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Consistent pattern between physical activity measures and chronic pain levels: the Tromsø Study 2015-2016.

Mats Kirkeby Fjeld[1,2]; Anders Pedersen Årnes[3]; Bo Engdahl[1]; Bente Morseth[4]; Laila Arnesdatter Hopstock[5]; Alexander Horsch[6]; Audun Stubhaug[2,7]; Bjørn Heine Strand[1,8,9]; Christopher Sivert Nielsen[1,7]; Ólöf Anna Steingrímsdóttir[1,10]

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

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

[3]Department of Pain, University Hospital of North Norway; Tromsø. Norway

[4]School of Sport Sciences, UiT The Arctic University of Norway; Tromsø. Norway

[5]Department of Community Medicine, UiT The Arctic University of Norway; Tromsø. Norway

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

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

[8]Norwegian National Advisory Unit on Ageing and Health, Tønsberg, Norway

[9]Department of Geriatric Medicine, Oslo University Hospital, Oslo, Norway

[10]Department of Research and Development, Division of Emergencies and Critical Care, Oslo University Hospital, Oslo, Norway

*Corresponding author: Mats Kirkeby Fjeld, Division of Mental and Physical Health, Norwegian Institute of Public Health, Oslo, Norway. Address: Norwegian Institute of Public Health, Postbox 222 Skøyen, 0213 Oslo Tel: +47 482 73 252, Email: matskirkeby.fjeld@fhi.no

Abstract

Epidemiological literature on the relationship between physical activity and chronic pain is scarce and inconsistent. Hence, our aim was to assess the relationship applying comprehensive methodology, including self-reported and accelerometer measures of physical activity and different severity levels of chronic pain. We used data from the Tromsø Study (2015-2016). All residents in the municipality, aged 40 years and older were invited to participate (n=32,591, 51% women). A total of 21,083 (53% women) reported on questionnaires. Additionally, 6,778 participants (54% women) were invited to wear accelerometers (6,125 with complete measurements). Our exposure measures were self-reported leisure time physical activity, exercise frequency, duration and intensity and two accelerometer-measures (steps per day and minutes of moderate to vigorous physical activity per day). Outcome measurements were chronic pain and moderate-to-severe chronic pain. We used Poisson regression to estimate chronic pain prevalence and prevalence ratios for each physical activity measure, with adjustments for sex, age, education level, smoking history, and occupational physical activity. Our main analyses showed an inverse dose-response relationships between all physical activity measures and both severity measures of chronic pain, except that the dose-response relationship with exercise duration was only found for moderate-to-severe pain. All findings were stronger for the moderate-to-severe pain outcomes than for chronic pain. Robustness analyses gave similar results as the main analyses. We conclude that an inverse dose-response association between physical activity and chronic pain is consistent across measures. To summarize, higher levels of physical activity is associated with less chronic pain and moderate-to-severe chronic pain.

Keywords: Physical activity; exercise; chronic pain; Epidemiology; Population-based; Public Health; Pain Severity; Accelerometers

1.0 INTRODUCTION

The global level of physical inactivity among adults is estimated to be about 30 percent [18] and likely to be a growing issue among the next generation [18]. Similarly, approximately one third of the adult population report chronic pain in epidemiological studies [50]. Individuals with chronic pain report impaired quality of life and reduced physical function and work capacity resulting in socioeconomic burden [6]. It has been maintained that physical activity reduces the risk and severity of chronic pain, and physical activity is often recommended for managing chronic pain [3; 13]. This notion has partly been supported by findings from randomized controlled trials, presented in an overview of Cochrane reviews[14] . The reviews showed that physical activity interventions had small-to-moderate beneficial effects on pain severity among adults with specific clinical chronic pain conditions [14]. However, the authors emphasized the inconsistency of the results and considered the quality of the evidence to be low [14].

, Previous population-based studies on physical activity and chronic pain mainly focused on pain in specific body regions such as upper extremities [33] or back [2; 20; 21].However, the findings are inconsistent, and may not be generalizable to chronic pain regardless of body regions. To the best of our knowledge, only three population-based studies address the association between physical activity levels and chronic pain in general [16; 29; 56]. Overall, these three cross-sectional studies show positive associations from being physically active. However, one of the studies suggests a u-shaped relationship whereby very high levels of physical activity is associated with higher prevalence of chronic pain [29]. The likelihood and impact of such detrimental effect has been, and still is, an important part of the clinical discussion, especially for site-specific pain [1; 20; 21; 42].

There are several factors that complicate the interpretation of the existing epidemiological findings. None of the cross-sectional studies mentioned above included data on physical activity at work, which may relate differently to chronic pain than leisure time physical activity. All these studies used self-reported questionnaire solely instead of a combination of different tools, such as questionnaire reports and accelerometer measured physical activity. Moreover, the results from these studies should be interpreted in context with the limitations that follow the cross-sectional study design.

Heterogeneity in assessment methods of physical activity and chronic pain is a general challenge within this research field. Hence, with data from a large, population-based study, our aim was to determine the absolute and relative associations between physical activity and chronic pain in general, and to investigate whether the relationship was consistent across different physical activity measurement methods and different severity levels of chronic pain.

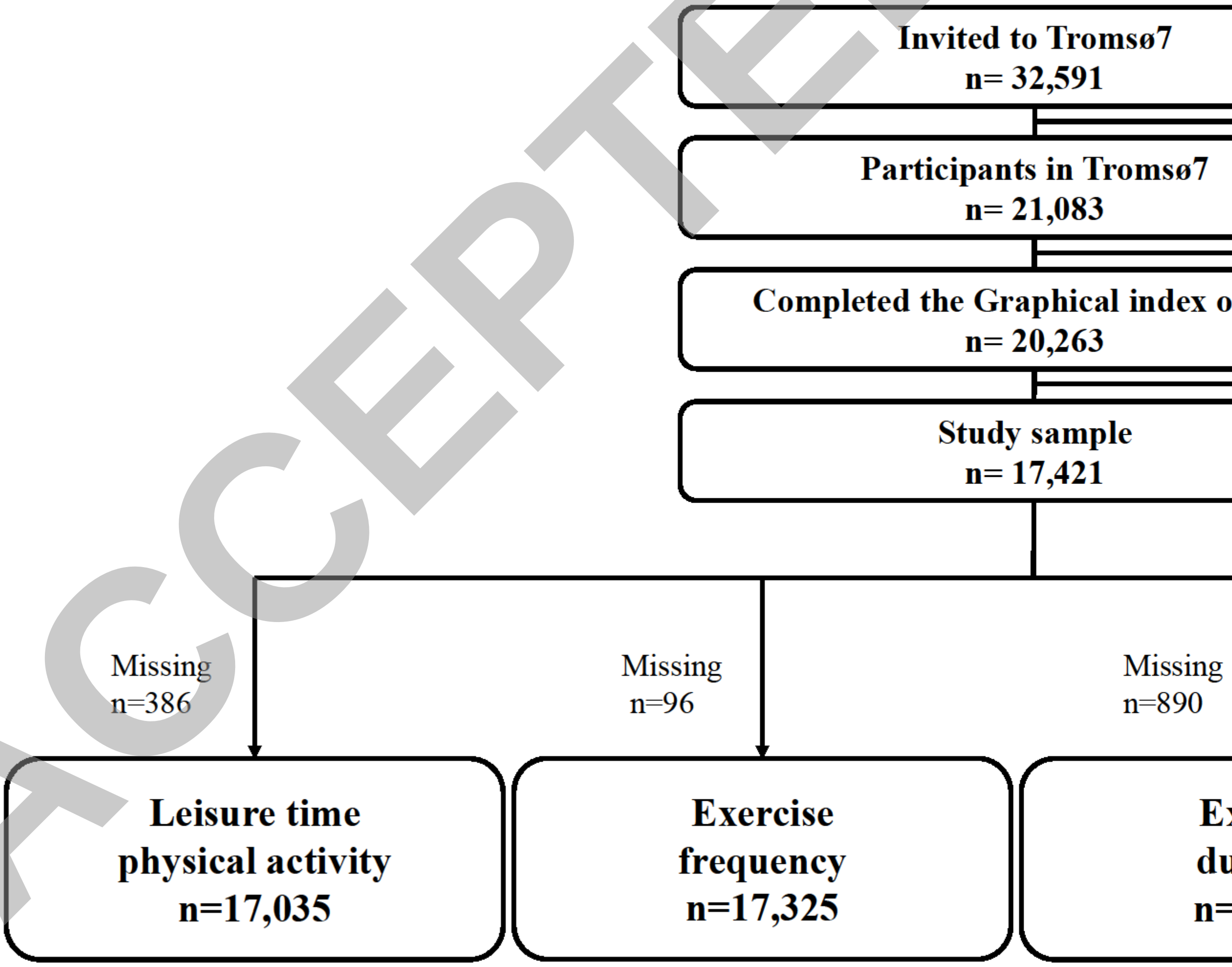
2.0 METHODS

2.1 Study population and samples

We used data from the population-based Tromsø Study, which has been conducted in seven waves since 1974 [24]. The respondents included in the current study attended the 7th wave (Tromsø7, 2015-2016). All residents in the municipality of Tromsø aged 40 or more (N=32,591) were invited to attend the study (visit 1). A total of 10,009 men and 11,074 women participated in the study, corresponding to a participation rate of 65%. All self-reported data used in the present study were obtained during visit 1. Figure 1 shows a flow chart of the study population.

In visit 2, a sub-sample (N=13,028) was pre-marked for extended examinations approximately 3-4 weeks later. The sub-sample consisted of a random sample of the total population invited to Tromsø7 (20% aged 40-59 and 50% aged 60-84; n=9,925), as well as participants attending DXA, ECHO- and/or eye examination in Tromsø6 (n=3,103). Participation in visit 2 required attendance at visit 1. In total 8,346 attended visit 2 (comprising 64% of the originally pre-marked visit 2 sample), and of those, 6,778 were invited to wear an ActiGraph. After exclusion of participants due to non-returned accelerometers (n=6), accelerometer error (n=37) or invalid wear time data (n=165), our final sample included 6,125 participants with valid measurements (wear time >=4 days >= 10 hours). For more detailed description of Tromsø7, see Hopstock et al. 2022 [23].

Figure 1. Flowchart. The Tromsø Study 2015-2016.


Invited to Tromsø7
n= 32,591
Participants in Tromsø7
n= 21,083
Completed the Graphical index o
n= 20,263
Study sample
n= 17,421
Missing
n=386
Missing
n=96
Missing
n=890
Leisure time
physical activity
n=17,035
Exercise
frequency
n=17,325
Ex
du
n=

2.2 Physical activity exposures

2.2.1 Self-reported leisure time physical activity

We used an updated version of the Saltin-Grimby physical activity scale for leisure time physical activity (LTPA) [17; 41]. The respondents were asked as follows: *"Describe your 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 year*". Four different levels were given;*" Reading, watching TV, or other sedentary activity.", "Walking, cycling, or other forms of exercise at least 4 hours a week (here including walking or cycling to place of work, Sunday-walking, etc.)*", *"Participation in recreational sports, heavy gardening, etc. (note: duration of activity at least 4 hours a week)."* and *"Participation in hard training or sports competitions, regularly several times a week."*. In the present study, these four levels were renamed *"inactive"*, *"low"*, *"moderate"* and *"vigorous"*, respectively.

2.2.2 Self-reported physical exercise

Exercise was assessed through three questions on frequency, duration, and intensity, where the respondents were asked to estimate their weekly average. The frequency dimension was obtained through the question "*How often do you exercise (i.e walking, skiing, swimming or training/sports)?*". The response options were; "*Never*", "*Less than once a week*", "*Once a week*", "*2-3 times a week*" or "*Approximately every day*". The duration dimension was estimated through the question "*For how long time do you exercise?*" with the response options "*Less than 15 minutes*", "*15-29 minutes*", "*30-60 minutes*" or "*More than 1 hour*". The intensity dimension was assessed through the question "*If you exercise – how hard do you exercise*" with the options "*Easy – you do not become short-winded or sweaty*" renamed "*low*", "*You become short-winded and sweaty*" renamed "*moderate*" or "*Hard – you become exhausted*" renamed "*hard*".

2.2.3 Accelerometer-measured physical activity

Accelerometers were used to measure physical activity in three axes at a sampling frequency of 100 Hz (ActiGraph wGTX, ActiGraph corp., Pensacola, Florida). The accelerometers were placed on the hip, and the participants were instructed to wear them for 24 hours for seven consecutive days, removing the device only for showering, bathing, or swimming. Wear-time requirements for a valid measurement were set to a minimum of 4 days and 10 hours per day. Non-wear time was calculated according to the Hecht 2009 algorithm [19] on 1-minute epochs. To classify a minute as wear time, the algorithm requires at least two of the following conditions being fulfilled; 1) >5 counts during this minute, 2) at least two minutes with counts >5 during the following 20 minutes, and/or 3) at least two minutes with counts >5 during the preceding 20 minutes. The valid measurements were further processed and divided into different levels of intensity according to cut-offs proposed by Sasaki et al. [36] and Peterson et al. [39]. These cut-offs were set to sedentary (<150 counts per minute), low (150-2,689 counts per minute), moderate (2,690-6,166 counts per minute), vigorous (6,167-9,642 counts per minute) and very vigorous (>9,642 counts per minute). We chose to study moderate-to-vigorous physical activity (MVPA) in a combined category, with the cut-off set to ≥2,690 counts per minute. Daily MVPA was further stratified into quartiles. The 1st to 4th quartiles had the following mean (standard deviation, range) values respectively: 10.0 min per day (5.6, 0.0 to 19.1), 27.4 min per day (4.9, 19.2 to 36.1), 46.0 min per day (6.3, 36.1 to 58.0), and 83 min per day (23.4, 58.1 to 221.4).

Steps per day were classified according to a graduated step index developed by Tudor-Locke and Bassett [54]. The index consists of five categories: <5,000 steps/day (sedentary/inactive), 5,000-7,499 steps/day (low active), 7,500-9,999 steps/day (somewhat active), 10,000-12,499 steps/day (active) and >12,500 steps/day (highly active).

2.3 Chronic pain outcomes

Pain-related characteristics and chronic pain definition

Information on pain and pain-related characteristics were obtained by a pain questionnaire, the Graphical Index of Pain (GRIP) [49]. The instrument consists of a hierarchical digital body map divided into 10 first tier regions (head, neck, left arm, right arm, upper and lower back, left leg, right leg, chest, abdomen, genitals/pelvic floor/urethra/anus) followed by detailed second tier regions (not included in this study). Respondents were instructed to report pain experienced *within the last 4 weeks*, and to omit transient brief pain. Women were instructed not to report menstrual pain. The respondents further specified characteristics of the pain reported on the ten first tier regions, such as pain intensity, episode duration, number of days and the level of bother. Information on pain and the pain-related characteristics were used to construct two outcome variables, *a)* chronic pain and *b)* moderate-to-severe chronic pain, as described below.

The assessment of chronic pain was based upon the ICD-11 definition, with pain persisting or recurring for longer than 3 months [52]. The respondents reported in GRIP the time since first onset of their pain with the response options "*Less than 4 weeks*", "*1-2 months*", "*3-5 months*", "*6-11 months*", "*1-2 years*", "*3-5 years*" or "*more than 5 years*". Respondents reporting "*more than 5 years*" were asked to specify the age of onset. Hence, we defined chronic pain as pain experienced within the last 4 weeks in at least one of the 10 first tier body regions with an onset 3 months or longer ago.

The ICD-11 definition of moderate-to-severe chronic pain requires information on three pain-related parameters: 1) pain intensity, 2) pain-related distress, and 3) task interference [53]. In this study, all three parameters were measured on an 11-point numeric rating scale (NRS 0-10): a) pain intensity (anchors: No pain / The strongest imaginable pain),

b) bothering, as a proxy of pain-related distress (anchors: Not bothered/The greatest imaginable bother), and c) impact on daily activities, as a proxy of task interference using the question – *"To what extent does the pain prevent you from performing your daily activities?"* (anchors: Not at all / Can't do anything) [49]. We regarded moderate-to-severe chronic pain to be present if a respondent reported pain within the last 4 weeks in at least one of the 10 first tier with an onset 3 months ago or earlier, and with >3 NRS on each of the following parameters (pain intensity, bothering and impact on daily activities). To explore potential bias related to physical limitation, we made additional analyses where we removed the impact of daily activities parameter from the definition of moderate-to-severe chronic pain.

GRIP is a new screening instrument that underwent pretesting and piloting before the data collection, but validation of instructions and questions have not been completed [49]. Hence, for the sake of robustness, we included two additional chronic pain outcomes from another questionnaire in the same data collection. The first question was about chronic pain, i.e. "*Do you have persistent or recurrent pain that has lasted for at least three months* "(yes/no). The second question was regarding chronic musculoskeletal pain in the following regions: neck, shoulder, arms/hands, hip, leg or feet, upper part of the back, lumbar region, or other. "*Have you during the last year suffered from pain and/or stiffness in muscles or joints in *region* lasting for at least 3 consecutive months*" with the response options "no", "little complaints" or "severe complaints" (little and severe were pooled as yes). See table 1 for outcomes used in this study.

Table 1. Table of outcomes included in this study. The Tromsø Study 2015-2016

	Outcome	**Instrument**
Main	Chronic pain	Graphical Index of Pain
	Moderate-to-severe chronic pain	Graphical Index of Pain
Additional for robustness	Chronic musculoskeletal pain	Tromsø7 questionnaire
	Chronic pain questionnaire	Tromsø7 questionnaire
	Moderate-to-severe chronic pain without ADL-criteria	Graphical Index of Pain

2.4 Confounders

A directed acyclic graph was used to illustrate possible confounders (fig. S1, available at http://links.lww.com/PAIN/B713). We choose not to include two of the variables illustrated in the graph, e.g. self-reported health and body mass index, as the variables were regarded as collider and mediator, respectively. The following variables were identified as possible confounders and were included in the analysis: age, sex, education, smoking, and occupational physical activity. Data on education were obtained by the question "*What is the highest level of education you have completed?*" with four classifications "*primary/partly secondary education (up to 10 years of schooling)*", "*upper secondary education: (a minimum of 3 years)*", "*tertiary education short: college/university less than 4 years*" or "*tertiary education long: college/university 4 years or more*". Smoking was assessed through the question "*Do you/did you smoke daily?*" with three answers "*yes, now*", "*previously*" or "*never*". Occupational physical activity was assessed by the question "*If you have paid or unpaid work, which statement describes your work best?*" with four categories; "*mostly sedentary work (e.g. office work, mounting)*", "*work that requires a lot of walking (e.g. shop assistant, light industrial work)*", "*work that requires a lot of walking and lifting (e.g. nursing, construction)*", or "*heavy manual labour*". We added a fifth category including participants that answered *"retired", "unemployed"* or *"disability benefit recipient/work assessment allowance"* when they were asked about their main occupation/activity.

2.5 Statistical analysis

The associations between *i*) physical activity and chronic pain; and *ii*) physical activity and moderate to severe chronic pain were assessed using generalized linear models (GLM) with Poisson family log link function and robust variance. Absolute prevalence and relative prevalence ratios (PR) with accompanying 95% confidence intervals (CI) were estimated (see table S1 and S2, available at http://links.lww.com/PAIN/B713). All GLMs were adjusted for age (continuous), education level (categorical), smoking (categorical), occupational physical activity (categorical) and sex (dichotomous). Due to the non-linear distribution of age, we tested for non-linearity in our models. We addressed the issue using a) squared age and b) with cubic spline including 4 knots (results not shown). The results did not differ from the analyses presented in this manuscript. Moreover, previous epidemiological papers have reported stratified results either on age and/or sex. Therefore ,we tested for interactions between a) the various measures of PA and sex (12 models) and b) the various measures of PA and age (12 models). Accelerometers included 24-hour measurements, obtaining physical activity both at leisure time and work. Therefore, we conducted an additional analysis on accelerometers without adjustment for occupational physical activity. We also estimated models where the two chronic pain outcomes from the Graphical Index of Pain were replaced with two other chronic pain outcomes from questionnaires (see table 1) and compared estimates of these. Lastly, based on the estimates from the GLM-models, we performed sensitivity analyses to assess the strength of unmeasured confounding as described by VanderWeele and Ding [58]. We estimated E-values to show the minimum strength of the association that unmeasured confounding would have to explain away the observed association. E-values were estimated for the prevalence ratio estimate and the confidence interval closest to null (table S3, available at http://links.lww.com/PAIN/B713) [58]. All statistical analyses were performed in Stata 15 (StataCorp LP, College Station, Texas).

2.6 Missing, exclusion and multiple imputation

A total of 20,236 respondents completed GRIP. Of those, 2,812 participants (60 percent women) had missing values for one or more variables in either outcome or covariables (table S4, available at http://links.lww.com/PAIN/B713). For GRIP, thirty respondents (14 women) were classified as false positive for chronic pain and excluded from the analysis. To classify as false positive the participants had to report >3 months of duration for the pain and 0 on the pain intensity scale. For exposures, missing values were as follows: leisure time physical activity = 386, exercise frequency = 96, exercise duration = 890, exercise intensity = 989 (table S5, available at http://links.lww.com/PAIN/B713).

We used multiple imputation with chained equation under the assumption of missing at random to assess the impact of missing data on our self-reported models. The imputation model was based upon complete response rate in age and sex and imputed values in outcomes, exposure and covariables. For derived variables we used “Impute, then transform” approach [60]. We used predictive mean matching with random seed and added 10 imputed datasets. The results from the imputed model only showed minor changes in the effect estimates (results not shown). Hence, the assessment supported that complete-case analyses could be used.

2.7 Ethics

Tromsø7 was approved by the Norwegian Data Protection Authority (14/01463-4/CGN) and by the Regional Committee for Medical and Health Research Ethics (REC), (2014/940 REC North). The present study was approved by REC (2016/1794 REC North). The participants have given written informed consent.

2.8 Patient and public involvement

There is an agreement with the Norwegian Rheumatism Association to enhance user involvement in our projects. The organization is advisory in the present project, especially when it comes to dissemination and communication of the findings to the general population and to the members of their association.

3.0 RESULTS

3.1 Characteristics of the study population

After accounting for missing, 17,421 (51 percent women, mean age of 56.8 years) reported on GRIP (fig.1). The prevalence of chronic pain was 59.5% and moderate-to-severe chronic pain 18.8%. For women, the prevalence of chronic pain was 64.1% and moderate-to-severe chronic pain was 23.5%. The prevalence of chronic pain was lower for men with 54.6% and 13.8% for moderate-to-sever chronic pain. More information about the characteristics of the study population is given in table 1.

Table 2. Descriptive characteristics of the study population. The Tromsø Study 2015-2016

		Total	Women	Men
Number of respondents				
	Frequency, n (%)	17,421 (100)	8,944 (51.3)	8,477 (48.7)
Chronic pain				
	Yes	10,366 (59.5)	5,736 (64.1)	4,630 (54.6)
Moderate-to-severe chronic pain				
	Yes	3,269 (18.8)	2,099 (23.5)	1,170 (13.8)
Age				
	Mean (SD)	56.8 (11.1)	56.7 (11.1)	56.9 (11.2)
Education, n (%)				
	Primary/partly secondary	3,791 (21.8)	1,999 (22.4)	1,792 (21.1)
	Upper secondary	4,836 (27.8)	2,261 (25.3)	2,575 (30.4)
	Tertiary education - short	3,407 (19.6)	1,587 (17.7)	1,820 (21.5)
	Tertiary education - long	5,387 (30.9)	3,097 (34.6)	2,290 (27.0)
Smoking, n (%)				
	Yes - now	2,353 (13.5)	1,285 (14.4)	1,068 (12.6)
	Yes - previously	7,645 (43.9)	3,883 (43.4)	3,762 (44.4)
	Never	7,423 (42.6)	3,776 (42.2)	3,647 (43.0)
Physical activity at work, n (%)				
	Sedentary	8,110 (46.6)	3,827 (42.8)	4,283 (50.5)
	Walking	3,465 (19.9)	1,922 (21.5)	1,543 (18.2)
	Walking and lifting	2,256 (13.0)	1,132 (12.7)	1,124 (13.3)
	Manual labour	339 (2.0)	84 (0.9)	255 (3.0)
	Retired, disability benefit	3,251 (18.7)	1,979 (22.1)	1,272 (15.0)
Leisure time physical activity, n (%)				
	Sedentary	2,377 (13.6)	1,143 (12.8)	1,234 (14.6)
	Low	9,822 (56.4)	5,622 (62.9)	4,200 (49.6)
	Moderate	4,280 (24.6)	1,701 (19.0)	2,579 (30.4)
	Vigorous	556 (3.2)	218 (2.4)	338 (4.0)
	Missing	386 (2.2)	260 (2.9)	126 (1.5)
Exercise frequency, n (%)				
	Never	637 (3.7)	282 (3.2)	355 (4.2)
	Less than once a week	2,047 (11.8)	842 (9.4)	1,205 (14.2)
	Once a week	2,541 (14.6)	1,154 (12.9)	1,387 (16.4)
	2-3 times a week	7,251 (41.6)	3,864 (43.2)	3,387 (40.0)
	Approximately every day	4,849 (27.8)	2,750 (30.8)	2,099 (24.8)
	Missing	96 (0.6)	52 (0.6)	44 (0.5)
Exercise duration, n (%)				

	Less than 15 minutes	748 (4.3)	301 (3.4)	447 (5.3)
	15-29 minutes	2,672 (15.3)	1,363 (15.2)	1,309 (15.4)
	30-60 minutes	9,431 (54.1)	5,205 (58.2)	4,226 (49.9)
	More than 1 hour	3,680 (21.1)	1,655 (18.5)	2,025 (23.9)
	Missing	890 (5.1)	420 (4.7)	470 (5.5)
Exercise intensity, n (%)				
	Low	6,222 (35.7)	3,479 (38.9)	2,743 (32.4)
	Moderate	9,485 (54.5)	4,713 (52.7)	4,772 (56.3)
	Hard	725 (4.1)	284 (3.2)	441 (5.2)
	Missing	989 (5.7)	468 (5.2)	521 (6.2)
Number of steps daily				
	<5 000	1,295 (7.4)	683 (7.6)	612 (7.2)
	5 000-7 499	1,758 (10.1)	905 (10.1)	853 (10.1)
	7 500-9 999	1,244 (7.1)	651 (7.3)	593 (7.0)
	10 000-12 499	540 (3.1)	299 (3.3)	241 (2.8)
	≥12 500	235 (1.4)	132 (1.5)	103 (1.2)
Moderate to vigorous minutes/day*				
	1.quartile	1,268 (7.3)	668 (3.8)	603 (3.5)
	2.quartile	1,268 (7.3)	669 (3.8)	598 (3.4)
	3.quartile	1,271 (7.3)	666 (3.8)	602 (3.5)
	4.quartile	1,265 (7.3)	667 (3.8)	599 (3.4)

*Does not add up to total due to differences in moderate to vigorous minutes per day, separate analyses displayed in supplementary

3.2 Associations between different measurements of physical activity and chronic pain

Out of 12 age-interaction models we only found one significant interaction. This was for moderate exercise intensity where prevalence of chronic pain increased with age (p=0.046). Therefore, we choose not to display age-stratified results. Tests for sex-interactions were non-significant for all the 12 models, except for the association between the 2nd quartile of MVPA-minutes and chronic pain (p=0.043). Hence, we chose to present all the results for women and men in pooled samples (sex stratified estimates are displayed in fig. S2-S5, available as supplemental digital content at http://links.lww.com/PAIN/B713).

3.2.1 Self-reported leisure time physical activity

The absolute estimates of chronic pain and moderate-to-severe chronic pain prevalence decreased with increased levels of leisure time physical activity (fig. 2A). The same dose-response pattern was found for the relative estimates for both chronic pain and moderate-to-severe chronic pain (fig. 3). The largest reduction was in those reporting the highest leisure time activity level, with PR 0.80 (95% CI 0.73 to 0.87) for chronic pain and PR 0.49 (95% CI 0.36 to 0.62) for moderate-to-severe chronic pain (fig. 3).

3.2.2 Self-reported physical exercise

Frequency: The absolute prevalence of chronic pain or moderate-to-severe chronic pain was highest among those reporting never exercising, and lowest for those reporting exercising approximately every day (fig. 2B). For the PRs, reporting an exercise frequency of 2-3 times a week was associated with less chronic pain with PR 0.93 (95% CI 0.87 to 0.99) (fig 3.). Less chronic pain was also observed in those reporting exercising approximately every day with PR 0.90 (95% CI 0.84 to 0.96). For moderate-to-severe chronic pain the association was stronger, with a PR 0.78 (95% CI 0.66 to 0.89) for those reporting exercising less than once a week, PR 0.79 (95% CI 0.68 to 0.91) for those exercising once a week, PR 0.70 (95% CI 0.60 to 0.79) for those exercising 2-3 times a week, and PR 0.63 (95% CI 0.55 to 0.72) for those reporting exercising approximately every day.

Duration: The association between exercise duration and chronic pain prevalence was different from all other physical activity measurements, as we did not observe any clear pattern for the association (fig. 2C). For moderate-to-severe chronic pain, an increase in exercise duration was associated with less prevalent moderate-to-severe chronic pain (fig. 2C). For relative estimates, the associations between physical activity levels and chronic pain were not statistically significant different from the reference group (fig. 3). However, for moderate-to-severe chronic pain, we found those reporting exercising 30-60 minutes a week had PR 0.77 (95% CI 0.67 to 0.88) and those reporting more than 1 hour had PR 0.73 (95% CI 0.63 to 0.84).

Intensity: We found lowest absolute prevalence estimates of chronic pain in the highest exercise intensity level (fig. 2D). Similarly, lower prevalence of moderate-to-severe chronic pain was related to higher intensity levels. Relative estimates showed less chronic pain in those reporting hard intensity level with PR 0.89 (95% CI 0.83 to 0.95) (fig 3). For moderate-to-severe chronic pain there was an inverse dose-response relationship with exercise intensity, resulting in PR 0.85 (95% CI 9.79 to 0.9) for moderate intensity and PR 0.69 (95% CI 0.55 to 0.83) for hard intensity.

3.2.3 Accelerometer measured physical activity

Number of steps per day: The absolute prevalence estimates of chronic pain and moderate-to-severe chronic pain decreased with increasing number of steps per day (fig. 2E). A similar pattern was found for the relative estimates; there was less chronic pain among those reporting 7500 steps or more (fig 3). Similarly, for more severe chronic pain, there was a statistically significant inverse dose-response relationship with number of steps per day.

MVPA-minutes per day: We found lower absolute estimates of chronic pain and moderate-to-severe chronic pain per increase in quartile of MVPA-minutes per day (fig. 2F). An inverse dose-response relationship was observed for the relative association between minutes of MVPA per day and chronic pain and moderate-to-severe chronic pain (fig. 3). The relationship was stronger for moderate-to-severe chronic pain.

Figure 2. Association between different measurements of physical activity and the absolute prevalence of chronic pain (green dotted line) and moderate-to-severe chronic pain (orange line). In Poission regression models, the prevalence estimates with 95% confidence intervals are adjusted for sex, age, smoking history, education level and occupational physical activity. The Tromsø Study 2015-2016.

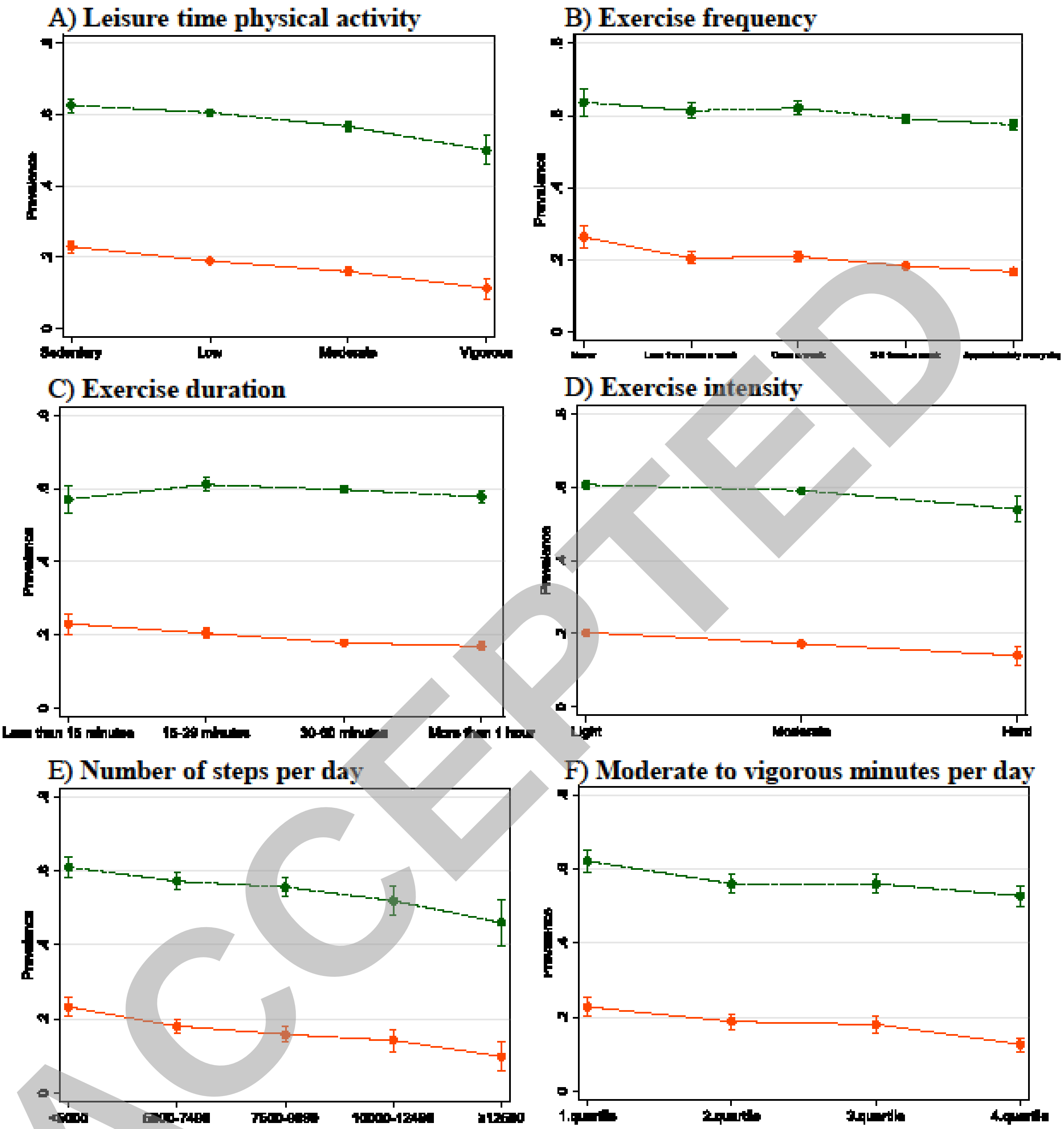
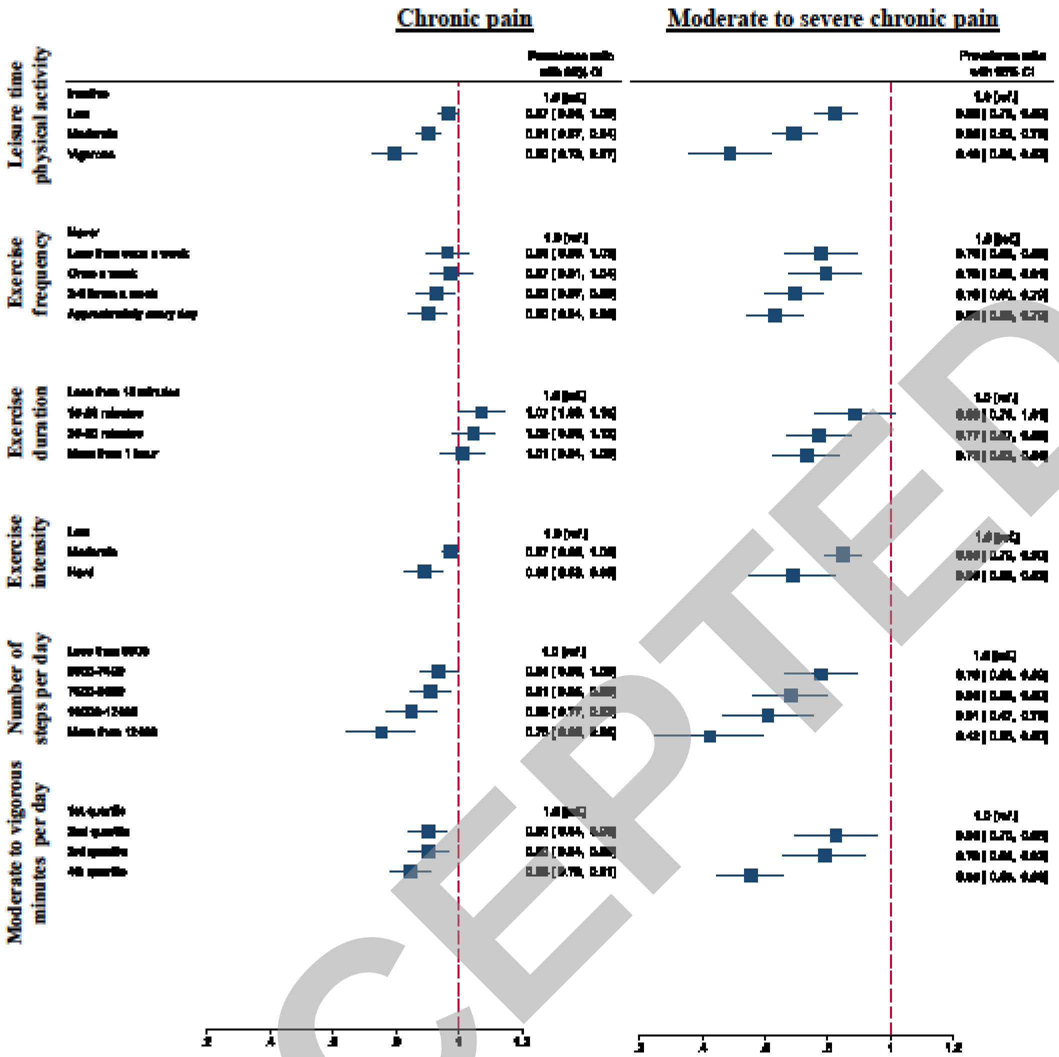

A) Leisure time physical activity
Prevalence
0
.2
.4
.6
.8
Sedentary
Low
Moderate
Vigorous
B) Exercise frequency
Prevalence
0
.2
.4
.6
.8
Never
Less than once a week
Once a week
2-3 times a week
Approximately everyday
C) Exercise duration
Prevalence
0
.2
.4
.6
.8
Less than 15 minutes
15-29 minutes
30-60 minutes
More than 1 hour
D) Exercise intensity
Prevalence
0
.2
.4
.6
.8
Light
Moderate
Hard
E) Number of steps per day
Prevalence
0
.2
.4
.6
.8
<5000
5000-7499
7500-9999
10000-12499
≥12500
F) Moderate to vigorous minutes per day
Prevalence
0
.2
.4
.6
.8
1.quartile
2.quartile
3.quartile
4.quartile

Figure 3. Association between different measurements of physical activity and the relative prevalence of chronic pain and moderate-to-severe chronic pain. The Poission regression models display prevalence ratios with 95% confidence intervals are adjusted for sex, age, smoking history, education level and occupational physical activity. The Tromsø Study 2015-2016.



3.3 Sensitivity analyses

We observed similar results when omitting the impact of daily activities parameter from the definition of moderate-to-severe chronic pain (fig. S6, available at http://links.lww.com/PAIN/B713). Omitting adjustments for physical activity at work for the analysis of accelerometer-measured physical activity did not change the direction of the association, statistical significance, or size of the effect estimates (results not shown). When replacing the GRIP chronic pain outcomes (see 2.3), we found that the pattern and strength of the association between physical activity and chronic musculoskeletal complaints were similar to the results from chronic pain in GRIP, whereas the chronic pain reported in the other questionnaire showed similar results as moderate-to-severe chronic pain reported in GRIP (results not shown).

Overall, the E-values were higher in the analyses including moderate-to-severe chronic pain than in chronic pain (Table S3, available at http://links.lww.com/PAIN/B713). The E-values imply that larger unmeasured confounding would need to be present to explain away the observed associations in this paper, especially for moderate-to-severe chronic pain. For example, the observed PR of 0.49 for vigorous leisure time activity could be explained away by an unmeasured confounder that was associated with physical activity and moderate-to-severe chronic pain by a PR at least 3.5-fold each. For the confidence interval nearest null, the unmeasured confounder would need to be associated with exposure and outcome by a PR of 2.61-fold or more each to include the null, but weaker confounding would not explain away the association.

4.0 DISCUSSION

In this population-based study, we found an inverse dose-response relationship between all self-reported and accelerometer based physical activity measures and moderate-to-severe chronic pain. The pattern was similar, but weaker for chronic pain in general. This indicates that severity of chronic pain plays an important role for the strength of the association with activity levels, regardless of physical activity measurement, and does not indicate that high levels of physical activity are detrimental.

The innovative part of our study is the wide spectrum of measurements and analyses compared to the earlier literature. We present absolute and relative prevalence estimates and include results from several different measurements of physical activity and different grades of chronic pain severity. This is to the best of our knowledge a broader perspective than in previous studies in this field.

Comparisons with earlier findings

One of the studies supporting our findings is from Grasdalsmoen et al. (2020) [16], who showed a dose-response relationships between weekly average exercise frequency, duration and intensity and chronic pain among students. The same pattern was observed in a study from Landmark et al. (2011) among adults aged 65 or more, but they found a different pattern for adults between the age of 20 and 64. The authors observed a u-shaped relationship between physical activity and chronic pain in the younger age group, with the lowest and highest exercise levels being associated with higher prevalence of chronic pain [29]. The different pattern might partly be explained by methodological differences, such as the definition of exercising groups. Neither do our results correspond with findings from the sixth survey of the Tromsø Study, where the authors did not find higher levels of physical activity to be associated with lower levels of chronic musculoskeletal complaints [4]. This inconsistency with our study might also be explained by methodological differences, as the assessment of the chronic state and the statistical analyses were different from ours. Firstly, the prior publication included stiffness and/or pain in the definition of musculoskeletal complaints[4], while the current study focuses solely on pain. Secondly, we chose not to adjust for self-perceived health status in our statistical model. Our reasoning was that such adjustment might introduce collider bias in analysis of associations between the level of physical activity and the chronic pain status, because both factors might influence an individual’s self-perceived health status [59]. Thirdly, we did not adjust for body mass index as it might be considered a potential mediator or collider for the association between physical activity and chronic pain [57]. Finally, we adjusted for occupational physical activity in our statistical model [59], which is in contrast with the other studies [16; 29; 56]. Our reasoning was that occupational physical activity might bias estimates since occupation is associated with the attained level of leisure time physical activity [27] and certain chronic pain conditions [22]. In a study with opposite order of exposure and outcome, focusing on chronic pain as exposure and the amount of leisure time physical activity as outcome, found similar results as presented in our study. The authors showed that localized or widespread chronic pain was associated with lower levels of physical activity at leisure time compared to no chronic pain, especially for moderate and vigorous physical activity [56].

Possible mechanisms

Several mechanisms might influence the relationship between physical activity and chronic pain [7; 31; 32; 38; 46-48]. Exercise induced-hypoalgesia (EIH) is a known response to exercise and refers to the decrease of pain sensitivity after bouts of acute exercise [38]. The underlying mechanisms behind EIH are complex and theorized to include several biological systems, for review see [34; 38]. EIH is observed in healthy and pain-free individuals. However, the result for chronic pain is ambiguous (see review [34]). The review displays small to large EIH-effects for people with regional chronic pain when exercising at low to moderate intensity. On the other hand, the effects were non-existing for individuals with chronic widespread pain [34]. This indicates that severity and distribution of chronic pain and chronic pain conditions may be of importance for the analgesic effect from exercise. However, findings from animal studies suggest that regular physical activity is of importance for preventing the development of chronic pain [7; 32; 46; 48], through different pathways, such as activation of inhibitory systems or by an increased level of anti-inflammatory mechanisms [7; 32; 46; 48]. Such mechanistic studies are most often conducted in animals [7;

31; 32; 38; 46; 48] or pain-free individuals [38], and the clinical relevance for individuals with chronic pain conditions remains uncertain. Additionally, other factors may contribute to more chronic pain among the physically inactive. For example, an inactive lifestyle is strongly related to obesity [11] which is associated with increased mechanical stress on articular cartilage and higher levels of pro-inflammatory proteins such as C-reactive protein and interleukin-6 and interleukin-1β, for review see [61]. Physical activity normally reduces fat mass, levels of inflammatory proteins and increases muscle strength, joint support and stability and thereby may help reduce chronic pain among obese people [61].

Direction of the association

Though our findings provide strong evidence that physical activity and chronic pain are inversely associated in a dose dependent pattern, they do not give inference about the direction of the association. While physical activity may indeed prevent or reduce the severity of chronic pain, for instance through anti-inflammatory mechanisms [15], it is also plausible that chronic pain leads to decreased mobility by inhibiting physical activity and promoting a more sedentary lifestyle, partly through fear of potential harm or exacerbation of pain when performing physical activity [3; 9; 10; 26]. However, our robustness analyses did not indicate that physical limitation was an important factor in the relationship between physical activity and moderate-to-severe chronic pain. Additionally, physical activity can be used as a treatment strategy in the management of pain and chronic pain [5; 55], which might reduce the strength of the relationship found in this study. Nor can one preclude the possibility of a bi-directional relationship between physical activity and pain. This notion is supported by a longitudinal study, where the authors found low levels of exercise to be both a risk and a consequence of pain reported for the past four weeks [30]. Whether these findings are relevant for chronic pain remains to be determined.

Strengths and limitations

The strengths of our study include the large number of participants, the different measures of the exposure and outcome, and the collection of health- and lifestyle related factors that allows adjustments for potential confounders. This allowed us to investigate the relationship with several physical activity measurement methods and different severity definitions of chronic pain. All the included physical activity measurements have been validated, displaying fair to good results [8; 17; 28; 40; 45]. A full discussion of the methodological differences between self-reported physical activity questionnaires and accelerometer-measured physical activity is beyond the scope of this study but have been reviewed elsewhere [12; 25; 35; 43; 45]. One limitation is the potential for misclassification in the self-reported data, as respondents report back in time and need to recollect past experiences [44] or report inconsistently with actual attained levels of physical activity [25; 35; 37]. Another limitation is the potential impact of selection bias. However, this has partly been accounted for by adjusting for several variables that might be related to non-response. Additionally, although GRIP has been piloted before use, validation of the instrument against clinically diagnosed cases has yet to be done. However, in our sensitivity analyses we used previously validated items on chronic pain/complaints which showed similar results.

5.0 CONCLUSION

This population-based study showed an inverse dose-response relationship between both self-reported and accelerometer-measured physical activity and chronic pain, as well as moderate to severe chronic pain. The associations were stronger for moderate to severe chronic pain. To summarize, our finding showed that more physical activity is associated with less chronic pain and moderate-to-severe chronic pain

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	Outcome	**Instrument**
Main	Chronic pain	Graphical Index of Pain
	Moderate-to-severe chronic pain	Graphical Index of Pain
Additional for robustness	Chronic musculoskeletal pain	Tromsø7 questionnaire
	Chronic pain questionnaire	Tromsø7 questionnaire
	Moderate-to-severe chronic pain without ADL-criteria	Graphical Index of Pain

		Total	**Women**	**Men**
	Number of respondents			
	Frequency, n (%)	17,421 (100)	8,944 (51.3)	8,477 (48.7)
	Chronic pain			
	Yes	10,366 (59.5)	5,736 (64.1)	4,630 (54.6)
	Moderate-to-severe chronic pain			
	Yes	3,269 (18.8)	2,099 (23.5)	1,170 (13.8)
	Age			
	Mean (SD)	56.8 (11.1)	56.7 (11.1)	56.9 (11.2)
	Education, n (%)			
	Primary/partly secondary	3,791 (21.8)	1,999 (22.4)	1,792 (21.1)
	Upper secondary	4,836 (27.8)	2,261 (25.3)	2,575 (30.4)
	Tertiary education - short	3,407 (19.6)	1,587 (17.7)	1,820 (21.5)
	Tertiary education - long	5,387 (30.9)	3,097 (34.6)	2,290 (27.0)
	Smoking, n (%)			
	Yes - now	2,353 (13.5)	1,285 (14.4)	1,068 (12.6)
	Yes - previously	7,645 (43.9)	3,883 (43.4)	3,762 (44.4)
	Never	7,423 (42.6)	3,776 (42.2)	3,647 (43.0)
	Physical activity at work, n (%)			
	Sedentary	8,110 (46.6)	3,827 (42.8)	4,283 (50.5)
	Walking	3,465 (19.9)	1,922 (21.5)	1,543 (18.2)
	Walking and lifting	2,256 (13.0)	1,132 (12.7)	1,124 (13.3)
	Manual labour	339 (2.0)	84 (0.9)	255 (3.0)
	Retired, disability benefit	3,251 (18.7)	1,979 (22.1)	1,272 (15.0)
Self-reported	Leisure time physical activity, n (%)			
	Sedentary	2,377 (13.6)	1,143 (12.8)	1,234 (14.6)
	Low	9,822 (56.4)	5,622 (62.9)	4,200 (49.6)
	Moderate	4,280 (24.6)	1,701 (19.0)	2,579 (30.4)
	Vigorous	556 (3.2)	218 (2.4)	338 (4.0)
	Missing	386 (2.2)	260 (2.9)	126 (1.5)
	Exercise frequency, n (%)			
	Never	637 (3.7)	282 (3.2)	355 (4.2)
	Less than once a week	2,047 (11.8)	842 (9.4)	1,205 (14.2)
	Once a week	2,541 (14.6)	1,154 (12.9)	1,387 (16.4)
	2-3 times a week	7,251 (41.6)	3,864 (43.2)	3,387 (40.0)
	Approximately every day	4,849 (27.8)	2,750 (30.8)	2,099 (24.8)
	Missing	96 (0.6)	52 (0.6)	44 (0.5)
	Exercise duration, n (%)			
	Less than 15 minutes	748 (4.3)	301 (3.4)	447 (5.3)
	15-29 minutes	2,672 (15.3)	1,363 (15.2)	1,309 (15.4)
	30-60 minutes	9,431 (54.1)	5,205 (58.2)	4,226 (49.9)
	More than 1 hour	3,680 (21.1)	1,655 (18.5)	2,025 (23.9)
	Missing	890 (5.1)	420 (4.7)	470 (5.5)
	Exercise intensity, n (%)			
	Low	6,222 (35.7)	3,479 (38.9)	2,743 (32.4)
	Moderate	9,485 (54.5)	4,713 (52.7)	4,772 (56.3)
	Hard	725 (4.1)	284 (3.2)	441 (5.2)
	Missing	989 (5.7)	468 (5.2)	521 (6.2)
Accelerometer-measured	Number of steps daily			
	<5 000	1,295 (7.4)	683 (7.6)	612 (7.2)
	5 000-7 499	1,758 (10.1)	905 (10.1)	853 (10.1)
	7 500-9 999	1,244 (7.1)	651 (7.3)	593 (7.0)
	10 000-12 499	540 (3.1)	299 (3.3)	241 (2.8)
	≥12 500	235 (1.4)	132 (1.5)	103 (1.2)
	Moderate to vigorous minutes/day*			
	1.quartile	1,268 (7.3)	668 (3.8)	603 (3.5)
	2.quartile	1,268 (7.3)	669 (3.8)	598 (3.4)
	3.quartile	1,271 (7.3)	666 (3.8)	602 (3.5)
	4.quartile	1,265 (7.3)	667 (3.8)	599 (3.4)

*Does not add up to total due to differences in moderate to vigorous minutes per day, separate analyses displayed in supplementary