Physical activity and cold pain tolerance in the general population

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Category: Original article.
Funding sources: This work was funded by a grant from the Northern Norway Regional Health Authority (grant number HNF1352-17). All authors declare that they have no conflicts of interests related to this study.

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.

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 (2007-08; 2015-16), 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 seconds), 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 minutes 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 ($p<0.001$; $p=0.011$; $p<0.001$). 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.

1 Introduction

Several reviews summarize how acute bouts of physical activity (PA) reduce sensitivity to experimental pain stimuli, manifested as temporary change in parameters like 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 and Defrin 2013; Tesarz et al., 2012), or looking at self-reported (Lemming et al., 2015; 2017; Naugle and Riley 2014) or device-measured PA (Ellingson et al., 2012; Naugle et al., 2017; Ohlman et al., 2018), with heat, cold, pressure, or ischemic 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 and Golightly 2015; Holth et al., 2008), part of this effect is thought to occur through upregulating 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 (2007-08) and Tromsø 7 (2015-16). 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).

Insert Figure 1 approximately here

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 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 4 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. 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.

2.2.1.1 Accelerometer recordings

PA was measured using an ActiGraph wGT3X (ActiGraph Corp, Pensacola, Florida). Participants were asked to wear the accelerometer on the hip for seven consecutive days except during showering/bathing or swimming. Acceleration was measured in three axes at a sampling rate of 100Hz 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: 1) >5 counts per minute; 2) at least two minutes with counts>5 in the following 20 minutes; 3) at least two minutes with counts >5 in the preceeding 20 minutes. For processing of the counts 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; second, a variable expressing moderate to very vigorous PA (MVPA) minutes per day occurring in bouts of activity lasting >10 minutes. 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 >9642. Counts per minute >2690 were aggregated into moderate to very vigorous PA (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 four days with at least 10 hours 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 has 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 plexi-glass vat containing continuously circulated 3.0°C water. Temperature control was provided by an attached cooling circulator (Julabo FP40HE, Julabo Labortechnik GmbH Germany, 22 liters/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 seconds in Tromsø 6 and 120 seconds in Tromsø 7. Since maximum times differed for the two surveys, Tromsø Study tolerance times were censored at 106 seconds 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 three years, college/university less than four years, college/university for four 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 one and ten cigarettes daily, smokes more than ten cigarettes daily); c) self-reported health (very bad, bad, neither good or bad, good, 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, 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 centimeters on body height in centimeters 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-minute bout MVPA was right-skewed. We therefore used median and inter-quartile 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 seconds were right-censored, i.e. 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 minutes 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 cases-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 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 cases-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-cases models only. Figure 1 shows 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-cases model. Multiple imputation was performed using chained equations on 100 imputed datasets with predictive mean matching (known nearest neighbors=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 seconds. Total median CPT tolerance was 49 seconds for women and 95 seconds for men. Median CPT tolerance for only those participants who withdrew their hand was 32 seconds (IQR 27); 30 seconds for women (IQR 27), and 34 seconds for men (IQR 28).

According to accelerometry-measured PA, median daily amount of MVPA performed in bouts of 10 minutes or more was 7.6 minutes (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 six years older than the main study sample.

*****Insert Table 1 approximately here*****

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 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 that 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 ≥ 3months), 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 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-minute 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).

*****Insert Table 2 & Figure 2 approximately here*****

4 Discussion

In this study, self-reported LTPA, EI, and ED were positively associated with CPT tolerance in a dose-response relationship whilst 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 and 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 and Kirsch 1991; Geva and 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 and Defrin 2013; Tesarz et al., 2012), when comparing self-reported PA levels (Lemming et al., 2015; 2017; Naugle and 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 six-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 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 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 levels scale correlates well with both VO_2 max, resting heart rate (Emaus et al., 2010), and physical fitness as work capacity (Lochen and Rasmussen 1992), and is significantly associated with 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 to “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 regards 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 and Fillingim 2013; Bulls et al., 2015; Defrin et al., 2009; Hashmi and 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 and Fillingim 2013; Defrin et al., 2009; Mogil 2012; 2018; Sorge and 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 and Gintzler 2000; Loyd and 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).

4.1.2 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 heterogenous. 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 heterogenous 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 intra-class 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 and 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 two 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 heterogenous 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 possible relationships between accelerometer-measured LTPA, as well as occupational PA, and pain tolerance.

Acknowledgements

We extend our most sincere gratitude towards senior researcher Hein Stigum and senior scientist Bjørn Heine Strand at the Norwegian Institute of Public Health for invaluable statistical counsel. We also direct a heartfelt thanks to the staff and participants of the Tromsø Study, without whom it would not be possible to do what we do.

Conflicts of interest

All authors declare that they have no conflicts 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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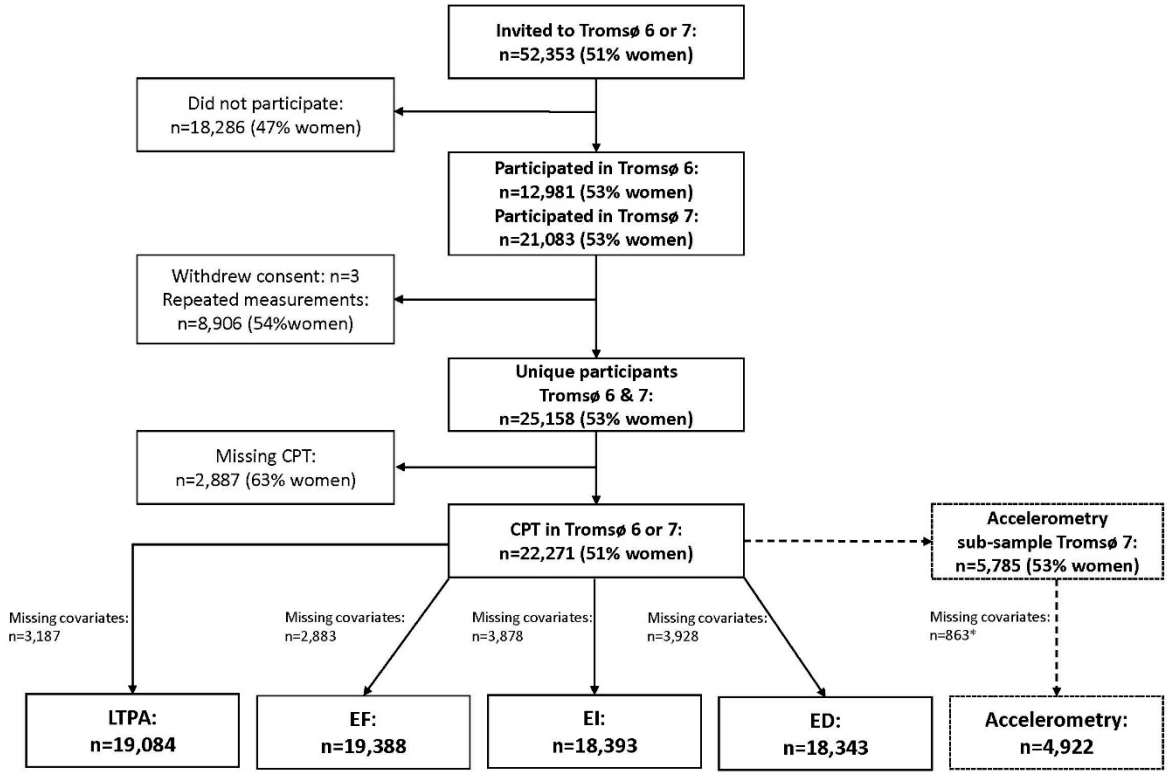
Figure Legends:

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.

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


Invited to Tromsø 6 or 7:
n=52,353 (51% women)
Did not participate:
n=18,286 (47% women)
Participated in Tromsø 6:
n=12,981 (53% women)
Participated in Tromsø 7:
n=21,083 (53% women)
Withdrew consent: n=3
Repeated measurements:
n=8,906 (54%women)
Unique participants
Tromsø 6 & 7:
n=25,158 (53% women)
Missing CPT:
n=2,887 (63% women)
CPT in Tromsø 6 or 7:
n=22,271 (51% women)
Accelerometry
sub-sample Tromsø 7:
n=5,785 (53% women)
Missing covariates:
n=3,187
Missing covariates:
n=2,883
Missing covariates:
n=3,878
Missing covariates:
n=3,928
Missing covariates:
n=863*
LTPA:
n=19,084
EF:
n=19,388
EI:
n=18,393
ED:
n=18,343
Accelerometry:
n=4,922

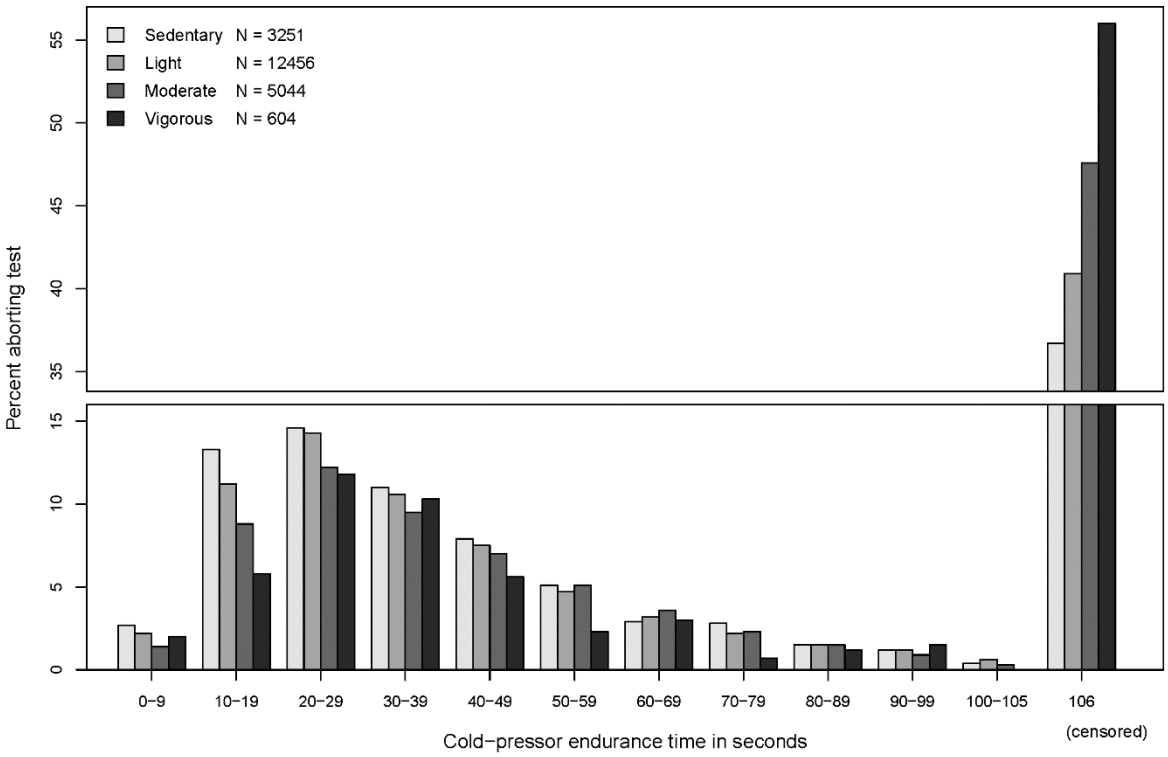

Sedentary N = 3251
Light N = 12456
Moderate N = 5044
Vigorous N = 604
Percent aborting test
0
5
10
15
35
40
45
50
55
0–9
10–19
20–29
30–39
40–49
50–59
60–69
70–79
80–89
90–99
100–105
106
(censored)
Cold–pressor endurance time in seconds

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 sec.)	Endured CPT (CPT = 105.6 sec.)
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
Exercise intensity (%)[c]:				
Light	40	44	42	37
Moderate	56	53	54	58
Vigorous	4	3	4	5
Exercise duration (%)[c]:				
0-29 minutes	21	20	22	18
30-60 minutes	57	57	57	57
More than 60 minutes	22	23	21	25
Accelerometry [d]:				
Daily total counts (mean (SD))	-	536 (178)	530 (177)	543 (180)
Daily 10-minute 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)

[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

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

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-minute MVPA [b]		0.98 (0.94-1.02)	0.218	1.00 (0.94-1.05)	0.95 (0.90-1.01)

[a] Cox proportional hazards regression.

[b] Hazard ratio for 1SD increase

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.

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

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.