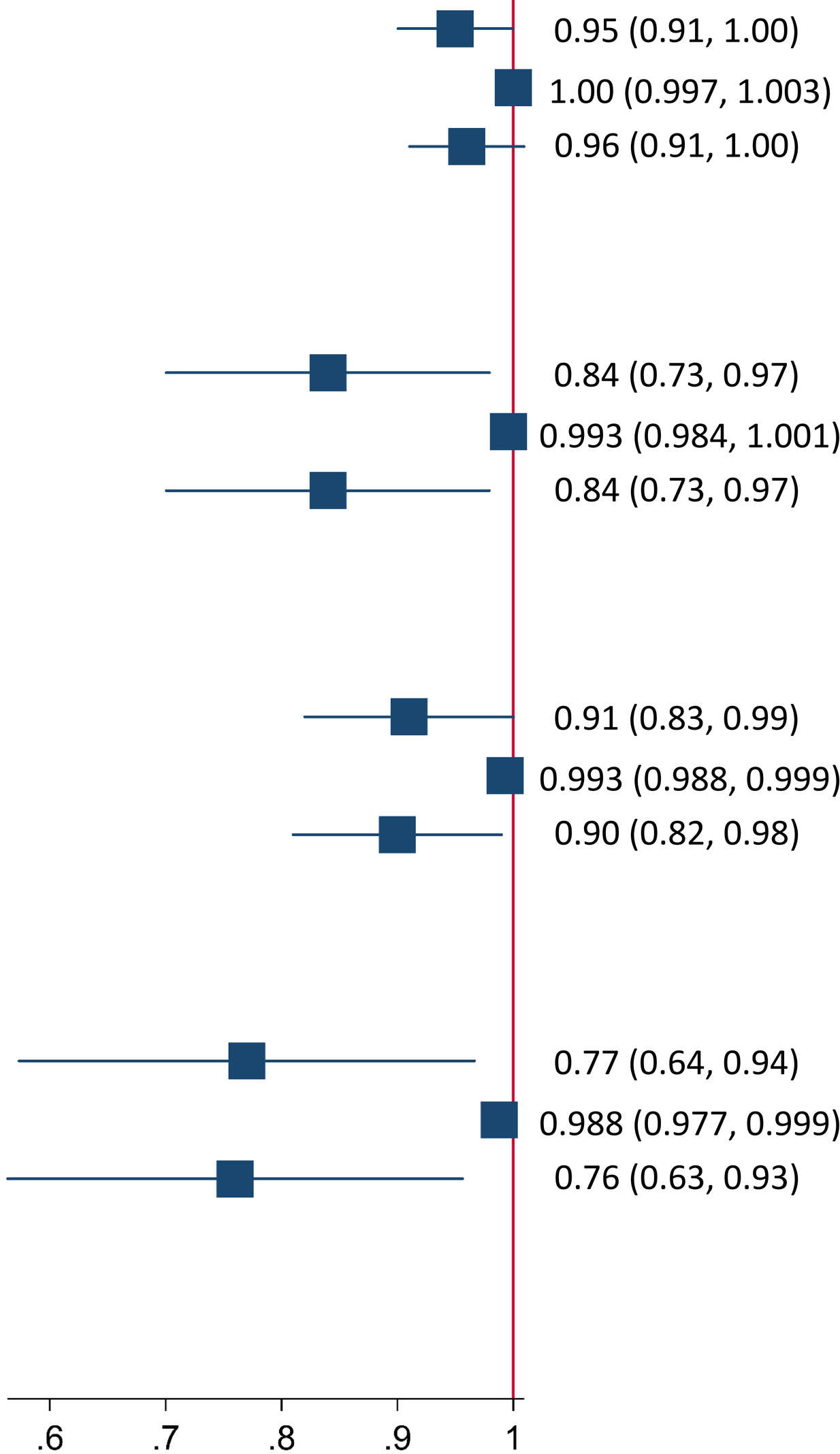


Table 1: Baseline (Tromsø6) characteristics and follow-up (Tromsø7) outcomes in total follow-up population and complete study sample, and according to present chronic pain at follow-up. The Tromsø Study 2007-2016.

Characteristics:	Total follow-up population[1]	Complete study sample[2]	Chronic pain[3]	Widespread chronic pain[3]	Moderate-to-severe chronic pain[3]	Widespread moderate-to-severe chronic pain[3]
Number of participants (%)	8,906 (100)	6,834 (100)	4,916 (100)	666 (100)	1,678 (100)	364 (100)
Age, mean (SD)	55.8 (11.2)	54.8 (10.9)	54.5 (11.2)	52.7 (10.7)	55.4 (11.4)	53.8 (10.9)
Female, %:	53.6	51.5	58.3	72.7	66.6	75.6
Daily smoking, %:	8,814 (99.0)	6,783 (99.3)	4,871 (99.1)	660 (99.1)	1,661 (99.0)	360 (98.9)
Yes, now	18.0	17.9	18.7	24.6	22.3	26.9
Yes, previously	43.4	43.4	42.9	39.5	42.3	40.0
Never	38.6	38.7	38.4	35.9	35.4	33.1
Average alcohol consumption frequency, %:	8,821 (99.1)	6,797 (99.5)	4,880 (99.3)	663 (99.6)	1,664 (99.2)	362 (99.5)
Never	8.5	7.0	7.9	8.7	10.0	11.0
Monthly or less frequently	27.2	26.0	28.0	32.9	31.4	32.9
2-4 times a month	40.5	42.1	41.1	38.3	39.4	37.6
2-3 times a week	18.5	19.5	18.0	16.6	15.2	15.2
4 or more times a week	5.3	5.4	5.0	3.5	4.0	3.3
Household income previous year:	8,391 (94.2)	6,545 (95.8)	4,665 (95.0)	629 (94.4)	1,568 (93.5)	340 (93.4)
0-300k	19.5	16.6	19.2	22.4	24.8	27.9
300-700k	51.0	52.1	52.0	55.2	54.0	54.4
Above 700k	29.5	31.3	28.8	22.4	21.2	17.7
Education level, %:	8,818 (99.0)	6,793 (99.4)	4,867 (99.0)	658 (98.8)	1,659 (98.9)	360 (98.9)
Primary/secondary school, up to 10 years	24.9	22.2	23.7	25.4	28.8	28.6
Technical, vocational, high school	34.3	34.4	34.4	38.5	38.0	39.2
College/university, less than 4 years	18.9	20.1	19.4	17.6	17.3	17.5
College/university, 4 years or more	21.9	23.3	22.5	18.5	15.9	14.7
Physical activity leisure time, %:	8,354 (93.8)	6,834 (100)	4,636 (94.3)	627 (94.1)	1,565 (93.3)	342 (94.0)
Sedentary	17.7	17.3	18.6	22.7	20.4	24.0

Light	60.9	61.1	61.2	61.1	63.3	62.3
Moderate	19.6	19.7	18.7	15.5	15.3	13.1
Vigorous	1.8	1.9	1.6	0.8	1.0	0.6
Occupational physical activity, %:	8,760 (98.4)	6,742 (98.7)	4,839 (98.4)	661 (99.3)	1,660 (98.9)	362 (99.5)
Sedentary	39.1	42.2	39.7	36.3	32.4	30.7
Light	18.2	19.0	17.8	17.7	17.6	19.1
Moderate	12.8	13.3	13.4	13.3	13.1	11.6
Heavy	2.4	2.4	2.6	3.0	3.0	3.6
Retired	26.6	22.3	25.4	28.0	32.5	33.1
Disability/sick leave	0.9	0.8	1.1	1.7	1.4	1.9
CPT tolerance time (seconds), means (SD):	89.6 (27.6)	89.7 (27.5)	88.9 (27.9)	85.1 (29.8)	85.5 (29.9)	81.6 (31.6)
Follow-up outcomes[4]:						
Chronic pain prevalence:	4,916/8,270 (59.4)	3,953/6,625 (59.7)	4,916/4,916 (100)	666/666 (100)	1,678/1,678 (100)	364/364 (100)
Widespread chronic pain prevalence:	666/8,047 (8.3)	540/6,459 (8.4)	666/4,916 (13.5)	666/666 (100)	N/A	364/364 (100)
Moderate-to-severe chronic pain prevalence:	1,678/7,811 (21.5)	1,297/6,259 (20.7)	1,678/4,916 (34.1)	589/666 (88.4)	1,678/1,678 (100)	364/364 (100)
Widespread moderate-to-severe chronic pain prevalence:	364/7,537 (4.8)	289/6,052 (4.8)	364/4,916 (7.4)	589/666 (88.4)	364/1,678 (21.7)	364/364 (100)

[1] All participants of both Tromsø6 and Tromsø7.

[2] Responded to questionnaire on leisure-time physical activity, participated in cold-pressor test (Tromsø6), and responded to Graphical Index of Pain-questionnaire on chronic pain (Tromsø7).

[3] All participants of both Tromsø6 and Tromsø7 reporting chronic pain outcomes present in Tromsø7: Chronic pain=constant or recurring pain ≥3 months; chronic widespread pain=reported constant or recurring pain in more than three regions on body map ≥3 months; moderate-to-severe chronic pain=constant or recurring pain ≥3 months with intensity, bother, and impact on ADL ≥3 on 11-point NRS; widespread moderate-to-severe chronic pain=participants reporting both chronic moderate-to-severe and widespread pain.

[4] All participants and complete cases denominators differ due to missing information on the Graphical Index of Pain-questionnaire used to compute outcomes.

SD=standard deviation; CPT=Cold-pressor tolerance.

Table 2: Risk[1] of chronic pain at follow up, in controlled direct-, natural indirect, and marginal total effects, for one level increase in leisure-time physical activity (exposure) on all chronic pain outcomes[2]: Complete study sample[3]. The Tromsø Study 2007-2016.

Model	Chronic pain	Widespread chronic pain	Moderate-to-severe chronic pain	Widespread moderate-to-severe chronic pain
Unadjusted, n=	*6,625*	*6,459*	*6,259*	*6,052*
CDE	**0.95 (0.90, 0.99)**	**0.80 (0.70, 0.91)**	**0.84 (0.77, 0.91)**	**0.73 (0.61, 0.87)**
NIE	0.997 (0.993, 1.001)	**0.983 (0.972, 0.994)**	**0.98 (0.98, 0.99)**	**0.970 (0.955, 0.985)**
MTE	**0.94 (0.90, 0.99)**	**0.78 (0.69, 0.89)**	**0.82 (0.76, 0.89)**	**0.71 (0.59, 0.84)**
Sex & age-adjusted, n=	*6,625*	*6,459*	*6,259*	*6,052*
CDE	**0.95 (0.91, 1.00)**	**0.81 (0.71, 0.92)**	**0.86 (0.79, 0.93)**	**0.74 (0.61, 0.89)**
NIE	1.00 (0.996, 1.003)	0.993 (0.984, 1.001)	**0.990 (0.984, 0.996)**	**0.983 (0.971, 0.995)**
MTE	**0.95 (0.91, 1.00)**	**0.80 (0.70, 0.91)**	**0.85 (0.78, 0.92)**	**0.72 (0.60, 0.87)**
Multivariable adjusted[4] n=	*6,248*	*6,091*	*5,906*	*5,713*
CDE	0.95 (0.91, 1.00)	**0.84 (0.73, 0.97)**	**0.91 (0.83, 0.99)**	**0.77 (0.64, 0.94)**
NIE	1.00 (0.997, 1.003)	0.996 (0.988, 1.003)	**0.993 (0.988, 0.999)**	**0.988 (0.977, 0.999)**
MTE	0.96 (0.91, 1.00)	**0.84 (0.73, 0.97)**	**0.90 (0.82, 0.98)**	**0.76 (0.63, 0.93)**

[1] Counterfactual mediation analysis with Poisson modelling of chronic pain outcome. All effects are risk ratios. Direct effects per level of physical activity. Indirect effects per second cold-pressor test tolerance.

[2] Chronic pain=constant or recurring pain ≥3 months; chronic widespread pain=reported constant or recurring pain in more than three regions on body map ≥3 months; moderate-to-severe chronic pain=constant or recurring pain ≥3 months with intensity, bother, and impact on ADL ≥3 on 11-point NRS; widespread moderate-to-severe chronic pain=participants reporting both chronic moderate-to-severe and widespread pain.

[3] Responded to questionnaire on leisure-time physical activity, participated in cold-pressor test (Tromsø6), and responded to Graphical Index of Pain-questionnaire on chronic pain (Tromsø7).

[4] Adjusted for baseline sex, age, occupational physical activity, daily smoker status, alcohol consumption frequency, household income, education level. Statistically significant results in **bold**. LTPA=leisure-time physical activity; CDE=controlled direct effect (the direct effect of LTPA); NIE=natural indirect effect (the indirect effect of cold pain tolerance); MTE=marginal total effect (the combined direct and indirect effect of increasing LTPA by one level on chronic pain).

Table 3: Risk[1] of chronic pain at follow up, in controlled direct-, natural indirect, and marginal total effects, for one level increase in leisure-time physical activity (exposure) on all chronic pain outcomes[2]: Baseline sample without chronic pain[3]. The Tromsø Study 2007-2016.

Model	Chronic pain	Widespread chronic pain	Moderate-to-severe chronic pain	Widespread moderate-to-severe chronic pain
Unadjusted, n=	4,175	4,519	4,175	4,264
CDE	**0.89 (0.81, 0.98)**	0.91 (0.72, 1.14)	**0.77 (0.67, 0.88)**	**0.65 (0.46, 0.92)**
NIE	0.995 (0.988, 1.002)	0.986 (0.968, 1.005)	0.990 (0.980, 1.001)	0.979 (0.953, 1.005)
MTE	**0.89 (0.81, 0.97)**	0.89 (0.71, 1.12)	**0.76 (0.66, 0.87)**	**0.63 (0.45, 0.90)**
Sex & age-adjusted, n=	4,175	4,519	4,175	4,264
CDE	**0.89 (0.81, 0.98)**	0.91 (0.72, 1.15)	**0.78 (0.68, 0.89)**	**0.65 (0.45, 0.94)**
NIE	0.999 (0.993, 1.005)	0.994 (0.979, 1.010)	0.995 (0.987, 1.004)	0.987 (0.965, 1.009)
MTE	**0.89 (0.81, 0.98)**	0.91 (0.72, 1.15)	**0.77 (0.67, 0.89)**	**0.65 (0.45, 0.93)**
Multivariable adjusted[4], n=	3,971	4,276	3,971	4,040
CDE	0.92 (0.83, 1.02)	0.98 (0.77, 1.25)	**0.83 (0.72, 0.96)**	0.73 (0.50, 1.07)
NIE	0.999 (0.994, 1.005)	0.996 (0.982, 1.011)	0.997 (0.990, 1.005)	0.989 (0.969, 1.009)
MTE	0.92 (0.83, 1.01)	0.98 (0.76, 1.24)	**0.83 (0.72, 0.96)**	0.72 (0.49, 1.05)

[1] Counterfactual mediation analysis with Poisson modelling of chronic pain outcome. All effects are risk ratios. Direct effects per level of physical activity. Indirect effects per second cold-pressor test tolerance.

[2] Chronic pain=constant or recurring pain ≥3 months; chronic widespread pain=reported constant or recurring pain in more than three regions on body map ≥3 months; moderate-to-severe chronic pain=constant or recurring pain ≥3 months with intensity, bother, and impact on ADL ≥3 on 11-point NRS; widespread moderate-to-severe chronic pain=participants reporting both chronic moderate-to-severe and widespread pain.

[3] Reported no present chronic pain in Tromsø6.

[4] Adjusted for baseline sex, age, occupational physical activity, daily smoker status, alcohol consumption frequency, household income, education level. Statistically significant results in **bold**. LTPA=leisure-time physical activity; CDE=controlled direct effect (the direct effect of LTPA); NIE=natural indirect effect (the indirect effect of cold pain tolerance); MTE=marginal total effect (the combined direct and indirect effect of increasing LTPA by one level on chronic pain).

Table S1: Baseline (Tromsø6) characteristics for complete study sample, imputed study sample, and complete survey population of Tromsø6. The Tromsø Study 2007-2016.

Characteristics:	Complete study sample[1]	Imputed study sample[2]	Complete survey population[3]
Number of participants (%)	6,834 (100)	8,906 (100)	12,981 (100)
Female, %:	54.3	53.6	53.4
Age, mean (SD)	54.8 (10.9)	55.8 (11.9)	57.5 (12.7)
Daily smoking, %:	6,783 (99.3)	8,906 (100)	12,784 (98.5)
Yes, now	17.9	17.9	20.4
Yes, previously	43.4	43.4	42.3
Never	38.7	38.7	37.3
Average alcohol consumption frequency, %:	6,797 (99.5)	8,906 (100)	12,790 (98.5)
Never	7.0	8.6	11.3
Monthly or less frequently	26.0	27.3	28.7
2-4 times a month	42.1	40.4	38.1
2-3 times a week	19.5	18.4	16.9
4 or more times a week	5.4	5.3	5.0
Household income previous year:	6,545 (95.8)	8,906 (100)	11,967 (92.2)
0-300k	16.6	20.7	24.7
300-700k	52.1	50.9	49.4
Above 700k	31.3	28.4	25.9
Education level, %:	6,793 (99.4)	8,906 (100)	12,798 (98.6)
Primary/secondary school, up to 10 years	22.2	25.1	28.7
Technical, vocational, high school	34.4	34.4	33.5
College/university, less than 4 years	20.1	18.8	17.6
College/university, 4 years or more	23.3	21.7	20.2
Physical activity leisure time, %:	6,834 (100)	8,906 (100)	11,921 (91.8)
Sedentary	17.3	18.0	20.6
Light	61.1	60.9	59.6
Moderate	19.7	19.4	18.2
Vigorous	1.9	1.7	1.6
Occupational physical activity, %:	6,742 (98.7)	8,906 (100)	12,735 (98.1)

Sedentary	42.2	39.1	35.2
Light	19.0	18.2	16.6
Moderate	13.3	12.8	12.0
Heavy	2.4	2.4	2.3
Retired	22.3	26.6	32.9
Disability/sick leave	0.8	0.9	1.0
CPT tolerance time (seconds), (SD):	89.7 (27.5)	89.0 (32.0)	88.2 (28.4)
Follow-up outcomes[4]:			
Chronic pain prevalence:	3,953/6,625 (59.7)	5,370/8,906 (60.3)	4,916/8,270 (59.4)
Widespread chronic pain prevalence:	540/6,459 (8.4)	828/8,906 (9.3)	666/8,047 (8.3)
Moderate-to-severe chronic pain prevalence:	1,297/6,259 (20.7)	1,861/8,906 (20.9)	1,678/7,811 (21.5)
Widespread moderate-to-severe chronic pain prevalence:	289/6,052 (4.8)	454/8,906 (5.1)	364/7,537 (4.8)

[1] Responded to questionnaire on leisure-time physical activity, participated in cold-pressor test (Tromsø6), and responded to Graphical Index of Pain-questionnaire on chronic pain (Tromsø7).

[2] Imputed all missing information for all participants of both Tromsø6 and Tromsø7. Multiple imputation with chained equations (predictive mean modelling (known nearest neighbors=20), 30 imputations × 10 iterations).

[3] All participants of Tromsø6.

[4] Chronic pain=constant or recurring pain ≥3 months; chronic widespread pain=reported constant or recurring pain in more than three regions on body map ≥3 months; moderate-to-severe chronic pain=constant or recurring pain ≥3 months with intensity, bother, and impact on ADL ≥3 on 11-point NRS; widespread moderate-to-severe chronic pain=participants reporting both chronic moderate-to-severe and widespread pain. Complete study sample and complete survey population participant denominators differ due to missing information on the Graphical Index of Pain-questionnaire used to compute outcomes.
SD=standard deviation; CPT=Cold-pressor tolerance.

Table S2: Missingness on baseline covariates for complete study sample (n=6,834). The Tromsø Study 2007-2016.

Covariate:	n (%)
Sex	0 (0)
Age	0 (0)
Occupational physical activity	92 (1.4)
Daily smoking status[1]	51 (0.8)
Avg. alcohol consumption frequency[2]	37 (0.5)
Household income previous year	289 (4.2)
Education level	41 (0.6)

[1] "Do you currently smoke daily?"
[2] Categorical: "How often do you usually drink alcohol?"

Table S3: Risk[1] of chronic pain at follow up, in controlled direct-, natural indirect, and marginal total effects, for one level increase in leisure-time physical activity (exposure) on all chronic pain outcomes[2]: imputed study sample versus complete study sample. The Tromsø Study 2007-2016.

Model	Chronic pain	Widespread chronic pain	Moderate-to-severe chronic pain	Widespread moderate-to-severe chronic pain
Imputed[3], n=:	*8,906*	*8,906*	*8,906*	*8,906*
Unadjusted				
CDE	**0.95 (0.91, 0.99)**	**0.78 (0.67, 0.89)**	**0.85 (0.78, 0.93)**	**0.73 (0.58, 0.87)**
NIE	0.996 (0.992, 1.00)	**0.98 (0.97, 99)**	**0.990 (0.983, 0.996)**	**0.970 (0.955, 0.984)**
MTE	**0.94 (0.90, 0.99)**	**0.77 (0.66, 0.88)**	**0.84 (0.77, 0.92)**	**0.70 (0.56, 0.85)**
Sex & age-adjusted				
CDE	**0.95 (0.91, 0.99)**	**0.79 (0.68, 0.91)**	**0.90 (0.82, 0.97)**	**0.74 (0.59, 0.89)**
NIE	0.999 (0.996, 1.002)	**0.990 (0.982, 0.999)**	**0.993 (0.988, 0.999)**	**0.982 (0.970, 0.994)**
MTE	**0.95 (0.91, 0.99)**	**0.79 (0.68, 0.90)**	**0.89 (0.82, 0.97)**	**0.73 (0.57, 0.88)**
Multivariable adjusted[4]				
CDE	0.96 (0.91, 1.00)	**0.84 (0.73, 0.96)**	**0.90 (0.82, 0.97)**	**0.80 (0.65, 0.96)**
NIE	1.00 (0.997, 1.002)	0.994 (0.987, 1.001)	**0.993 (0.988, 0.999)**	**0.988 (0.979, 0.998)**
MTE	0.96 (0.91, 1.00)	**0.84 (0.72, 0.95)**	**0.89 (0.82, 0.97)**	**0.79 (0.64, 0.95)**
Complete cases[5]:				
Unadjusted, n=	*6,625*	*6,459*	*6,259*	*6,052*
CDE	**0.95 (0.90, 0.99)**	**0.80 (0.70, 0.91)**	**0.84 (0.77, 0.91)**	**0.73 (0.61, 0.87)**
NIE	0.997 (0.993, 1.001)	**0.983 (0.972, 0.994)**	**0.98 (0.98, 0.99)**	**0.970 (0.955, 0.985)**
MTE	**0.94 (0.90, 0.99)**	**0.78 (0.69, 0.89)**	**0.82 (0.76, 0.89)**	**0.71 (0.59, 0.84)**
Sex & age-adjusted, n=	*6,625*	*6,459*	*6,259*	*6,052*
CDE	**0.95 (0.91, 1.00)**	**0.81 (0.71, 0.92)**	**0.86 (0.79, 0.93)**	**0.74 (0.61, 0.89)**
NIE	1.00 (0.996, 1.003)	0.993 (0.984, 1.001)	**0.990 (0.984, 0.996)**	**0.983 (0.971, 0.995)**
MTE	**0.95 (0.91, 1.00)**	**0.80 (0.70, 0.91)**	**0.85 (0.78, 0.92)**	**0.72 (0.60, 0.87)**
Multivariable adjusted, n=	*6,248*	*6,091*	*5,906*	*5,713*
CDE	0.95 (0.91, 1.00)	**0.84 (0.73, 0.97)**	**0.91 (0.83, 0.99)**	**0.77 (0.64, 0.94)**
NIE	1.00 (0.997, 1.003)	0.996 (0.988, 1.003)	**0.993 (0.988, 0.999)**	**0.988 (0.977, 0.999)**

MTE	0.96 (0.91, 1.00)	**0.84 (0.73, 0.97)**	**0.90 (0.82, 0.98)**	**0.76 (0.63, 0.93)**

[1] Counterfactual mediation analysis with Poisson modelling of chronic pain outcome. All effects are risk ratios. Direct effects per level of physical activity. Indirect effects per second cold-pressor test tolerance.

[2] Chronic pain=constant or recurring pain ≥3 months; chronic widespread pain=reported constant or recurring pain in more than three regions on body map ≥3 months; moderate-to-severe chronic pain=constant or recurring pain ≥3 months with intensity, bother, and impact on ADL ≥3 on 11-point NRS; widespread moderate-to-severe chronic pain=participants reporting both chronic moderate-to-severe and widespread pain.

[3] All modelling with multiple imputation with chained equations (predictive mean modelling (known nearest neighbours=20), 30 imputations × 10 iterations).

[4] Adjusted for baseline sex, age, occupational physical activity, daily smoker status, alcohol consumption frequency, household income, education level. Statistically significant results in **bold**.

[5] Responded to questionnaire on leisure-time physical activity, participated in cold-pressor test (Tromsø6), and responded to Graphical Index of Pain-questionnaire on chronic pain (Tromsø7).

LTPA=leisure-time physical activity; CDE=controlled direct effect (the direct effect of LTPA); NIE=natural indirect effect (the indirect effect of cold pain tolerance); MTE=marginal total effect (the combined direct and indirect effect of increasing LTPA by one level on chronic pain).

Table S4: Risk[1] of chronic pain at follow up, in controlled direct-, natural indirect, and marginal total effects, for one level increase in leisure-time physical activity (exposure) on all chronic pain outcomes[2]: Complete study sample, sex-stratified. The Tromsø Study 2007-2016.

	Chronic pain			
	All	***p***	**Women**	**Men**
Unadjusted, n=	*6,625*		*3,408*	*3,217*
CDE	**0.95 (0.90, 0.99)**	**0.024**	0.98 (0.92, 1.06)	0.94 (0.88, 1.00)
NIE	0.997 (0.993, 1.001)	0.128	0.999 (0.996, 1.002)	1.00 (0.993, 1.007)
MTE	**0.94 (0.90, 0.99)**	**0.017**	0.98 (0.92, 1.06)	0.94 (0.88. 1.00)
Age-adjusted, n=	*6,625*		*3,408*	*3,217*
CDE	**0.95 (0.91, 1.00)**	**0.033**	0.97 (0.90, 1.04)	**0.94 (0.877, 0.997)**
NIE	1.00 (0.996, 1.003)	0.797	0.999 (0.996, 1.003)	1.00 (0.994, 1.007)
MTE	**0.95 (0.91, 1.00)**	**0.031**	0.97 (0.90, 1.04)	**0.94 (0.878. 0.997)**
Multivariable adjusted[3], n=	*6,248*		*3,146*	*3,102*
CDE	0.95 (0.91, 1.00)	0.065	0.97 (0.90, 1.05)	0.94 (0.88, 1.01)
NIE	1.00 (0.997, 1.003)	0.943	1.00 (0.998, 1.002)	1.00 (0.994, 1.007)
MTE	0.96 (0.91, 1.00)	0.065	0.97 (0.90, 1.05)	0.94 (0.88, 1.01)

	Widespread chronic pain			
	All	***p***	**Women**	**Men**
Unadjusted, n=	*6,459*		*3,317*	*3,142*
CDE	**0.80 (0.70, 0.91)**	**0.001**	0.90 (0.76, 1.07)	**0.72 (0.58, 0.89)**
NIE	**0.983 (0.972, 0.994)**	**0.002**	0.992 (0.983, 1.002)	0.998 (0.977, 1.019)
MTE	**0.78 (0.69, 0.89)**	**<0.001**	0.89 (0.75, 1.06**)**	**0.71 (0.57, 0.89)**
Age-adjusted, n=	*6,459*		*3,317*	*2,730*
CDE	**0.81 (0.71, 0.92)**	**0.001**	0.87 (0.73, 1.03)	**0.72 (0.58, 0.89)**
NIE	0.993 (0.984, 1.001)	0.094	0.992 (0.983, 1.002)	0.999 (0.978, 1.02)
MTE	**0.80 (0.70, 0.91)**	**0.001**	0.86 (0.73, 1.03)	**0.72 (0.58, 0.88)**
Multivariable adjusted, n=	*6,091*		*3,060*	*2,646*

CDE	**0.84 (0.73, 0.97)**	**0.018**	0.93 (0.78, 1.11)	**0.74 (0.59, 0.93**)
NIE	0.996 (0.988, 1.003)	0.260	0.996 (0.989, 1.003)	1.003 (0.982, 1.024)
MTE	**0.84 (0.73, 0.97)**	**0.015**	0.93 (0.77, 1.11)	**0.74 (0.60, 0.93**)

	Moderate-to-severe chronic pain			
	All	***p***	**Women**	**Men**
Unadjusted, n=	*6,259*		*3,195*	*3,064*
CDE	**0.84 (0.77, 0.91)**	**<0.001**	**0.86 (0.77, 0.97)**	**0.86 (0.76, 0.97)**
NIE	**0.98 (0.98, 0.99)**	**<0.001**	0.995 (0.989, 1.001)	**0.980 (0.967, 0.993)**
MTE	**0.82 (0.76, 0.89)**	**<0.001**	**0.86 (0.76, 0.97)**	**0.84 (0.74, 0.95)**
Age-adjusted, n=	*6,259*		*3,195*	*3,064*
CDE	**0.86 (0.79, 0.93)**	**<0.001**	**0.86 (0.77, 0.97)**	**0.86 (0.76, 0.97)**
NIE	**0.990 (0.984, 0.996)**	**0.002**	0.994 (0.987, 1.001)	**0.980 (0.967, 0.993)**
MTE	**0.85 (0.78, 0.92)**	**<0.001**	**0.86 (0.76, 0.97)**	**0.84 (0.74, 0.95)**
Multivariable adjusted, n=	*5,906*		*2,952*	*2,954*
CDE	**0.91 (0.83, 0.99)**	**0.029**	0.92 (0.81, 1.04)	0.90 (0.79, 1.02)
NIE	**0.993 (0.988, 0.999)**	**0.016**	0.997 (0.992, 1.002)	**0.983 (0.970, 0.995)**
MTE	**0.90 (0.82, 0.98)**	**0.020**	0.92 (0.81, 1.04)	0.88 (0.77, 1.01)

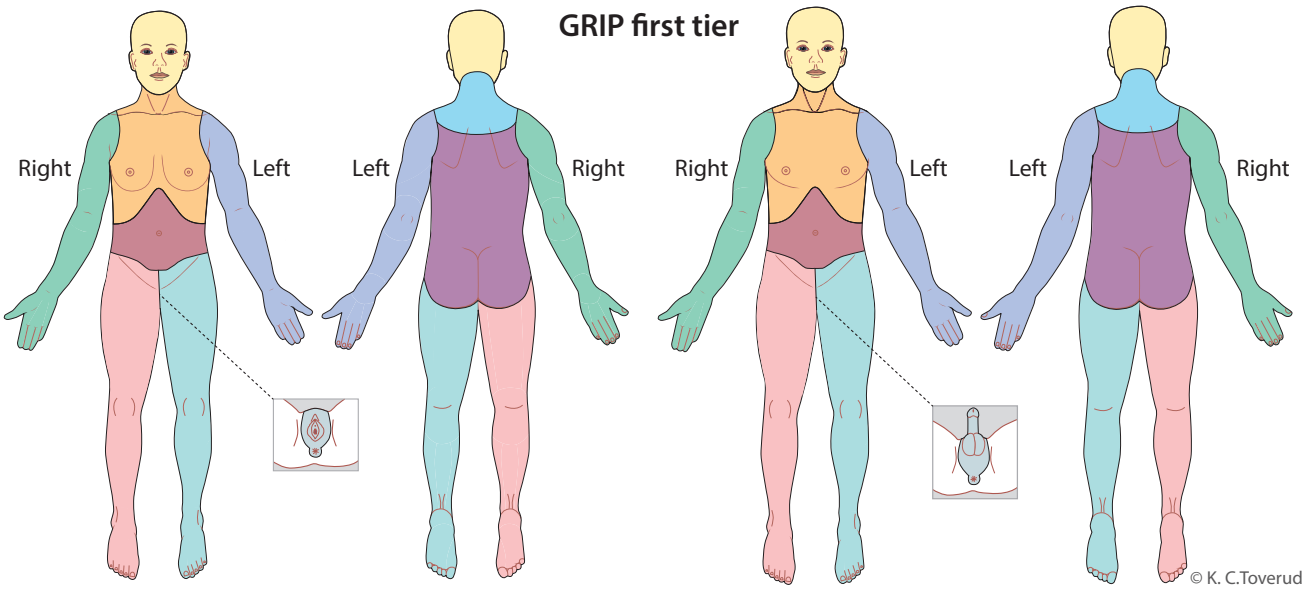
	Widespread moderate-to-severe chronic pain			
	All	***p***	**Women**	**Men**
Unadjusted, n=	*6,052*		*3,082*	*2,970*
CDE	**0.73 (0.61, 0.87)**	**0.001**	0.85 (0.67, 1.07)	**0.59 (0.42, 0.81)**
NIE	**0.970 (0.955, 0.985)**	**<0.001**	**0.984 (0.970, 0.999)**	0.992 (0.964, 1.020)
MTE	**0.71 (0.59, 0.84)**	**<0.001**	0.84 (0.66, 1.06)	**0.58 (0.42, 0.80)**
Age-adjusted, n=	*6,052*		*3,082*	*2,970*
CDE	**0.74 (0.61, 0.89)**	**0.001**	0.83 (0.66, 1.04)	**0.59 (0.43, 0.81)**
NIE	**0.983 (0.971, 0.995)**	**0.006**	**0.983 (0.968, 0.999)**	0.992 (0.965, 1.021)
MTE	**0.72 (0.60, 0.87)**	**0.001**	0.81 (0.65, 1.03)	**0.58 (0.43, 0.80)**
Multivariable adjusted, n=	*5,713*		*2,848*	*2,865*
CDE	**0.77 (0.64, 0.94)**	**0.011**	0.91 (0.71, 1.16)	**0.57 (0.41, 0.80)**
NIE	**0.988 (0.977, 0.999)**	**0.026**	0.990 (0.977, 1.003)	0.999 (0.971, 1.027)
MTE	**0.76 (0.63, 0.93)**	**0.007**	0.90 (0.71, 1.15)	**0.57 (0.41, 0.80)**

[1] Counterfactual mediation analysis with Poisson modelling of chronic pain outcome. All effects are risk ratios. Direct effects per level of physical activity. Indirect effects per second cold-pressor test tolerance.

[2] Chronic pain=constant or recurring pain ≥3 months; chronic widespread pain=reported constant or recurring pain in more than three regions on body map ≥3 months; moderate-to-severe chronic pain=constant or recurring pain ≥3 months with intensity, bother, and impact on ADL ≥3 on 11-point NRS; widespread moderate-to-severe chronic pain=participants reporting both chronic moderate-to-severe and widespread pain.

[3] Adjusted for baseline age, occupational physical activity, daily smoker status, alcohol consumption frequency, household income, education level. Statistically significant results in **bold**.

LTPA=leisure-time physical activity; CDE=controlled direct effect (the direct effect of LTPA); NIE=natural indirect effect (the indirect effect of cold pain tolerance); MTE=marginal total effect (the combined direct and indirect effect of increasing LTPA by one level on chronic pain).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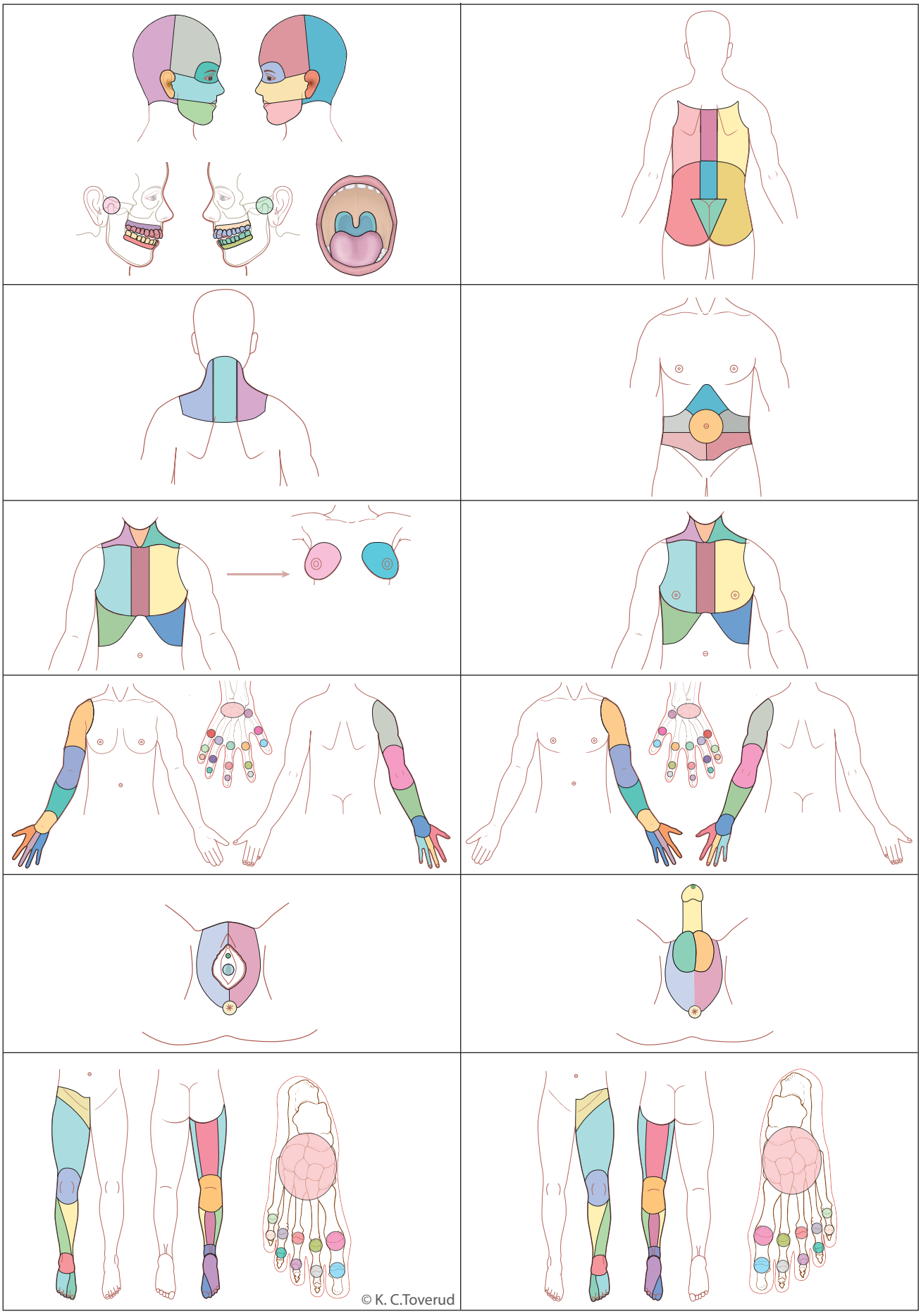
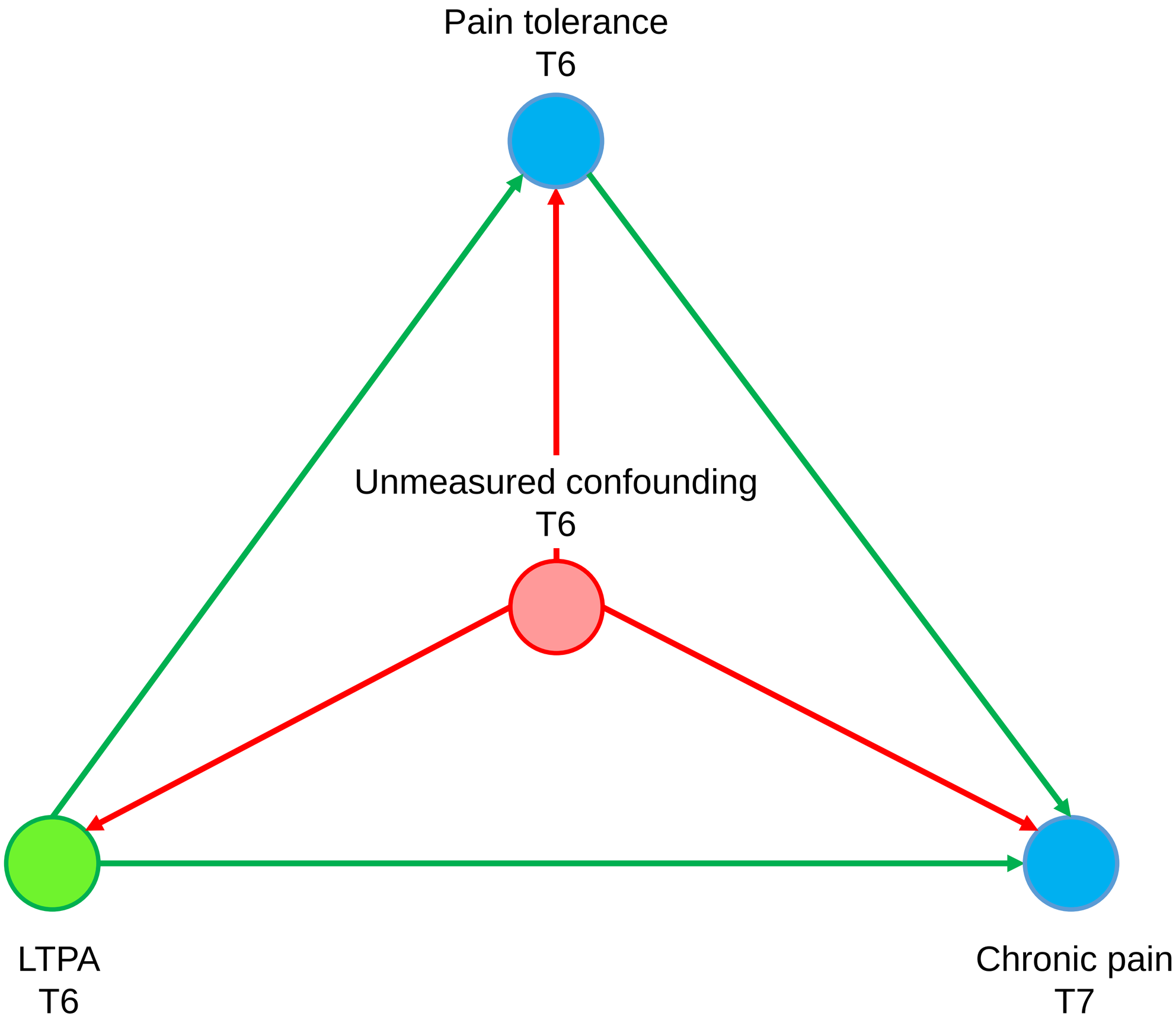
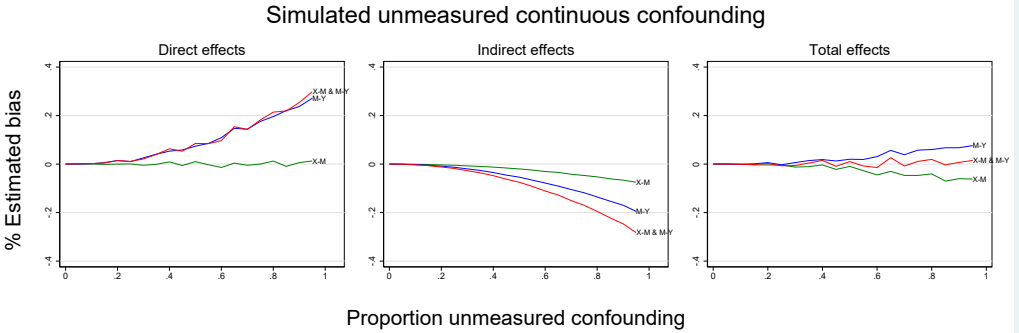
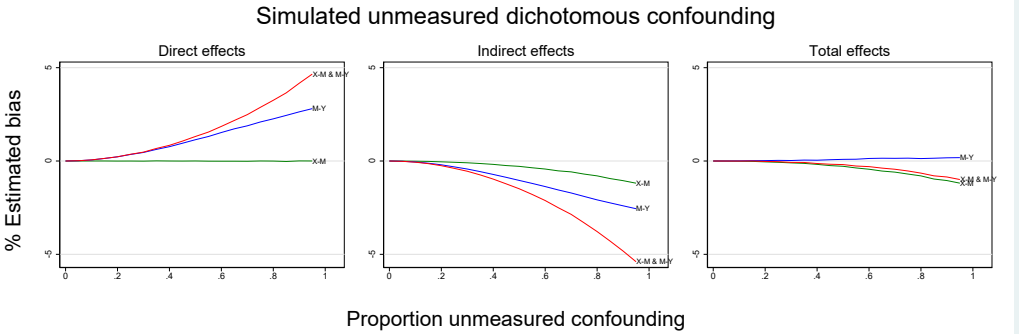
© K. C.Toverud




Pain tolerance
T6
Unmeasured confounding
T6
LTPA
T6
Chronic pain
T7





N=10000000, XY=.9, XM=2.6, MY=.996

Table S5: AGReMA Statement short form checklist for reporting on mediation analyses after Lee et al.[1]

Section and topic	Item Description
Objectives	Described at end of section 1.
Effects of interest	Described under 2.3.
Causal assumptions	Described under 2.2.4 and 2.3.
Measurement	Described under 2.2.1-2.2.3.
Statistical methods	Described under 2.3. and 2.4.
Participants	Described under 2.1., 2.4., and tables 1 and S1.
Outcomes and estimates	Described under 3.2 and tables 2, 3, S3.
Limitations	Described under 4.4.
Interpretation	Discussed under 4.3, 4.4, 4.5.

[1] Lee H, Cashin AG, Lamb SE, Hopewell S, Vansteelandt S, VanderWeele TJ, MacKinnon DP, Mansell G, Collins GS, Golub RM, McAuley JH, group AG, Localio AR, van Amelsvoort L, Guallar E, Rijnhart J, Goldsmith K, Fairchild AJ, Lewis CC, Kamper SJ, Williams CM, Henschke N. A Guideline for Reporting Mediation Analyses of Randomized Trials and Observational Studies: The AGReMA Statement. JAMA 2021;326(11):1045-1056.

Appendices

A. Invitation for Tromsø6 [Norwegian]
B. Information about Tromsø6 for participants [Norwegian]
C. Information about Tromsø7 for participants [Norwegian]
D. Consent form Tromsø6, for participants [Norwegian]
E. Consent form Tromsø7, for participants [Norwegian]
F. The first questionnaire (Q1) in the Tromsø study: Tromsø6 [Norwegian]
G. The second questionnaire (Q2) in the Tromsø study: Tromsø6 [Norwegian]
H. The first questionnaire (Q1) in the Tromsø study: Tromsø7 [Norwegian]
I. The second questionnaire (Q2) in the Tromsø study: Tromsø7 [Norwegian]
J. Ethical approval for the study from the Regional Committees for Medical and Health Research Ethics (REK North) [Norwegian]
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L. Ethical approval for the Tromsø study: Tromsø7, by the Regional Committees for Medical and Health Research Ethics (REK North) [Norwegian]

Appendix A

Invitation for Tromsø6 [Norwegian]

Den 6. Tromsøundersøkelsen er i gang!

Vi spør deg om du vil delta i den sjette Tromsøundersøkelsen. Den varer i om lag ett år med oppstart oktober 2007. Vedlagt finner du en informasjonsbrosjyre hvor du kan lese om hva Tromsøundersøkelsen går ut på.

Hvor og når

Undersøkelsen vil foregå ved den gamle husmorskolen, Gamle Breivang.

Åpningstidene for Tromsøundersøkelsen er:

Mandag og torsdag:	10.30-13.30 og 14.30-18.00
Tirsdag og onsdag:	08.30-11.30 og 12.30-16.00
Fredag:	08.30-11.30 og 12.30-14.00

Vi holder stengt i juleuken (uke 52) 2007, påskeuken (uke 12), samt hele juli 2008.

Du har fått tildelt fremmøtetid:

Adressen er: Breivangveien 23, 9010 Tromsø

Kan du ikke komme på dette tidspunktet er du velkommen når som helst i åpningstiden vår. Du behøver ikke gi beskjed om du skulle komme til en annen tid.

Buss

Følgende buss kan brukes:
Fra Sentrum (Wi-To) og Giæverbukta: Rute 24. Stoppested: Dramsveien
Fra Sentrum (Wi-To): Rute 20 og 24. Stoppested: Dramsveien
Rute 27,32 og 42. Stoppested: Stakkevollveien.

Kart

Kart som viser hvor Tromsøundersøkelsen foregår, finnes på baksida av dette arket.

Det medisinske fakultet
Institutt for samfunnsmedisin
Tromsøundersøkelsen
Universitetet i Tromsø
N-9037 Tromsø, Norge

tromsous@ism.uit.no
www.tromso6.no
tlf.77 64 48 16
Undersøkelsessted:
Breivangvn.23, 9010 Tromsø

Forberedelser til undersøkelsen

Av hensyn til måling av blodtrykk bør du ha på klær som ikke strammer på armer og bein. Ha gjerne et kortermet plagg innerst.

Du vil bli intervjuet om hvilke legemidler du har brukt regelmessig de siste fire ukene. Navn på legemidler du bruker fast kan besvares i det vedlagte spørreskjemaet. Intervjuet vil foregå på en skjermet plass.

Du vil bli spurt om hva du har brukt av smertestillende midler det siste døgnet. Et utvalg vil bli spurt om bruk av antibiotika (penicillin og lignende legemidler) det siste døgnet. Det vil bli spurt om navnet på legemiddelet og hvor mye du har brukt.

Kvinnene vil få spørsmål om menstruasjon og eventuell bruk av hormoner som påvirker menstruasjonen.

Ta gjerne med deg legemidlene du bruker ved frammøte til undersøkelsen.

Du finner mer informasjon om undersøkelsen i vedlagte brosjyre.

Med vennlig hilsen

Tromsøundersøkelsen

Appendix B

Information about Tromsø6 for participants [Norwegian]

Tromsø 6
- en del av Tromsøundersøkelsen

Vil du være med i den 6. Tromsøundersøkelsen?

» viktig forskning
» undersøkelse av egen helse
» forebygging av helseproblemer

Hva er Tromsøundersøkelsen?

Tromsøundersøkelsen er et stort forskningsprosjekt. Opplysninger som samles inn skal brukes til å gi oss kunnskap som kan bedre menneskers helse.

Den første Tromsøundersøkelsen ble gjennomført allerede i 1974, og dette er den sjette i rekken. Et viktig mål med undersøkelsen er å få kunnskap om hvorfor noen blir syke mens andre beholder god helse gjennom livet.

Visste du at ..?

Den som deltar på Tromsøundersøkelsen får også en enkel undersøkelse av sin egen helse.

Hva forskes det på i Tromsøundersøkelsen?

Tromsøundersøkelsen gjennomføres først og fremst for å kunne øke kunnskapen om de store folkehelseproblemene og forhold som påvirker disse, blant annet:

- Hjerte- og karsykdommer
- Lungesykdommer (f.eks. KOLS)
- Diabetes
- Stoffskiftesykdommer
- Kreftsykdommer
- Psykiske plager
- Demens
- Muskel- og skjelettplager

Undersøkelsen vil også bli benyttet til forskning om bruk og effekter av legemidler, trivsel, livskvalitet, livsstil, døgnrytme, smerter, sosial ulikhet, fysisk aktivitet, kosthold, bruk av helsetjenester og alternativ behandling. Det vil også bli undersøkt om miljøgifter kan påvises i blodet og om disse innvirker på helsa.

Videre vil det bli gjort forskning på kvinnesykdommer, sykdommer i fordøyelsesorganer, allergi, nyrer og urinveier, nervesystemet, sanseorganer og hud. Det vil også bli forsket på arbeidsuførhet som følge av disse sykdommene eller tilstandene. En del av prosjektene vil spesielt undersøke samspillet mellom arv, miljø, sykdom og helse. Til slike prosjekter vil det bli hentet ut DNA (arvestoff) fra blodprøvene.

Det er allerede planlagt mange forskningsprosjekter som skal benytte data fra Tromsøundersøkelsen. Du vil finne en liste over disse på vår internettside:

http://www.tromso6.no

Vil du delta?

Ved å delta på Tromsøundersøkelsen er du med på å bidra til forskning om hvordan sykdom kan forebygges og behandles, hva som fremmer god helse, og hva som er årsak til helseproblemer.

Hvorfor spør vi deg?

Alle som møtte til spesialundersøkelsene i Tromsøundersøkelsen i 1994 og 2001, og et tilfeldig uttrukket utvalg av personer som er over 30 år og som er innbyggere i Tromsø kommune, blir spurt om å delta.

Alle er viktige!

Hver deltaker er like viktig, enten du er ung eller gammel, frisk eller syk. Det har vært stort frammøte til de tidligere Tromsøundersøkelsene. Godt oppmøte er viktig for gode forskningsresultater. Det er en styrke for forskningen at de som har vært med i tidligere Tromsøundersøkelser møter fram på nytt.

Frivillig

Det er frivillig å delta. Det vil ikke få noen konsekvenser for deg dersom du ikke deltar eller velger å trekke deg fra undersøkelsen på et senere tidspunkt. Du må ikke gi noen begrunnelse dersom du ønsker å trekke deg fra undersøkelsen.

Visste du at ..?

Du kan delta på Tromsøundersøkelsen selv om det er deler av undersøkelsen du ikke ønsker å være med på.

Din helse

Cirka fire uker etter undersøkelsen vil du få et brev med resultatene fra målinger av kolesterol og blodtrykk. Dersom det er nødvendig, vil du bli anbefalt å ta kontakt med din fastlege. Det blir ikke gitt rutinemessig tilbakemelding om resultater av andre blodprøver eller målinger.

Dersom resultatet av prøvene viser at det er nødvendig med oppfølging av lege eller henvisning til spesialist, vil du bli orientert om det. Ved behov for henvisning til spesialist, vi vil sørge for at slik henvisning blir sendt.

Du kan reservere deg mot å få vite resultatene av prøvene dine. Men hvis et prøveresultat er slik at det er nødvendig med rask legebehandling, vil du uansett bli kontaktet.

Tromsøundersøkelsen er gratis. Trenger du videre undersøkelse / oppfølging av fastlegen eller i spesialisthelsetjenesten, betaler du vanlig egenandel.

Slik foregår undersøkelsen

Sammen med dette informasjonsskrivet ligger det et ark med praktiske opplysninger og beskjed om hvor og når du kan møte fram. Her står også åpningstidene for undersøkelsen. Hvis du vil delta og den foreslåtte tiden ikke passer, kan du komme en annen dag. Du trenger ikke melde fra om dette på forhånd.

Unngå før undersøkelsen

For at resultatene skal bli mest mulig korrekt, er det en fordel om du avstår fra alkohol og smertestillende medisiner 12 timer før undersøkelsen.

Påkledning

Vekt og høyde, liv- og hoftevidde måles med lett påkledning, men uten sko. For at det skal gå raskt å måle blodtrykk, er det en fordel om du har plagg som ikke strammer over armen og benet. Ha gjerne et kortermet plagg innerst.

Spørreskjema

Sammen med denne brosjyren har du fått et spørreskjema som du skal fylle ut og ta med til undersøkelsen. Hvis du er i tvil om hvordan du skal svare på et eller flere av spørsmålene, lar du det stå åpent. Personalet på undersøkelsen hjelper deg da med utfyllingen om du ønsker det.

Utfylte svar i spørreskjema er like viktig for forskningen som resultater fra blodprøver og undersøkelser.

Regelmessig bruk av legemidler

Ved frammøte til undersøkelsen vil du bli intervjuet om hva slags legemidler du har brukt regelmessig de siste fire ukene, og om noen av de legemidlene du har brukt siste 24 timer. Navn på legemidler du bruker fast kan besvares i skjemaet på forhånd. Ta gjerne med deg legemidlene du bruker ved frammøte til undersøkelsen.

Undersøkelser

Når du møter fram, vil kvalifisert helsepersonell veilede deg gjennom undersøkelsen og svare på spørsmål. Du vil bli intervjuet og få utlevert et nytt spørreskjema med en frankert svarkonvolutt. Spørreskjemaet kan også besvares mens du er tilstede på undersøkelsen, og du vil kunne få hjelp underveis. Hver enkelt undersøkelse varer bare noen minutter. Totalt vil undersøkelsen vare cirka en time.

De måler høyde, vekt, hoftevidde og livvidde, de måler blodtrykket og tar blodprøve av deg. I tillegg vil følgende undersøkelser bli gjort:

- Beintetthetsmåling (måling av beinmasse) i den ene armen med svake røntgenstråler. Målingene brukes til å undersøke risiko for beinskjørhet og brudd.
- Bakterieprøve fra nese og hals fra om lag halvparten av deltagerne, for å se etter gule stafylokokker, en bakterie som normalt finnes på hud og slimhinner hos mennesker, men som i enkelte tilfeller kan forårsake alvorlige infeksjoner. Prøven gjøres med fuktet vattpensel.
- Smerteølsomhet som måler hvordan kroppen reagerer på smerte. Du blir bedt om å holde hånden i isvann i opptil 1 minutt. Underveis registreres blodtrykk og du angir hvor mye smerte du kjenner. Du kan ta hånden ut av vannet før tiden er ute hvis det blir for ubehagelig.
- Hårprøve. Vi vil be om å få noen hårstrå for å undersøke forekomsten av spormetaller som kvikksølv.
- Fysisk aktivitet og kosthold. Vi planlegger at utvalgte deltakere vil bli bedt om å registrere fysisk aktivitet (aktivitetsmålere som skritttellere og lignende) og kosthold i en periode.

Blodprøver

Blodet fordeles på fem glass, men til sammen utgjør det ikke mer enn 45 milliliter, som er mindre enn en tidel av det en blodgiver gir. For de aller fleste vil det være tilstrekkelig med ett stikk. Disse analysene blir gjort:

- Måling av kolesterol og andre fettstoffer, blodsukker, blodlegemer, stoffskifteprøver, hormoner, markører for betennelsesreaksjoner, allergi, mage- og tarmfunksjon, lever- og nyrefunksjon samt muskel- og beinmarkører.
- DNA (arvestoff) vil bli lagret til bruk i forskningsprosjekter som er omtalt i denne brosjyren og som kartlegger sammenhengen mellom arv og miljø, sykdom og helse. DNA vil ikke bli brukt til andre formål enn forskning.
- Miljøgifter, blant annet sporstoffer, spormetaller og organiske stoffer. Forekomsten i blodet skal sammenlignes med tilsvarende målinger i andre befolkninger. Forskere vil studere om miljøgifter kan påvirke helsa vår.

Spesialundersøkelsen

Når første del av Tromsøundersøkelsen er gjennomført, kan du bli forespurt om å delta i en eller flere deler av Spesialundersøkelsen noen uker senere. Over halvparten vil bli spurt om dette. Hele Spesialundersøkelsen vil vare cirka en time, og

varigheten vil være avhengig av hvor mange deler du blir spurt om å være med på. Ved oppmøte til Spesialundersøkelsen vil det bli tatt ny blodprøve som skal brukes til samme formål som beskrevet for første del av undersøkelsen. Deler av blodprøven blir frosset ned for senere bruk i forskning som er beskrevet i denne brosjyren.

Hvilke undersøkelser gjøres i Spesialundersøkelsen?

- Ultralyd av blodårene (arteriene) på halsen. Undersøkelsen gjøres for å se etter forkalkninger og innsnevringer av årene. Undersøkelsen kartlegger også blodforsyningen til hjernen.
- Ultralyd av hjertet gjøres for å undersøke hjertets form og funksjon.
- Måling av beintetthet i rygg/hofte og kroppens fettmengde. Målingene brukes til å undersøke risiko for beinskjørhet og brudd, og for studier om sammenhengen mellom kroppsfett, beinmasse og brudd.
- Fotografering av øyebunn. Fotografiet vil vise tilstanden for blodkarene i øyet som også sier noe om blodkarene i kroppen. Ved øyestasjonen tas fotografi av øyebunnen din. Deltagerne får en øyedråpe i hvert øye en tid før fotografering for at pupillene skal utvide seg. Dette kan svi noe og synet kan forbigående bli noe uklart. Effekten går gradvis over, og etter en time er den borte. I tillegg vil det gjøres en enkel synstest som du vil få svar på umiddelbart.
- Tester av hukommelse gjøres ved hjelp av enkle spørsmål og omfatter også evne til gjenkjenning av ord og grad av fingerbevegelighet.
- EKG og blodtrykk. EKG er en registrering av hjerterytmen som også kan gi informasjon om hjertesykdom. Ved registrering festes ledninger til kroppen. Blodtrykket måles både på overarmen og ved ankelen.
- Pusteprøve. Dette er en enkel undersøkelse av lungefunksjonen. Du skal puste så hardt du klarer gjennom et munnstykke. Hvor mye luft som blåses ut pr. sekund, er et mål på lungefunksjonen din.
- Ny bakterieprøve fra nese og hals. Prøven utføres på samme måte som i første del av undersøkelsen.
- Urinprøve. Du vil bli bedt om å avlevere urinprøver fra de tre siste dagene før spesialundersøkelsen. Du gis alt nødvendig utstyr. Urinen blir lagret til bruk i forskning som er beskrevet i denne brosjyren.

For å sikre høy kvalitet på forskningsdata ønsker vi å undersøke et lite utvalg som møter til undersøkelsen to ganger med circa en ukes mellomrom. De som er aktuelle vil bli forespurt om dette ved frammøte.

Nye prosjekter

Noen deltakere vil i ettertid bli spurt om å delta i videre undersøkelser. Hvis dette gjelder deg, vil du få en forespørsel i posten. Du er ikke forpliktet til å delta selv om du har deltatt i andre deler av Tromsøundersøkelsen. Omtale av alle delprosjektene finner du på nettsiden vår:

http://www.tromso6.no

Forsikring og finansiering

Deltakere i Tromsøundersøkelsen er forsikret gjennom Norsk Pasientskadeerstatning.

Tromsøundersøkelsen er finansiert av Universitetet i Tromsø, Helse Nord HF samt ulike forskningsfond.

Etikk, personvern og sikkerhet

Du kan være trygg på at informasjon som gis til Tromsøundersøkelsen vil bli behandlet med respekt for personvern og privatliv, og i samsvar med lover og forskrifter. Alle medarbeidere som jobber med undersøkelsen har taushetsplikt. Opplysningene som samles inn vil bare bli brukt til godkjente forskningsformål.

Alle opplysninger om deltakere vil bli lagret på datamaskin. Navn og personnummer blir fjernet og erstattet med en kode. Kodenøkkelen oppbevares separat og kun noen få, autoriserte medarbeidere har tilgang til denne.

Den enkelte forsker får ikke tilgang til opplysninger som gjør det mulig å identifisere enkeltpersoner. Hver enkelt deltaker har en rett til å vite hvilke opplysninger som er lagret om en selv.

For alle prosjekter kreves det at prosjektlederen tilhører en kompetent forskningsinstitusjon.

Tromsøundersøkelsen har konsesjon fra Datatilsynet og er godkjent av Regional komité for medisinsk forskningsetikk, Nord-Norge.

Sammenstilling med andre registre

Opplysninger om deg fra den sjette Tromsøundersøkelsen kan bli knyttet sammen med opplysninger fra tidligere Tromsøundersøkelser. For enkelte prosjekter kan det være aktuelt å sammenstille opplysninger om deg med opplysninger fra barn, søsken, foreldre og besteforeldre hvis disse har deltatt i Tromsøundersøkelsen.

For spesielle forskningsprosjekter kan det være aktuelt å sammenstille informasjon fra Tromsøundersøkelsen med nasjonale helseregistre som Reseptregisteret, Medisinsk fødselsregistrer, Kreftregisteret, Norsk pasientregister og Dødsårsaksregisteret, og andre nasjonale registre over sykdommer som det forskes på i Tromsøundersøkelsen.

I tillegg kan det være aktuelt å innhente helseopplysninger fra primær- og spesialisthelsetjenesten til bruk i forskning på sykdommer og helseproblemer som er nevnt i denne brosjyren, for eksempel hjerte-karsykdom, diabetes og beinbrudd. I slike tilfeller innhentes nytt samtykke, eller annen type godkjenning (dispensasjon fra taushetsplikten).

Informasjon fra Tromsøundersøkelsen kan også bli sammenstilt med registre ved Statistisk sentralbyrå, for eksempel om miljø, befolkning, utdanning, inntekt, offentlige ytelser, yrkesdeltakelse og andre forhold som kan ha betydning for helsa.

Slike sammenstillinger krever noen ganger forhåndsgodkjenning av offentlige instanser, for eksempel Regional komité for medisinsk forskningsetikk, Datatilsynet eller NAV.

Bruk av innsamlede data i framtiden

Data fra Tromsøundersøkelsen vil kun bli brukt til forskning og vil ikke kunne brukes til andre formål.

Opplysninger og prøver som du gir, blir oppbevart på ubestemt tid til bruk i forskning til formål som nevnt i denne brosjyren. I noen tilfeller kan det bli aktuelt å gjøre analyser av blodprøver ved forskningsinstitusjoner i utlandet. Hvis dette gjøres, vil det skje i en slik form at våre utenlandske samarbeidspartnere ikke kan knytte prøvene opp mot deg som person.

Hva som er aktuelle problemstillinger i medisinsk forskning forandrer seg hele tiden. I framtiden kan data bli brukt i forskningsprosjekter som i dag ikke er planlagt, forutsatt at det er i samsvar med gjeldende lover og forskrifter. For alle slike nye prosjekter kreves det at prosjektet er godkjent av Regional komité for medisinsk forskningsetikk og Datatilsynet.

Tromsøundersøkelsen informerer om nye forskningsprosjekter på: http://www.tromso6.no
Her kan du også lese om forskningsresultatene fra Tromsøundersøkelsen. Forskningsresultater vil ellers bli publisert i internasjonale og nasjonale tidsskrifter, på faglige konferanser og møter. Det vil ikke være mulig å identifisere enkeltpersoner når forskningsresultatene offentliggjøres.

Samtykke

Hvis du vil delta i den sjette Tromsøundersøkelsen, må du gi skriftlig samtykke til dette. Personalet på Tromsøundersøkelsen vil kunne gi mer informasjon om undersøkelsen, og kan svare deg dersom du har spørsmål i forbindelse med samtykket.

Det er viktig å vite at selv om du sier ja til dette nå, kan du senere ombestemme deg. Du kan når som helst etter undersøkelsen trekke ditt samtykke tilbake. Allerede innsamlede data blir lagret videre, men kan ikke lenger knyttes til deg som person, og dine data vil ikke bli brukt i nye forskningsprosjekter. Du kan be om at blodprøven din blir ødelagt.

Hvis du vil trekke tilbake ditt samtykke, henvend deg til:

Tromsøundersøkelsen, Inst. for samfunnsmedisin
Universitetet i Tromsø
9037 Tromsø
telefon: 77 64 48 16
telefaks: 77 64 48 31
e-post: tromsous@ism.uit.no
internett: www.tromso6.no

Hvis vi i framtiden ønsker å forske på nye spørsmål som ikke er beskrevet i denne brosjyren, kan det bli nødvendig å be deg om et nytt samtykke.

Vil du delta?

Følgende tekst er en kopi av dokumentet du blir bedt om å signere når du møter fram til undersøkelsen:

Samtykke til bruk av helseopplysninger i forskning - den 6. Tromsøundersøkelsen

I brosjyren jeg har fått tilsendt, har jeg lest om undersøkelsens innhold og formål, og jeg har hatt mulighet til å stille spørsmål. Jeg samtykker herved i å delta i undersøkelsen [dato/signatur].

Tromsø-
undersøkelsen

Tromsøundersøkelsen
Institutt for samfunnsmedisin, Universitetet i Tromsø
9037 TROMSØ
telefon: 77 64 48 16
telefaks: 77 64 48 31
epost: tromsous@ism.uit.no
internett: www.tromso6.no

www.GnistDesign.no

Appendix C

Information about Tromsø7 for participants [Norwegian]

UiT

NORGES
ARKTISKE
UNIVERSITET

Vil du være med i **Tromsøundersøkelsen?**

UNIVERSITETET I TROMSØ

Forespørsel om deltakelse i Tromsøundersøkelsen

Hva er Tromsøundersøkelsen?

Tromsøundersøkelsen er en folkehelseundersøkelse. Formålet er å samle inn opplysninger til forskning som gir økt kunnskap om helse og sykdom, og hvordan folkehelsen kan forbedres gjennom forebygging og behandling.

Tromsøundersøkelsen startet i 1974 med bakgrunn i den høye forekomsten av hjerte -og karsykdom i Nord-Norge. Siden den gang er undersøkelsen gjennomført med 6-7 års mellomrom og dette er den sjuende runden.

Ved å delta bidrar du til viktig forskning om forekomst, forebygging og behandling av sykdom, hva som fremmer god helse, og hva som er årsak til helseproblemer.

Ditt bidrag teller!

Hvorfor spør vi deg?

Alle innbyggere i Tromsø kommune fra 40 år og oppover spørres om å delta. I tillegg inviterer vi ca.1000 personer i alderen 21-25 år. Hver deltaker er like viktig, enten du er ung eller gammel, frisk eller syk.

Sammen med denne informasjonsbrosjyren finner du en invitasjon med praktiske opplysninger om undersøkelsen.

Det er gratis å delta i Tromsøundersøkelsen. Trenger du videre undersøkelse eller oppfølging av fastlegen eller spesialisthelsetjenesten, betaler du vanlig egenandel.

Slik foregår undersøkelsen

Alle deltakere inviteres til en hovedundersøkelse som omfatter spørreskjema, intervju, blodprøver og undersøkelser. Et helt tilfeldig utvalg av deltakere inviteres tilbake til en spesialundersøkelse som omfatter flere prøver og mer omfattende undersøkelser. Alle undersøkelsene gjennomføres av helsepersonell.

Tilbakemelding

Noen uker etter undersøkelsen får du et brev med noen resultater, det vil si høyde, vekt, BMI, hemoglobin, blodtrykk, kolesterolnivå og om du har diabetes. Det gis ikke rutinemessig tilbakemelding om resultater av andre blodprøver eller målinger. Dersom prøveresultatet viser at det er nødvendig med oppfølging av lege eller henvisning til spesialist, vil du få råd om det. Ved behov for henvisning til spesialist, sørger vi for å sende henvisning.

Du kan reservere deg mot å få vite resultatene av prøvene dine. Men hvis et prøveresultat krever rask legebehandling, vil du likevel bli kontaktet.

Du vil også få informasjon om undersøkelsen underveis gjennom aviser, sosiale medier (Facebook, Twitter m.m) samt på arrangementer som "Lørdagsuniversitetet" og "Forskningsdagene".

Frivillig deltakelse

Det er frivillig å delta i Tromsøundersøkelsen.
Om du sier ja til å delta, kan du når som helst trekke tilbake samtykket.

Hva omfatter den sjuende Tromsøundersøkelsen?

Hva skal vi forske på?

I denne runden av Tromsøundersøkelsen er det mer enn 50 prosjekter som skal forske på forekomst, forebygging og behandling av folkehelseproblemer.

Det skal blant annet forskes på hjerte- og karsykdommer, kreft, lunge-sykdommer, aldring og demens, fedme, diabetes, legemiddelbruk, psykisk helse, kronisk smerte, tannhelse, muskel- og skjelettplager, risikofaktorer som alkohol, fysisk aktivitet og kosthold, nyrer og urinveier, hudproblemer, miljøgifter, infeksjoner og antibiotikaresistens, nervesystemet, sosial ulikhet, samspill mellom arv og miljø, søvn og bruk av helsetjenester.

Du finner mer informasjon om forskningen på vår internettside, www.tromsoundersokelsen.no

Spørreskjema

Deltakernes informasjon om egen helse er en svært viktig del av Tromsø-undersøkelsen. Vi ber deg derfor fylle ut to spørreskjema. Alle spørsmål kan besvares på nett. Det ene skjemaet er vedlagt i papirform, hvis du foretrekker det. Fyll det gjerne ut før du møter opp så sparer du tid under undersøkelsen. Hvis du trenger assistanse vil personalet hjelpe deg på undersøkelsen hvor det også er satt opp egne datamaskiner til dette.

Utfylte svar i spørreskjema er like viktig for forskningen som resultater fra blodprøver og kliniske undersøkelser.

Du kan delta på Tromsøundersøkelsen selv om du ikke ønsker å være med på alle deler av undersøkelsen.

Hovedundersøkelsen

Helsepersonell veileder deg gjennom undersøkelsen som varer ca. en time hvis du har fylt ut spørreskjemaene på forhånd. Du får også time til spesialundersøkelsen hvis du er valgt ut til denne.

Vi starter med noen enkle spørsmål knyttet til undersøkelsene du skal gjennomføre. Videre måler vi høyde, vekt, hofte- og livvidde, blodtrykk og puls.

Det tas deretter prøver og gjøres noen kliniske undersøkelser:

Blodprøve. Det tas blodprøver til bruk for forskning som samlet er mye mindre enn det en blodgiver gir. Det fryses ned prøver til bruk for senere analyser og forskning. Arvestoff (DNA/RNA) vil bli lagret til bruk for forskning.

Bakterieprøve fra nese og hals for å se etter gule stafylokokker, en bakterie som normalt finnes på hud og slimhinner hos mennesker, men som i enkelte tilfeller kan forårsake alvorlige infeksjoner. Prøvene tas med en fuktet vattpensel.

Spyttprøver til bruk for forskning knyttet til tannhelse, virusinfeksjon og kreft.

Smerteølsomhet måles med to metoder. Først holder du hånden i kaldt vann i opptil 90 sekunder,deretter får du en blodtrykksmansjett plassert rundt leggen som blåses opp. Underveis angir du hvor mye smerte du opplever, og kan avbryte testene når som helst hvis det blir for ubehagelig.

Tannsjekk som omfatter et røntgenbilde av kjeven, registrering av hull i tennene og betennelsessykdom i tannkjøttet.

Fysisk aktivitet og kosthold. Utvalgte deltakere blir bedt om å registrere fysisk aktivitet ved bruk av aktivitetsmåler og registrering av kosthold i en periode.

Du får også utdelt utstyr for innlevering av urin- og avføringsprøve hvis du er valgt ut til spesialundersøkelsen.

Spesialundersøkelsen

Et tilfeldig utvalg av deltakere inviteres til spesialundersøkelsen som gjennomføres noen uker etter hovedundersøkelsen. Denne varer totalt ca. 2 timer, avhengig av hvor mange deler du blir spurt om å være med på.

Ved oppmøte vil urinprøvene samles inn, og det tas noen nye blodprøver. Deler av blodprøvene fryses ned for senere forskning beskrevet i denne brosjyren.

Videre inviteres du til én eller flere av disse undersøkelsene:

EKG er en registrering av hjerterytmen som også kan gi informasjon om hjertesykdom. Ved registrering festes ledninger til kroppen.

Kognitiv funksjon testes ved hjelp av enkle spørsmål knyttet til gjenkjenning av ord, kopling av symboler og tall samt grad av fingerbevegelighet.

Fysisk funksjon undersøkes ved å teste balanse, gange og gripestyrke.

Ultralyd av halspulsåre gjøres for å se etter forkalkninger og innsnevringer av årene. Undersøkelsen kartlegger også blodforsyningen til hjernen.

Fotografering av øyebunnen gir bilder som både sier noe om synet og om tilstanden til blodkarene i kroppen. Det gis en øyendråpe i hvert øye en tid før fotografering for at pupillene skal utvide seg. Dette kan svi noe og synet kan forbigående bli noe uklart. Effekten går gradvis over, og er borte etter en time. I tillegg gjøres det en enkel synstest som du får svar på umiddelbart.

Lungefunksjonen testes ved at du puster så hardt du klarer gjennom et munnstykke. Hvor mye luft som blåses ut pr. sekund, er et mål på lungefunksjonen din. I tillegg vil det gjøres lydopptak av lungelyder og hjertelyder.

Måling av beintetthet. Ved hjelp av ultralyd foretas det beintetthetsmåling som brukes til å undersøke risiko for beinskjørhet og brudd.

Ultralyd av hjertet gjøres for å undersøke hjertets form og funksjon.

Videre bruk av opplysninger og prøver i forskning

Personvern

All informasjon du gir til Tromsøundersøkelsen behandles med respekt for personvern og privatliv, og i samsvar med lover og forskrifter.
Alle medarbeidere som jobber med undersøkelsen har taushetsplikt. Opplysningene som samles inn skal bare brukes til godkjente forskningsformål. Det vil ikke være mulig å identifisere deg når resultatene av forskningen publiseres.

UiT Norges arktiske universitet ved universitetsdirektøren er ansvarlig for behandlingen av personopplysninger. Tromsøundersøkelsen har konsesjon fra Datatilsynet. Regional komité for medisinsk og helsefaglig forskningsetikk i Nord-Norge (REK nord) har gjort en etisk og helsefaglig vurdering av undersøkelsene som gjennomføres, samt godkjent innsamlingen av prøver.

Hvilke data lagres i Tromsøundersøkelsen?

I Tromsøundersøkelsen lagres opplysninger gitt av deltakere i de forskjellige rundene av Tromsøundersøkelsen. Det lagres også opplysninger om kreftdiagnoser og dødsårsaker fra Kreftregisteret og Dødsårsaksregisteret.
For deltakere som har eller får diagnoser innen hjerte- og karsykdom, diabetes og beinbrudd, innhentes opplysninger fra sykejournalen i spesialist- og primærhelsetjenesten som er nødvendig for å kvalitetssikre aktuelle diagnoser. Dette for å sikre forskning av høy kvalitet. Tilsvarende vil også kunne bli aktuelt for andre sykdommer det forskes på i Tromsøundersøkelsen.

Hvordan lagres dine opplysninger og prøver?

Alle opplysningene og prøvene lagres uten navn og fødselsnummer.

En kode knytter deg til dine opplysninger og prøver. Det er kun noen få autoriserte personer som kan finne tilbake til deg gjennom en egen kodenøkkel.

De biologiske prøvene lagres i godkjent forskningsbiobank ved Institutt for samfunnsmedisin, UiT. Leder av Tromsøundersøkelsen er ansvarlig for biobanken. Den er registrert i Folkehelseinstituttets Biobankregister (nr 2397). Det biologiske materialet kan bare brukes etter godkjenning fra REK.

Utlevering av opplysninger og prøver til forskere

Hvis du sier ja til å delta i studien, samtykker du til at dine opplysninger og prøver kan brukes videre i forskning på ubestemt tid. Medisinsk forskning forandrer seg hele tiden, og i fremtiden kan data bli brukt i forskningsprosjekter forutsatt at det er i samsvar med gjeldende lover og forskrifter.

Alle forskningsprosjekter som får data fra Tromsøundersøkelsen må være i samsvar med lover og forskrifter. Prosjektleder må tilhøre en kompetent forskningsinstitusjon. Den enkelte forsker vil kun få tilgang til personidentifiserende opplysninger etter å ha innhentet nødvendige godkjenninger fra REK, og/eller Datatilsynet.

I noen forskningsprosjekter kan prøver og avidentifiserte opplysninger bli utlevert til andre land. Det vil skje i en slik form at våre utenlandske samarbeidspartnere ikke kan knytte prøvene opp mot deg som person.

I noen prosjekter kan det bli aktuelt å kontakte deg igjen for å samle inn flere data, f.eks. ved spørreskjema, intervju eller kliniske undersøkelser. Du vil da få ny informasjon og bes om nytt samtykke til det konkrete prosjektet.

Ved å delta i Tromsøundersøkelsen bidrar du til viktig forskning på sykdom og helse, oppbygging av fagmiljøer og bedre pasientbehandling.

Sammenstilling med andre registre

I noen forskningsprosjekter vil opplysninger om deg kunne bli sammenstilt med:

Opplysninger du har gitt i tidligere runder av Tromsøundersøkelsen hvis du har deltatt i Tromsøundersøkelsen før.

Opplysninger fra barn, søsken, foreldre og besteforeldre som har deltatt i Tromsøundersøkelsen.

Opplysninger om deg i nasjonale helseregistre som Reseptregisteret, Medisinsk fødselsregister, Kreftregisteret, Norsk pasientregister, Hjerte- og karregisteret, Dødsårsaksregisteret, infeksjonsregistre og andre nasjonale sykdoms- og kvalitetsregistre.

Helseopplysninger om deg fra primær- og spesialisthelsetjenesten.

Opplysninger om sosiale forhold som arbeid, utdanning, inntekt, boforhold osv. fra registre hos bl.a. Statistisk sentralbyrå og NAV.

Slike sammenstillinger krever som regel forhåndsgodkjenning av offentlige instanser, som REK og/eller Datatilsynet.

Rett til innsyn og sletting av dine opplysninger og prøver

Hvis du sier ja til å delta i studien, har du rett til å få innsyn i hvilke opplysninger som er registrert om deg. Du har også rett til å få korrigert eventuelle feil i opplysningene vi har registrert. Dersom du trekker deg fra studien, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller er brukt i vitenskapelige artikler.

Finansiering

Tromsøundersøkelsen er finansiert av UiT Norges arktiske universitet, Helse Nord RHF, Universitetssykehuset Nord-Norge (UNN) samt ulike forskningsfond.

Forsikring

Deltakere i Tromsøundersøkelsen er forsikret gjennom Norsk Pasientskadeerstatning.

Samtykke til deltakelse i studien

Hvis du vil delta i den sjuende Tromsøundersøkelsen, må du gi skriftlig samtykke ved oppmøte. Personalet vil gi mer informasjon og svare deg dersom du har spørsmål i forbindelse med samtykket.

Du kan når som helst trekke tilbake samtykket ditt.

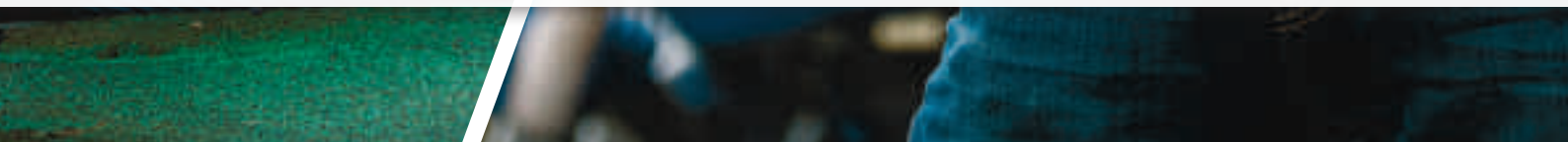
Her finner du oss:

Heiloveien 6 (tidligere Langnes legesenter)
9015 Tromsø

Telefon 77 62 07 00
Epost tromso7@uit.no
Nettside www.tromsoundersokelsen.no

Tromsø-undersøkelsen

UNIVERSITETET I TROMSØ



Appendix D

Consent form Tromsø6, for participants [Norwegian]

Samtykke til bruk av helseopplysninger i forskning, den 6. Tromsøundersøkelsen

I brosjyren jeg har fått tilsendt, har jeg lest om undersøkelsens innhold og formål, og jeg har hatt mulighet til å stille spørsmål. Jeg samtykker herved i å delta i undersøkelsen.

Dato:_____Signatur:_____

Appendix E

Consent form Tromsø7, for participants [Norwegian]

UiT
NORGES
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UNIVERSITET

Tromsø-
undersøkelsen

Samtykke til bruk av helseopplysninger i forskning –
den 7. Tromsøundersøkelsen.

I brosjyren jeg har fått tilsendt har jeg lest om undersøkelsens formål og innhold, og jeg har hatt mulighet til å stille spørsmål om samtykket ved oppmøtet.

Jeg samtykker herved i å delta i undersøkelsen.

Dato:_____Signatur:_____

UNIVERSITETET I TROMSØ

Appendix F

The first questionnaire (Q1) in the Tromsø study: Tromsø6 [Norwegian]

Tromsø-undersøkelsen

Skjemaet skal leses optisk. Vennligst bruk blå eller sort penn. Du kan ikke bruke komma, bruk blokkbokstaver.

2007 – 2008 KONFIDENSIELT

HELSE OG SYKDOMMER

1 **Hvordan vurderer du din egen helse sånn i alminnelighet?**

- ☐ Meget god
- ☐ God
- ☐ Verken god eller dårlig
- ☐ Dårlig
- ☐ Meget dårlig

2 **Hvordan synes du at helsen din er sammenlignet med andre på din alder?**

- ☐ Mye bedre
- ☐ Litt bedre
- ☐ Omtrent lik
- ☐ Litt dårligere
- ☐ Mye dårligere

3 **Har du eller har du hatt?**

	Ja	Nei	Alder første gang
Hjerteinfarkt	☐	☐	
Angina pectoris *(hjertekrampe)*	☐	☐	
Hjerneslag/hjerneblødning	☐	☐	
Hjerteflimmer *(atrieflimmer)*	☐	☐	
Høyt blodtrykk	☐	☐	
Beinskjørhet *(osteoporose)*	☐	☐	
Astma	☐	☐	
Kronisk bronkitt/emfysem/KOLS	☐	☐	
Diabetes	☐	☐	
Psykiske plager *(som du har søkt hjelp for)*	☐	☐	
Lavt stoffskifte	☐	☐	
Nyresykdom, unntatt urinveisinfeksjon	☐	☐	
Migrene	☐	☐	

4 **Har du langvarige eller stadig tilbakevendende smerter som har vart i 3 måneder eller mer?**

☐ Ja ☐ Nei

5 **Hvor ofte har du vært plaget av søvnløshet de siste 12 måneder?**

- ☐ Aldri, eller noen få ganger
- ☐ 1-3 ganger i måneden
- ☐ Omtrent 1 gang i uken
- ☐ Mer enn 1 gang i uken

6 **Under finner du en liste over ulike problemer. Har du opplevd noe av dette den siste uken (til og med i dag)?** (Sett ett kryss for hver plage)

	Ikke plaget	Litt plaget	Ganske mye	Veldig mye
Plutselig frykt uten grunn	☐	☐	☐	☐
Føler deg redd eller engstelig	☐	☐	☐	☐
Matthet eller svimmelhet	☐	☐	☐	☐
Føler deg anspent eller oppjaget	☐	☐	☐	☐
Lett for å klandre deg selv	☐	☐	☐	☐
Søvnproblemer	☐	☐	☐	☐
Nedtrykt, tungsindig	☐	☐	☐	☐
Følelse av å være unyttig, lite verd	☐	☐	☐	☐
Følelse av at alt er et slit	☐	☐	☐	☐
Følelse av håpløshet mht. framtida	☐	☐	☐	☐

BRUK AV HELSETJENESTER

7 **Har du i løpet av de siste 12 måneder vært hos:** Hvis JA; Hvor mange ganger?

	Ja	Nei	Ant ggr
Fastlege/allmennlege	☐	☐	
Psykiater/psykolog	☐	☐	
Legespesialist utenfor sykehus *(utenom fastlege/allmennlege/psykiater)*	☐	☐	
Fysioterapeut	☐	☐	
Kiropraktor	☐	☐	
Annen behandler *(homøopat, akupunktør, fotsoneterapeut, naturmedisiner, håndspålegger, healer, synsk el.l)*	☐	☐	
Tannlege/tannpleier	☐	☐	

8 **Har du i løpet av de siste 12 måneder vært på sykehus?**

	Ja	Nei	Ant ggr
Innlagt på sykehus	☐	☐	
Konsultasjon ved sykehus uten innleggelse;			
Ved psykiatrisk poliklinikk	☐	☐	
Ved annen sykehuspoliklinikk	☐	☐	

9 **Har du gjennomgått noen form for operasjon i løpet av de siste 3 årene?**

☐ Ja ☐ Nei

BRUK AV MEDISINER

10 **Bruker du, eller har du brukt, noen av følgende medisiner?** (Sett ett kryss for hver linje)

	Aldri brukt	Nå	Før	Alder første gang
Medisin mot høyt blodtrykk	☐	☐	☐	
Kolesterolsenkende medisin	☐	☐	☐	
Medisin mot hjertesykdom	☐	☐	☐	
Vanndrivende medisin	☐	☐	☐	
Medisin mot beinskjørhet *(osteoporose)*	☐	☐	☐	
Insulin	☐	☐	☐	
Diabetesmedisin *(tabletter)*	☐	☐	☐	
Stoffskiftemedisinene Thyroxin/levaxin	☐	☐	☐	

11 **Hvor ofte har du i løpet av de siste 4 ukene brukt følgende medisiner?** (Sett ett kryss pr linje)

	Ikke brukt siste 4 uker	Sjeldnere enn hver uke	Hver uke, men ikke daglig	Daglig
Smertestillende på resept	☐	☐	☐	☐
Smertestillende reseptfrie	☐	☐	☐	☐
Sovemidler	☐	☐	☐	☐
Beroligende medisiner	☐	☐	☐	☐
Medisin mot depresjon	☐	☐	☐	☐

12 **Skriv ned alle medisiner – både de med og uten resept – som du har brukt regelmessig i siste 4 ukers periode.** (Ikke regn med vitaminer, mineraler, urter, naturmedisin, andre kosttilskudd etc.)

Får du ikke plass til alle medisiner, bruk eget ark.

VED FRAMMØTE vil du bli spurt om du har brukt antibiotika eller smertestillende medisiner de siste 24 timene. Om du har det, vil vi be om at du oppgir preparat, styrke, dose og tidspunkt

FAMILIE OG VENNER

13 **Hvem bor du sammen med?** (Sett kryss for hvert spørsmål og angi antall)

	Ja	Nei	Antall
Ektefelle/samboer	☐	☐	
Andre personer over 18 år	☐	☐	
Personer under 18 år	☐	☐	

14 **Kryss av for de slektninger som har eller har hatt**

	Foreldre	Barn	Søsken
Hjerteinfarkt	☐	☐	☐
Hjerteinfarkt før fylte 60 år	☐	☐	☐
Angina pectoris *(hjertekrampe)*	☐	☐	☐
Hjerneslag/hjerneblødning	☐	☐	☐
Beinskjørhet *(osteoporose)*	☐	☐	☐
Magesår/tolvfingertarmsår	☐	☐	☐
Astma	☐	☐	☐
Diabetes	☐	☐	☐
Demens	☐	☐	☐
Psykiske plager	☐	☐	☐
Rusproblemer	☐	☐	☐

15 **Har du nok venner som kan gi deg hjelp når du trenger det?**

☐ Ja ☐ Nei

16 **Har du nok venner som du kan snakke fortrolig med?**

☐ Ja ☐ Nei

17 **Hvor ofte tar du vanligvis del i foreningsvirksomhet som for eksempel syklubb, idrettslag, politiske lag, religiøse eller andre foreninger?**

☐ Aldri, eller noen få ganger i året
☐ 1-2 ganger i måneden
☐ Omtrent 1 gang i uken
☐ Mer enn en gang i uken

ARBEID, TRYGD OG INNTEKT

18 **Hva er din høyeste fullførte utdanning?** (Sett ett kryss)

☐ Grunnskole, framhaldsskole eller folkehøyskole
☐ Yrkesfaglig videregående, yrkesskole eller realskole
☐ Allmennfaglig videregående skole eller gymnas
☐ Høyskole eller universitet, mindre enn 4 år
☐ Høyskole eller universitet, 4 år eller mer

19 **Hva er din hovedaktivitet?** (Sett ett kryss)

☐ Yrkesaktiv heltid
☐ Yrkesaktiv deltid
☐ Arbeidsledig
☐ Hjemmeværende
☐ Pensjonist/trygdet
☐ Student/militærtjeneste

20 **Mottar du noen av følgende ytelser?**

- ☐ Alderstrygd, førtidspensjon (AFP) eller etterlattepensjon
- ☐ Sykepenger (er sykemeldt)
- ☐ Rehabiliterings-/attføringspenger
- ☐ Uføreytelse/pensjon, hel
- ☐ Uføreytelse/pensjon, delvis
- ☐ Dagpenger under arbeidsledighet
- ☐ Overgangstønad
- ☐ Sosialhjelp/-stønad

21 **Hvor høy var husholdningens samlede bruttoinntekt siste år?** Ta med alle inntekter fra arbeid, trygder, sosialhjelp og lignende.

- ☐ Under 125 000 kr
- ☐ 125 000-200 000 kr
- ☐ 201 000-300 000 kr
- ☐ 301 000-400 000 kr
- ☐ 401 000-550 000 kr
- ☐ 551 000-700 000 kr
- ☐ 701 000 -850 000 kr
- ☐ Over 850 000 kr

22 **Arbeider du utendørs minst 25 % av tiden, eller i lokaler med lav temperatur, som for eksempel lager-/industrihaller?**

- ☐ Ja
- ☐ Nei

FYSISK AKTIVITET

23 **Hvis du er i lønnet eller ulønnet arbeid, hvordan vil du beskrive arbeidet ditt?**

- ☐ For det meste stillesittende arbeid *(f.eks. skrivebordsarbeid, montering)*
- ☐ Arbeid som krever at du går mye *(f.eks ekspeditørarbeid, lett industriarbeid, undervisning)*
- ☐ Arbeid der du går og løfter mye *(f.eks postbud, pleier, bygningsarbeider)*
- ☐ Tungt kroppsarbeid

24 **Angi bevegelse og kroppslig anstrengelse i din fritid. Hvis aktiviteten varierer meget f eks mellom sommer og vinter, så ta et gjennomsnitt. Spørsmålet gjelder bare det siste året.** (Sett kryss i den ruta som passer best)

- ☐ Leser, ser på fjernsyn eller annen stillesittende beskjeftigelse
- ☐ Spaserer, sykler eller beveger deg på annen måte minst 4 timer i uken *(her skal du også regne med gang eller sykling til arbeidsstedet, søndagsturer med mer)*
- ☐ Driver mosjonsidrett, tyngre hagearbeid, snømåking e.l. *(merk at aktiviteten skal vare minst 4 timer i uka)*
- ☐ Trener hardt eller driver konkurranseidrett regelmessig og flere ganger i uka

25 **Hvor ofte driver du mosjon?** (Med mosjon mener vi at du f.eks går en tur, går på ski, svømmer eller driver trening/idrett)

- ☐ Aldri
- ☐ Sjeldnere enn en gang i uken
- ☐ En gang i uken
- ☐ 2-3 ganger i uken
- ☐ omtrent hver dag

26 **Hvor hardt mosjonerer du da i gjennomsnitt?**

- ☐ Tar det rolig uten å bli andpusten eller svett.
- ☐ Tar det så hardt at jeg blir andpusten og svett
- ☐ Tar meg nesten helt ut

27 **Hvor lenge holder du på hver gang i gjennomsnitt ?**

- ☐ Mindre enn 15 minutter
- ☐ 15-29 minutter
- ☐ 30 minutter – 1 time
- ☐ Mer enn 1 time

ALKOHOL OG TOBAKK

28 **Hvor ofte drikker du alkohol?**

- ☐ Aldri
- ☐ Månedlig eller sjeldnere
- ☐ 2-4 ganger hver måned
- ☐ 2-3 ganger pr. uke
- ☐ 4 eller flere ganger pr.uke

29 **Hvor mange enheter alkohol** (en øl, et glass vin, eller en drink) **tar du vanligvis når du drikker?**

- ☐ 1-2
- ☐ 3-4
- ☐ 5-6
- ☐ 7-9
- ☐ 10 eller flere

30 **Hvor ofte drikker du 6 eller flere enheter alkohol ved en anledning?**

- ☐ aldri
- ☐ sjeldnere enn månedlig
- ☐ månedlig
- ☐ ukentlig
- ☐ daglig eller nesten daglig

31 **Røyker du av og til, men ikke daglig?**

- ☐ Ja
- ☐ Nei

32 **Har du røykt/røyker du daglig?**

- ☐ Ja, nå
- ☐ Ja, tidligere
- ☐ Aldri

33 **Hvis du har røykt daglig tidligere, hvor lenge er det siden du sluttet?**

Antall år ☐☐

34 **Hvis du røyker daglig nå eller har røykt tidligere: Hvor mange sigaretter røyker eller røykte du vanligvis daglig?**

Antall sigaretter ☐☐

35 **Hvor gammel var du da du begynte å røyke daglig?**

Antall år ☐☐

36 **Hvor mange år til sammen har du røykt daglig?**

Antall år ☐☐

37 **Bruker du, eller har du brukt, snus eller skrå?**

- ☐ Nei, aldri
- ☐ Ja, men jeg har sluttet
- ☐ Ja, av og til
- ☐ Ja, daglig

KOSTHOLD

38 **Spiser du vanligvis frokost hver dag?**

☐ Ja ☐ Nei

39 **Hvor mange enheter frukt og grønnsaker spiser du i gjennomsnitt per dag?** (Med enhet menes f.eks. en frukt, glass juice, potet, porsjon grønnsaker)

Antall enheter ☐☐

40 **Hvor mange ganger i uken spiser du varm middag?**

Antall ☐☐

41 **Hvor ofte spiser du vanligvis disse matvarene?**
(Sett ett kryss pr linje)

	0-1 g pr. mnd	2-3 g pr.mnd	1-3 g pr.uke	4-6 g pr.uke	1-2 g pr. dag
Poteter	☐	☐	☐	☐	☐
Pasta/ris	☐	☐	☐	☐	☐
Kjøtt *(ikke kvernet)*	☐	☐	☐	☐	☐
Kvernet kjøtt *(pølser, hamburger o.l)*	☐	☐	☐	☐	☐
Grønnsaker, frukt, bær	☐	☐	☐	☐	☐
Mager fisk	☐	☐	☐	☐	☐
Feit fisk *(f.eks.laks, ørret, makrell, sild, kveite,uer)*	☐	☐	☐	☐	☐

42 **Hvor mye drikker du vanligvis av følgende?**
(Sett ett kryss pr. linje)

	Sjelden/ aldri	1-6 glass pr. uke	1 glass pr. dag	2-3 glass pr. dag	4 glass el. mer pr. dag
Melk, kefir, yoghurt	☐	☐	☐	☐	☐
Fruktjuice	☐	☐	☐	☐	☐
Brus/leskedrikker med sukker	☐	☐	☐	☐	☐

43 **Hvor mange kopper kaffe og te drikker du daglig?**
(sett 0 for de typene du ikke drikker daglig)

	Antall kopper
Filterkaffe	☐☐
Kokekaffe/presskanne	☐☐
Annen kaffe	☐☐
Te	☐☐

44 **Hvor ofte spiser du vanligvis fiskelever?**
(For eksempel i mølje)

☐ Sjelden/aldri ☐ 1-3 g i året ☐ 4-6 g i året
☐ 7-12 g i året ☐ Oftere

45 **Bruker du følgende kosttilskudd?**

	Daglig	Iblant	Nei
Tran, trankapsler	☐	☐	☐
Omega 3 kapsler *(fiskeolje,selolje)*	☐	☐	☐
Kalktabletter	☐	☐	☐

SPØRSMÅL TIL KVINNER

46 **Er du gravid nå?**

☐ Ja ☐ Nei ☐ Usikker

47 **Hvor mange barn har du født?**

Antall ☐☐

48 **Hvis du har født, fyll ut for hvert barn: fødselsår og vekt samt hvor mange måneder du ammet.**
(Angi så godt som du kan)

Barn	Fødselsår	Fødselsvekt i gram	Ammet ant.mnd
1	☐☐☐☐	☐☐☐☐	☐☐
2	☐☐☐☐	☐☐☐☐	☐☐
3	☐☐☐☐	☐☐☐☐	☐☐
4	☐☐☐☐	☐☐☐☐	☐☐
5	☐☐☐☐	☐☐☐☐	☐☐
6	☐☐☐☐	☐☐☐☐	☐☐

49 **Har du i forbindelse med svangerskap hatt for høyt blodtrykk?**

☐ Ja ☐ Nei

50 **Hvis Ja, i hvilket svangerskap?**

☐ Første ☐ Senere

51 **Har du i forbindelse med svangerskap hatt protein (eggehvite) i urinen?**

☐ Ja ☐ Nei

52 **Hvis Ja, i hvilket svangerskap?**

☐ Første ☐ Senere

53 **Ble noen av disse barna født mer enn en måned for tidlig (før termin) pga. svangerskapsforgiftning?**

☐ Ja ☐ Nei

54 **Hvis Ja, hvilke(t) barn**

Barn 1	Barn 2	Barn 3	Barn 4	Barn 5	Barn 6
☐	☐	☐	☐	☐	☐

55 **Hvor gammel var du da du fikk menstruasjon første gang?**

Antall år ☐☐

56 **Bruker du for tiden reseptpliktige legemidler som påvirker menstruasjonen?**

P-pille, hormonspiral eller lignende ☐ Ja ☐ Nei
Hormonpreparat for overgangs-alderen ☐ Ja ☐ Nei

VED FRAMMØTE vil du få utfyllende spørsmål om menstruasjon og eventuell bruk av hormoner. Skriv gjerne ned på et papir navn på hormonpreparater du har brukt, og ta det med deg. Du vil også bli spurt om din menstruasjon har opphørt og eventuelt når og hvorfor.

LUNDBLAD MEDIA AS, TROMSØ, 77 75 32 50 - ONR 082222

Appendix G

The second questionnaire (Q2) in the Tromsø study: Tromsø6 [Norwegian]
Available at: https://uit.no/Content/531228/cache=20172908084211/Questionnaire_T6_2.pdf

Appendix H

The first questionnaire (Q1) in the Tromsø study: Tromsø7 [Norwegian]

Tromsø-undersøkelsen
2015–2016

KONFIDENSIELT

Skjemaet skal leses optisk. Vennligst bruk blå eller sort penn. Bruk blokkbokstaver. Du kan ikke bruke komma.

Dato for utfylling: ☐☐☐☐☐☐

HELSE OG SYKDOMMER

1.1 Hvordan vurderer du din egen helse sånn i alminnelighet?

Meget god	God	Verken god eller dårlig	Dårlig	Meget dårlig
☐	☐	☐	☐	☐

1.2 Hvordan synes du at helsen din er sammenlignet med andre på din alder?

Mye bedre	Litt bedre	Omtrent lik	Litt dårligere	Mye dårligere
☐	☐	☐	☐	☐

1.3 Har du eller har du hatt?
Sett ett kryss per linje.

	Nei	Ja nå	Før, ikke nå	Alder første gang
Høyt blodtrykk	☐	☐	☐	☐☐
Hjerteinfarkt	☐		☐	☐☐
Hjertesvikt	☐	☐	☐	☐☐
Atrieflimmer *(hjerteflimmer)*	☐	☐	☐	☐☐
Angina pectoris *(hjertekrampe)*	☐	☐	☐	☐☐
Hjerneslag/hjerneblødning	☐		☐	☐☐
Diabetes	☐	☐	☐	☐☐
Nyresykdom *(unntatt urinveisinfeksjon)*	☐	☐	☐	☐☐
Kronisk bronkitt/emfysem/KOLS	☐	☐	☐	☐☐
Astma	☐	☐	☐	☐☐
Kreft	☐	☐	☐	☐☐
Revmatoid artritt *(leddgikt)*	☐	☐	☐	☐☐
Artrose *(slitasjegikt)*	☐	☐	☐	☐☐
Migrene	☐	☐	☐	☐☐
Psykiske plager *(som du har søkt hjelp for)*	☐	☐	☐	☐☐

1.4 Har du langvarige eller stadig tilbakevendende smerter som har vart i 3 måneder eller mer?

☐ Nei ☐ Ja

TANNHELSE

2.1 Hvordan vurderer du din egen tannhelse?

	1	2	3	4	5	
Svært dårlig	☐	☐	☐	☐	☐	Svært god

2.2 Hvor fornøyd eller misfornøyd er du med tennene eller protesene dine?

	1	2	3	4	5	
Svært misfornøyd	☐	☐	☐	☐	☐	Svært fornøyd

BRUK AV HELSETJENESTER

3.1 Har du, grunnet egen helse, i løpet av de siste 12 måneder vært hos:

	Nei	Ja	Antall ganger
Fastlege/allmennlege	☐	☐	☐☐
Legevakt	☐	☐	☐☐
Psykiater/psykolog	☐	☐	☐☐
Legespesialist utenfor sykehus *(utenom fastlege/allmennlege/psykiater)*	☐	☐	☐☐
Tannlege/tannpleier	☐	☐	☐☐
Apotek *(for kjøp/råd om medisiner/behandling)*	☐	☐	☐☐
Fysioterapeut	☐	☐	☐☐
Kiropraktor	☐	☐	☐☐
Akupunktør	☐	☐	☐☐
Alternativ behandler *(homøopat, soneterapeut, healer etc)*	☐	☐	☐☐
Tradisjonell helbreder *(hjelper, «læser» etc)*	☐	☐	☐☐
Har du kommunisert via internett med noen av tjenestene over?	☐	☐	☐☐

3.2 Har du i løpet av de siste 12 måneder vært på sykehus?

	Nei	Ja	Antall ganger
Innlagt på sykehus	☐	☐	☐☐
Konsultasjon ved sykehus uten innleggelse:			
Ved psykiatrisk poliklinikk	☐	☐	☐☐
Ved annen sykehuspoliklinikk	☐	☐	☐☐

BRUK AV MEDISINER

4.1 Bruker du, eller har du brukt, noen av følgende medisiner? *Sett ett kryss per linje.*

	Aldri	Nå	Før, ikke nå	Alder første gang
Medisin mot høyt blodtrykk	☐	☐	☐	
Kolesterolsenkende medisin	☐	☐	☐	
Vanndrivende medisin	☐	☐	☐	
Annen medisin mot hjertesykdom *(f.eks. blodfortynnende, rytmestabiliserende, nitroglycerin)*	☐	☐	☐	
Insulin	☐	☐	☐	
Tabletter mot diabetes	☐	☐	☐	
Stoffskiftemedisin *(Levaxin/thyroxin)*	☐	☐	☐	

4.2 Hvor ofte har du i løpet av de siste 4 ukene brukt følgende medisiner? *Sett ett kryss per linje.*

	Ikke brukt siste 4 uker	Sjeldnere enn hver uke	Hver uke, men ikke daglig	Daglig
Smertestillende på resept	☐	☐	☐	☐
Smertestillende uten resept	☐	☐	☐	☐
Magesyrehemmende medisiner	☐	☐	☐	☐
Sovemidler	☐	☐	☐	☐
Beroligende medisiner	☐	☐	☐	☐
Medisin mot depresjon	☐	☐	☐	☐

4.3 Skriv alle medisiner (reseptfrie og reseptbelagte) du har brukt regelmessig siste 4 uker. *Ikke regn med reseptfrie vitamin-, mineral- og kosttilskudd, urter, naturmedisin etc.*

Får du ikke plass til alle medisinene, bruk eget ark.

KOSTHOLD

5.1 Spiser du vanligvis frokost hver dag?

☐ Nei ☐ Ja

5.2 Hvor mange porsjoner frukt og grønnsaker spiser du i gjennomsnitt per dag? *Med porsjon menes f.eks. et eple, en salatbolle.*

Antall porsjoner

5.3 Hvor ofte spiser du vanligvis disse matvarene? *Sett ett kryss per linje.*

	0–1 pr. mnd.	2–3 pr. mnd.	1–3 pr. uke	4–6 pr. uke	1 eller mer pr. dag
Rødt kjøtt *(alle produkter av storfe, får, svin)*	☐	☐	☐	☐	☐
Grønnsaker, frukt, bær	☐	☐	☐	☐	☐
Mager fisk *(torsk, sei)*	☐	☐	☐	☐	☐
Feit fisk *(laks, ørret, uer makrell, sild, kveite)*	☐	☐	☐	☐	☐

5.4 Hvor mange glass/beger drikker/spiser du vanligvis av følgende? *Sett ett kryss per linje.*

	Sjelden/ aldri	1–6 pr. uke	1 pr. dag	2–3 pr. dag	4 eller mer pr. dag
Melk/yoghurt tilsatt probiotika *(Biola, Cultura, Activia, Actimel, BioQ)*	☐	☐	☐	☐	☐
Fruktjuice	☐	☐	☐	☐	☐
Brus/leskedrikker:					
med sukker	☐	☐	☐	☐	☐
med kunstig søtning	☐	☐	☐	☐	☐

5.5 Hvor mange kopper kaffe og te drikker du daglig? *Sett 0 for de typene du ikke drikker daglig.*

	Antall kopper
Filterkaffe *(trakterkaffe)*	
Kokekaffe og/eller presskannekaffe	
Pulverkaffe	
Espressobasert kaffe *(fra kaffemaskin, kapsler etc)*	
Sort te *(f.eks. Earl Grey)*	
Grønn/hvit/oolong te	
Urtete *(f.eks. nype, kamille, Rooibos)*	

HELSEBEKYMRING

	Ikke i det hele tatt	Litt	Noe	En hel del	Svært mye
6.1 **Tror du at det er noe alvorlig galt med kroppen din?**	☐	☐	☐	☐	☐
6.2 **Er du svært bekymret over helsen din?**	☐	☐	☐	☐	☐
6.3 **Er det vanskelig for deg å tro på legen din dersom hun/han forteller deg at det ikke er noe å bekymre seg for?**	☐	☐	☐	☐	☐
6.4 **Er du ofte bekymret for muligheten for at du har en alvorlig sykdom?**	☐	☐	☐	☐	☐
6.5 **Hvis du blir gjort oppmerksom på en sykdom (f.eks. via TV, radio, internett, avis eller noen du kjenner), bekymrer du deg da for selv å få sykdommen?**	☐	☐	☐	☐	☐
6.6 **Opplever du at du plages av mange ulike symptomer?**	☐	☐	☐	☐	☐
6.7 **Har du tilbakevendende tanker (som er vanskelig å bli kvitt) om at du har en sykdom?**	☐	☐	☐	☐	☐

FYSISK AKTIVITET

7.1 **Hvis du er i lønnet eller ulønnet arbeid, hvordan vil du beskrive arbeidet ditt?** *Sett kryss i den ruta som passer best.*

- ☐ For det meste stillesittende arbeid *(f.eks. skrivebordsarbeid, montering)*
- ☐ Arbeid som krever at du går mye *(f.eks. ekspeditørarbeid, lett industriarbeid, undervisning)*
- ☐ Arbeid der du går og løfter mye *(f.eks. pleier, bygningsarbeider)*
- ☐ Tungt kroppsarbeid

7.2 **Angi bevegelse og kroppslig anstrengelse i din fritid det siste året.** *Hvis aktiviteten varierer gjennom året, ta et gjennomsnitt. Sett kryss i den ruta som passer best.*

- ☐ Leser, ser på TV / skjerm eller annen stillesittende aktivitet
- ☐ Spaserer, sykler eller beveger deg på annen måte minst 4 timer i uka *(inkludert gang eller sykling til arbeidsstedet, søndagsturer etc)*
- ☐ Driver mosjonsidrett, tyngre hagearbeid, snømåking etc minst 4 timer i uka
- ☐ Trener hardt eller driver konkurranseidrett regelmessig flere ganger i uka

7.3 **Siste uka, omtrent hvor lang tid tilbrakte du <u>sittende</u> på en typisk hverdag og fridag?** *F.eks. ved arbeidsbord, hos venner, mens du så på TV / skjerm.*

☐☐ timer sittende på en hverdag *(både jobb og fritid)*

☐☐ timer sittende på en fridag

ALKOHOL

8.1 **Hvor ofte drikker du alkohol?**

- ☐ Aldri
- ☐ Månedlig eller sjeldnere
- ☐ 2–4 ganger hver måned
- ☐ 2–3 ganger per uke
- ☐ 4 eller flere ganger per uke

8.2 **Hvor mange enheter alkohol (flaske øl, glass vin eller drink) tar du vanligvis når du drikker?**

1–2	3–4	5–6	7–9	10 eller flere
☐	☐	☐	☐	☐

8.3 **Hvor ofte drikker du 6 eller flere enheter alkohol ved en anledning?**

- ☐ Aldri
- ☐ Sjeldnere enn månedlig
- ☐ Månedlig
- ☐ Ukentlig
- ☐ Daglig eller nesten daglig

RØYK OG SNUS

9.1 **Har du røykt/røyker du daglig?**

☐ Aldri ☐ Ja, nå ☐ Ja, tidligere

9.2 **Har du brukt/bruker du snus eller skrå daglig?**

☐ Aldri ☐ Ja, nå ☐ Ja, tidligere

SPØRSMÅL OM KREFT

10.1 **Har du noen gang fått**

	Nei	Ja	**Hvis ja:** alder første gang	**Hvis ja:** alder siste gang
Utført mammografi	☐	☐		
Målt PSA (prostataspesifikt antigen)	☐	☐		
Utført tykktarmsundersøkelse (koloskopi, avføringsprøve)	☐	☐		

10.2 **Har noen i din nære biologiske familie hatt**

	Egne barn	Mor	Far	Mormor	Morfar	Farmor	Farfar	Tante	Onkel	Søsken
Brystkreft	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Prostatakreft	☐		☐		☐		☐		☐	☐
Tykktarmskreft	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

UTDANNING OG INNTEKT

11.1 **Hva er din høyeste fullførte utdanning?** *Sett ett kryss.*

- ☐ Grunnskole/framhaldsskole/folkehøyskole inntil 10 år
- ☐ Fagutdanning/realskole/videregående/gymnas minimum 3 år
- ☐ Høyskole/universitet mindre enn 4 år
- ☐ Høyskole/universitet 4 år eller mer

11.2 **Hva var din husstands samlede bruttoinntekt siste år?** *Ta med alle inntekter fra arbeid, trygder, sosialhjelp og lignende.*

- ☐ Under 150 000 kr
- ☐ 150 000–250 000 kr
- ☐ 251 000–350 000 kr
- ☐ 351 000–450 000 kr
- ☐ 451 000–550 000 kr
- ☐ 551 000–750 000 kr
- ☐ 751 000 –1 000 000 kr
- ☐ Over 1 000 000 kr

FAMILIE OG VENNER

12.1 **Hvem bor du sammen med?**

	Nei	Ja	Antall
Ektefelle/samboer	☐	☐	
Andre personer over 18 år	☐	☐	
Personer under 18 år	☐	☐	

12.2 **Har du nok venner som kan gi deg hjelp når du trenger det?**

☐ Ja ☐ Nei

12.3 **Har du nok venner som du kan snakke fortrolig med?**

☐ Ja ☐ Nei

12.4 **Hvor ofte deltar du vanligvis i foreningsvirksomhet som syklubb, idrettslag, politiske, religiøse eller andre foreninger?**

Aldri, eller noen få ganger i året	1–2 ganger i måneden	Omtrent 1 gang i uka	Mer enn 1 gang i uka
☐	☐	☐	☐

SPØRSMÅL TIL KVINNER

13.1 **Hvor gammel var du da du fikk menstruasjon første gang?**

Alder

13.2 **Er du gravid nå?**

☐ Nei ☐ Ja ☐ Usikker

13.3 **Hvor mange barn har du født?**

Antall barn

13.4 **Hvis du har født, fyll ut for hvert barn: fødselsår og vekt samt hvor mange måneder du ammet.** *Angi så godt du kan. Hvis flere barn, bruk ekstra ark.*

	Fødselsår	Fødselsvekt i gram	Ammet ant. mnd.
Barn 1			
Barn 2			
Barn 3			
Barn 4			
Barn 5			
Barn 6			

SPØRSMÅL TIL MENN

14.1 **Har du fått behandling for betennelse i prostata eller urinblæra?**

☐ Nei ☐ Ja

14.2 **Har du fått utført steriliseringsoperasjon?**

☐ Nei ☐ Ja **Hvis ja:** hvilket år

Tusen takk for ditt bidrag.

Appendix I

The second questionnaire (Q2) in the Tromsø study: Tromsø7 [Norwegian]
Available at:
https://uit.no/Content/709325/cache=20202011171303/FINAL%20Q2%20translation20190307.pdf

Appendix J

Ethical approval for the study from the Regional Committees for Medical and Health Research Ethics (REK North) [Norwegian]

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK nord			01.11.2016	2016/1794/REK nord
			Deres dato:	Deres referanse:
			20.09.2016	

Vår referanse må oppgis ved alle henvendelser

Òlöf Anna Steingrìmsdòttir
Avdeling for aldring og helse

2016/1794 Sammenheng mellom fysisk aktivitet og langvarig smerte

Forskningsansvarlig: Folkehelseinstituttet
Prosjektleder: Òlöf Anna Steingrìmsdòttir

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK nord) i møtet 20.10.2016. Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 10, jf. forskningsetikkloven § 4.

Prosjektleders prosjektomtale
Selv om fysisk aktivitet ofte er benyttet både til forebygging og behandling av langvarig smerte, er det fortsatt manglende kunnskap om sammenhenger mellom disse. Noen resultater tyder på en U-formet assosiasjon. Hensikten med prosjektet er å dokumentere sammenheng mellom fysisk aktivitet og smerte i en generell populasjon og undersøke hvilken rolle egenskaper for smerteinhibisjon og smertesensitivitet har for utvikling av (alvorlig) smerte. Vi benytter oss av tverrsnittdesign for å dokumentere a) sammenheng mellom fysisk aktivitet og selvrapportert smerte og b) sammenheng mellom fysisk aktivitet og eksperimentell smerte. Vi vil siden undersøke resultater fra tverrsnittanalysene i et longitudinal design. Det benyttes eksperimentelle, kliniske og epidemiologiske data fra Tromsøundersøkelsen.

Vurdering

Data
Data hentes fra Tromsøundersøkelsen (T1-T7), som gjelder spørreskjemadata på helse og helserelatert atferd, sosioøknomi, demografi, data fra kroppskart (f.eks. smerteutbredelse, intensitet, varighet, tretthet, søvn), kliniske undersøkelser, data fra eksperimentelle smerteundersøkelser, data fra undersøkelse av fysisk aktivitet (accelerometere), data for å lage en fitness score. Prosjektet vil bruke datafilen til å undersøke i dybden linken mellom smerte og fysisk aktivitet/trening, samt informasjon om sykdomsprosesser for blant annet å vurdere tak på aldersgrupper og ha mulighet til å kontrollere for «competing risk».

Data vil bli behandlet avidentifisert.

Samtykke
Forespørsel om deltakelses-vedlegg gjelder fra Tromsøundersøkelse 6, mens det i prosjektsøknaden framkommer at prosjektet ønsker å benytte data fra alle som har deltatt i Tromsøundersøkelsen T1-T7. Dette begrunnes med at hensikten med å inkludere alle syv innsamlingsperiodene er å ha større mulighet til å undersøke sammenhenger i et livsløpsperspektiv.

Det opplyses i prosjektsøknad at prosjektet senere vil sende inn en egen søknad om sammenstilling av

dataene fra Tromsøundersøkelsen til data fra NPR og Reseptregisteret, Komiteen tar ikke stilling til dette i behandling av prosjektsøknaden, selv om det vises til annet prosjekt (2011/1659) hvor deltakere har gitt samtykke til at data kan kobles til andre helseregistre. Komiteen vil vurdere dette når søknaden foreligger.

Forespørsel/informasjonsskriv/samtykkeskriv - Tromsøundersøkelsene
Det er innhentet samtykke for deltakere i Tromsø 4,5,6 og 7. Felles for disse er at de har mottatt informasjon om studien, samtykket til at innsamlede data kan brukes til medisinsk forskning, samt kobling mot ulike registre, herunder pasientjournal.

Tromsø 2 og 3 ble gjennomført i en tid da REK var under etablering, og krav om informert skriftlig samtykke til deltakelse i forskning ennå ikke var etablert praksis. Den enkelte deltaker fikk imidlertid skriftlig informasjon om at deltakelse ville innebære at resultatene ville bli anvendt i forskning og at blodprøver ville bli lagret for framtidige analyser i forskningsøyemed. I invitasjonsbrosjyren het det: *"Det er også viktig at resultatene blir anvendt i forskning, bl.a. ved at de følges opp m.h.p. framtidig forekomst av sykdom»*. I omtalen av blodprøvene heter det*:" Prøven vil bli frosset ned, slik at vi senere kan måle andre ting om det blir nødvendig"*.

Strukturen i Tromsøundersøkelsen er slik at de fleste deltakere er blitt invitert til flere av de seks undersøkelsene. Mange av deltakerne i Tromsø 2 og 3 har deltatt i Tromsø 4 – 7 og har da gitt samtykke til at resultatene kan kobles til tidligere undersøkelser. For dem som deltok i Tromsø 2 og 3 og ikke seinere, er det praktisk vanskelig og til dels umulig å innhente nytt samtykke. Undersøkelsen ligger 25 til 30 år tilbake i tid og mange deltakere har flyttet eller er døde.

Tromsøundersøkelsen har gjennom oppslag i pressen informert om retten til å trekke seg fra undersøkelsen og om å få sine data slettet. Tromsøundersøkelsens nettsider inneholder også informasjon om retten til å trekke seg og om fremgangsmåten for dette.

Helseforskningsloven § 15 gir hjemmel til ny eller endret bruk av innsamlede helseopplysninger. REK vurderer at deltakernes velferd og integritet er godt ivaretatt gjennom de prosedyrer det er lagt opp til ved datainnsamlingen.

Komiteen forutsetter at opplysningene for denne gruppen vaskes mot reservasjonsregisteret.

Komiteen vurderer at samtykket er dekkende.

Vedtak

Med hjemmel i helseforskningsloven §§ 2 og 10 godkjennes prosjektet.

Sluttmelding og søknad om prosjektendring
Prosjektleder skal sende sluttmelding til REK nord på eget skjema senest 01.07.2024, jf. hfl. § 12. Prosjektleder skal sende søknad om prosjektendring til REK nord dersom det skal gjøres vesentlige endringer i forhold til de opplysninger som er gitt i søknaden, jf. hfl. § 11.

Klageadgang
Du kan klage på komiteens vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes til REK nord. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK nord, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Med vennlig hilsen

May Britt Rossvoll
Sekretariatsleder

Kopi til:knut-Inge.Klepp@fhi.no
reksoknad@fhi.no

Appendix K

Ethical approval for the Tromsø study: Tromsø6, by the Regional Committees for Medical and Health Research Ethics (REK North) [Norwegian]

Anne Elise Eggen
Insitutt for samfunnsmedisin
Det medisinske fakultet
Universitetet i Tromsø
9037 TROMSØ

Deres ref.: 5.2006.2631 Vår ref.: 200605174-12/IAY/400 Dato: 21.05.2007

P REK NORD 121/2006 DEN SJETTE TROMSØUNDERSØKELSEN (TROMSØ 6) - SLUTTVURDERING - KOMITEEN HAR INGEN INNVENDINGER MOT AT PROSJEKTET GJENNOMFØRES

Vi viser til prosjektleders brev av 10.5.2007 med vedlegg innsendt i e-post 11.5.2007, samt prosjektleders e-post 17.5 og 19.5.2007 og vår e-post 18.5.2007.

Prosjektleders tilbakemelding på komiteens merknader til prosjektet i møtet 18.1.2007 (brev av 29.1.2007) tas til etterretning.

Regional komité for medisinsk forskningsetikk, Nord-Norge (REK Nord) har ingen innvendinger mot at prosjektet gjennomføres.

Det forutsettes at prosjektet er godkjent av aktuelle formelle instanser før det settes i gang.

Det forutsettes at prosjektet forelegges komiteen på nytt, dersom det under gjennomføringen skjer komplikasjoner eller endringer i de forutsetninger som komiteen har basert sin avgjørelse på.

Komiteen ber om å få melding dersom prosjektet ikke blir sluttført.

Vennlig hilsen

Ingunn Ytrehus
førstekonsulent
77645347

Appendix L

Ethical approval for the Tromsø study: Tromsø7, by the Regional Committees for Medical and Health Research Ethics (REK North) [Norwegian]

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK nord	Veronica Sørensen	77620758	10.02.2015	2014/940/REK nord
			Deres dato:	**Deres referanse:**
			18.12.2014	

Vår referanse må oppgis ved alle henvendelser

Anne Elise Eggen
Institutt for samfunnsmedisin

2014/940 Den sjuende Tromsøundersøkelsen (Tromsø 7)

Forskningsansvarlig institusjon: Institutt for samfunnsmedisin
Prosjektleder: Anne Elise Eggen

Prosjektleders prosjektomtale
Tromsøundersøkelsen er en forskerinitiert epidemiologisk kohortstudie med mulighet for å studere forekomst, forebygging og behandling av kroniske sykdommer og plager, sammenhengen mellom psyke og soma, tannhelse, bruk av helsetjenester og hvordan kronisk plager påvirker livskvalitet. Tromsøundersøkelsen har fulgt befolkningen i Tromsø siden 1974, og brukes til forskning og til å følge risikofaktorer for sykdom i befolkningen. I Tromsø 7 vil det samles inn helseopplysninger via spørreskjemaer, biologiske materiale, målinger og kliniske undersøkelser. Alle aktuelle deltakere blir forespurt til å delta i en del 1 (basisundersøkelse), med videre forespørsel om å delta i del 2 (omfattende, kliniske undersøkelser) til deler av utvalget. Oppstart er planlagt primo 2015 med avslutning ved årsskiftet 2016/17. Undersøkelsen er planlagt for invitasjon av alle 40-79 år, tidligere deltakere i Tromsøundersøkelsen 80 år og eldre, og tidligere deltakere i ungdomskohorten 22-25 år.

Vurdering
Vi viser til utfylt søknadsskjema, vedlagt protokoll og øvrige vedlegg.

Prosjektet var oppe til vurdering på komiteens møte 12.06.2014. Prosjektgruppen, representert ved Anne Elise Eggen, Heidi Johansen og Inger Njølstad var invitert til komiteens møte og hadde en gjennomgang av Tromsø 7. Komiteen fikk muntlig svar på spørsmål de hadde, men komiteen ba også om en revidert protokoll og informasjonsskriv. I tillegg ble det bedt om tilbakemelding på følgende merknader: Om beredskap/sikkerhet/tilbakemeldinger til deltakere, spørreskjema samt en nærmere avklaring av hva ungdomsgruppen Fit Future skulle inviteres til.

Prosjektleder har gitt tilfredsstillende tilbakemeldinger. REK har således ingen innvendinger mot Tromsø 7.

Prosjektleder har også lagt frem siste versjon av informasjonsskrivet. På side 6 under overskriften «Personvern» andre avsnitt, siste setning «…..(REK nord) har vurdert testene og undersøkelsene som gjennomføres samt godkjent innsamling av prøver « utgår. Dette er for upresist og må endres til «…….. (REK nord) «har gjort en etisk og helsefaglig vurdering av undersøkelsene som gjennomføres, samt godkjent innsamlingen av prøver.»

Etter fullmakt er det fattet slikt vedtak:

Vedtak
REK har vurdert helseundersøkelsens medisinske og etiske forsvarlighet og har ingen innvendinger.

Sluttmelding og søknad om prosjektendring
Prosjektleder skal sende sluttmelding til REK nord på eget skjema senest 30.06.2017, jf. hfl. § 12. Prosjektleder skal sende søknad om prosjektendring til REK nord dersom det skal gjøres vesentlige endringer i forhold til de opplysninger som er gitt i søknaden, jf. hfl. § 11.

Klageadgang
Du kan klage på komiteens vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes til REK nord. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK nord, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Med vennlig hilsen

May Britt Rossvoll
sekretariatsleder

Veronica Sørensen
rådgiver

Kopi til:magritt.brustad@uit.no