Clinical pain research

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Associations of physical activity or sedentary behaviour with pain sensitivity in young adults of the Raine Study

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Abstract

Background and aims: There is high level evidence for physical activity (PA) improving outcomes in persistent pain disorders and one of the mechanisms proposed is the effect of exercise on central nociceptive modulation. Although laboratory studies and small field intervention studies suggest associations between physical activity and pain sensitivity, the association of objectively measured, habitual PA and sedentary behaviour (SB) with pain sensitivity requires further investigation. Current evidence suggests PA typically lowers pain sensitivity in people without pain or with single-site pain, whereas PA is frequently associated with an increase in pain sensitivity for those with multisite pain. The aim of this study was to explore the relationships of PA and SB with pain sensitivity measured by pressure pain thresholds and cold pain thresholds, considering the presence of single-site and multisite pain and controlling for potential confounders.
Methods: Participants from the Western Australian Pregnancy Cohort (Raine) Study ($n=714$) provided data at age 22-years. PA and SB were measured via accelerometry over a 7-day period. Pain sensitivity was measured using pressure pain threshold (4 sites) and cold pain threshold (wrist). Participants were grouped by number of pain areas into "No pain areas" ($n=438$), "Single-site pain" ($n=113$) and "Multisite pain" ($n=163$) groups. The association of PA and SB variables with pain sensitivity was tested separately within each pain group by multivariable regression, adjusting for potential confounders.
Results: For those with "Single-site pain", higher levels (>13 min/day) of moderate-vigorous PA in ≥10 min bouts was associated with more pressure pain sensitivity ($p=0.035$). Those with "Multisite pain" displayed increased cold pain sensitivity with greater amounts of vigorous PA ($p=0.011$). Those with "No pain areas" displayed increased cold pain sensitivity with decreasing breaks from sedentary time ($p=0.046$).
Conclusions: This study was a comprehensive investigation of a community-based sample of young adults with "No pain areas", "Single-site pain" and "Multisite pain" and suggests some associations of measures of PA and SB with pain sensitivity.
Implications: The findings suggest that the pattern of accumulation of PA and SB may be important to inform improved clinical management of musculoskeletal pain disorders. This study provides a baseline for follow-up studies using the Raine Study cohort. Future research should consider temporal influences of PA and SB on pain sensitivity, pain experience and consider using a broader range of pain sensitivity measures.

Keywords: pain sensitivity; accelerometry; musculoskeletal; Raine Study; physical activity; sedentary behaviour.

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1 Introduction

There is high level evidence for increased levels of physical activity (PA) reducing disability and associated costs for persistent musculoskeletal disorders including lower limb osteoarthritis [1], chronic low back pain [2] and fibromyalgia syndrome [3]. Longitudinal general population

studies further suggest higher PA may reduce the risk for the onset of persistent musculoskeletal pain [4, 5]. Additionally, young adults spend much of their awake time sedentary [6], and links between sedentary behaviour (SB) and increased risk of musculoskeletal pain have been reported in adolescents [7] and adults [8]. One of the mechanisms proposed for PA improving outcomes in musculoskeletal pain disorders, is the effect of exercise on efficient central nociceptive modulation [9]. Measurement of pain sensitivity maybe important to improve the understanding of the relationship between physical activity and sedentary behaviour with pain disorders. Understanding this relationship in young adulthood is of particular importance as this life stage is a transition period when trajectories for persistent pain become established [10, 11] and there is already a significant burden from persistent musculoskeletal pain [12, 13].

Alterations in pain sensitivity in response to laboratory-based, acute bouts of exercise is variable, with evidence of transient decreases in pressure and cold pain sensitivity in pain-free, healthy participants [14], and both increases and decreases in participants with persistent pain [14–16]. This variability in participants with persistent pain may reflect different central nociceptive modulatory responses to exercise [9, 16]. Importantly, increased pressure pain sensitivity following exercise is more prevalent in people with persistent, multisite pain disorders, such as fibromyalgia, consistent with evidence of the presence of augmented central nociceptive processing [15, 17]. Based on laboratory studies, the optimal dose of prescribed exercise to improve pain sensitivity is inconclusive for persistent pain conditions [14].

While laboratory based exercise studies have measured immediate changes in pain sensitivity in response to single exercise sessions, the association of exercise interventions and habitual PA with pain sensitivity may provide more insight into the longer-term associations of PA with pain sensitivity in both clinical and community-based settings. Findings from a limited number of short to medium term (1–10 weeks) exercise intervention field studies, suggest the potential for increased PA to produce a medium term beneficial reduction of pressure pain sensitivity [18–20]. In healthy people, when habitual PA was measured via self-report, evidence suggests an association between higher levels of PA and decreased pressure and cold pain sensitivity [21, 22]. Observational studies using objective measurement of PA via accelerometry to investigate the association of habitual PA and pain sensitivity have inconclusive findings with either very limited participant numbers ($n = 21$) [23] or only using participants without pain [24].

There is little investigation of the association of objectively measured, habitual PA and SB with pain sensitivity in community based cohorts. The aim of this study was to explore the relationships of PA and SB with pain sensitivity measured by pressure pain thresholds (PPT) and cold pain thresholds (CPT), considering the presence of single-site and multisite pain and controlling for potential confounders.

2 Methods

2.1 Participants

Cross-sectional data for this study were obtained from the Western Australian Pregnancy Cohort (Raine) Study (http://www.rainestudy.org.au). This is an ongoing birth cohort study that commenced with 2900 women who enrolled in the study before the 18th gestation week with 2,868 children born entering the initial birth cohort. Data has been collected at 1, 2, 3, 5, 8, 10, 14, 17, 20 and 22-years. The current study used data obtained at the 22-year follow up that ran between March 2012 and July 2014, 2,086 were still "active" and contacted for participation. Of these, 1,234 took part in some aspect of the 22-year follow up that included an extensive range of questionnaires and physical assessments [25, 26]. The characteristics of the active participants were compared with census data collected in 2011 on all similarly aged young adults in Western Australia and showed that the sample remains widely representative on a range of variables including education level, employment status, income, marital status, number of offspring, hours worked and occupation [25]. The ethnicity of the active participants was 85.0% Caucasian, 0.9% Aboriginal and Torres Strait Islander, and 14.1% non-Caucasian.

2.2 Recruitment, sampling and data collection

Data for this study were collected as part of 4 h of testing followed by an overnight sleep study [25]. Questionnaires were completed before physical assessments and were checked for completion by a research assistant. Anthropometry measures, and pressure and cold pain threshold testing were part of the physical assessment protocol conducted by 12 Raine research staff, all of who were thoroughly trained in the data collection procedures and used standardised protocols. For this follow up, 773 (389 female and 384 male) participants wore Actigraph GT3X+ monitors 24 h/day over

a 1-week period. Participants were eligible for analysis if they had data for at least one "valid" day (≥10 h of waking wear time) and completed the Orebro Musculoskeletal Pain Questionnaire. The minimum of one "valid" day was chosen in order to maximize statistical power and to minimize selection bias. Of these, 714 individuals had valid PPT data and 702 individuals had valid CPT data.

2.3 Physical activity and sedentary behaviour

Physical activity and sedentary behaviour were objectively measured over a 1-week period using the Actigraph GT3X+ accelerometer (Actigraph, Pensacola, FL, USA) worn continuously on the right hip, except during bathing or aquatic activities. The GT3X+ was programmed to record raw data at a frequency of 30 Hz which were later reduced to vertical axis movement counts "per 60 s epoch" for the purpose of the current analyses. Accelerometer data were downloaded and processed in SAS (version 9.3, SAS Institute, Cary, NC, USA). The protocol and measured patterns of PA and SB in the Raine Study have previously been comprehensively described [6]. The "60 s epoch" was used as cut points in this age group have been validated for this length of epoch and this allows comparisons with other accelerometer data also processed using a 60 s epoch [27]. Common thresholds were used to class each minute as sedentary [<100 counts per minute (cpm)], light intensity (100–1951 cpm), moderate intensity (1952–5724 cpm) or vigorous intensity (>5,724 cpm) [6, 28]. All minutes in continuous periods of ≥90 min of zero cpm, allowing for <3 min with counts 1–50 cpm, were classed as non-wear. The algorithm used for identifying waking wear time has been reported as mostly good, and better than evaluated published alternatives [27]. Variables representing moderate PA, vigorous PA, combined moderate/vigorous PA (MVPA), sedentary time in minutes per day and sedentary time as a percentage of non-MVPA time during wake time were derived from these classifications. A further five variables captured the pattern of accumulation PA and SB as follows; MVPA min/day in ≥10 min bouts (allowing for 2 min below the cut-point), sedentary min/day in ≥20 min bouts and ≥30 min bouts, proportion of sedentary time per day accumulated in ≥20 min bouts and number of breaks from sedentary time per day.

2.3.1 Quantitative sensory testing

Due to the already significant time burden required of the participants in the broader Raine Study, pain sensitivity measures were limited to PPT and CPT. A standardised protocol ("method of limits") consistent with current best practice recommendations [29] was used to measure PPT and CPT at a constant room temperature. The protocol has been published previously and is also described below [24]. All testing was done in the early evening, minimising the influence of circadian rhythms on pain sensitivity [30]. All pain threshold measurements were taken from the right side of the body as it has been shown there is side to side consistency in pain sensitivity measurement in people with [31] and without pain [32]. PPT was tested first, followed by CPT, to minimise the risk of mechanical hyperalgesia [33]. Both PPT and CPT have demonstrated inter-examiner and intra-subject reliability with reasonable levels of standard error of measurement [34]. Excellent interrater and intrarater reliability for PPT testing by the Raine research staff has been demonstrated [35].

2.3.2 Pressure pain thresholds

Pressure pain threshold was established using a pressure algometer (Somedic AB, Sweden) with a contact area of 1 cm^2 applied perpendicularly to the skin with a ramp rate of 50 kPa/s. PPT was defined as the moment the sensation of pressure becomes one of pressure and pain. Standardised instructions were read to participants: "The moment the pressure increases to a point where it first feels uncomfortable or painful, press and release the button. This means the very first onset of discomfort or pain and not the most pressure that you can bear". A cut-off pressure value of 1,000 kPa was set for safety purposes. Four trials were performed with a minimum 10 s rest between trials. The mean threshold was calculated for each site from the last three trials. Four standardised sites were tested in the following sequence; the dorsal wrist, tibialis anterior, upper trapezius and lumbar spine. The wrist was tested at the middle of the dorsal aspect of the wrist joint line. The leg was tested at the muscle belly of tibialis anterior, approximately 2.5 cm lateral and 5 cm distal to the tibial tubercle. The upper trapezius was tested at the mid-point between the C7 spinous process and the lateral acromion. The lumbar spine was tested at the erector spinae, 2 cm lateral to the L4/L5 interspinous space.

2.3.3 Cold pain threshold

A Modular Sensory Analyzer (MSA) thermal stimulator (Somedic AB, Sweden) using a 12.5 cm^2 (25 mm × 50 mm) probe was used to obtain the CPT at one standardised body

site, on the skin at the middle of the dorsal aspect of the wrist joint line. The starting temperature was set as 32 °C with a cut off temperature of 5 °C. The temperature decreased at 1 °C/s until the participant first perceived pain and pressed the control switch to terminate the test. For CPT, the following instructions were given to participants "Allow the temperature to drop until the moment it reaches a point where it feels uncomfortably or painfully cold, and then press the button. This means the very first onset of discomfort or pain and not the most cold that you can bear". Four trials were performed with a 10 s rest period between trials. The mean threshold was calculated from the last three trials.

2.4 Musculoskeletal pain status

Pain experience was determined using items from the Örebro Musculoskeletal Pain Questionnaire (ÖMPQ). The number of musculoskeletal pain areas was determined from an individual question asking "Where do you have pain?" with instruction to select appropriate sites from the options of neck, shoulder, arm, upper back, lower back, leg and other ("please state"). In the Örebro questionnaire, pain was defined as "musculoskeletal (muscle and bone) aches or pains, such as back, shoulder or neck pain". Participants were classified by number of pain areas endorsed into "No pain areas", "Single-site pain" and "Multisite pain" (i.e. two or more pain areas) groups. Pain chronicity was categorized from the ÖMPQ question "How long have you had your current pain problem?" into less than 3 months, 3–12 months and >12 months. Pain frequency was determined using the ÖMPQ question "How often would you say that you have experienced pain episodes, on average, during the past three months?", using a numerical rating scale (NRS) with 1 indicating "never" and 10 indicating "always". Pain intensity was calculated from the mean of two ÖMPQ questions "How would you rate the pain that you have had during the past week?" and "In the past three months, on average, how bad was your pain on a 0–10 scale?", using an NRS with 1 indicating "no pain" and 10 indicating "pain as bad as it could be".

2.5 Other variables

A number of other variables were collected at 22-years to provide a profile of participants and to control for confounders of pain sensitivity. Potential confounders of the association between pain sensitivity and PA/SB measures were considered based on a previous investigation of correlates of PPT and CPT in the Raine cohort at the 22-year follow-up [24]. Statistically significant, known, independent correlates of increased pressure pain sensitivity measures were test site, sex (female), higher waist-hip ratio (WHR) and poorer mental health [as measured by the Mental Component Summary (MCS) of the Short Form-12, version 2 (SF-12)] [24]. Statistically significant, known, independent correlates of increased cold pain sensitivity measures were sex (female), poorer mental health and smoking [24].

Waist and hip circumference were measured using a metric tape measure and standard protocol, to calculate the WHR. Health-related quality of life was measured using the SF-12 [36], a validated and reliable measure of health related quality of life. Twelve questions produce two summary measures: a MCS; and Physical Component Summary (PCS) [36]. Each SF-12 scale is a norm-based score with a mean of 50 and standard deviation of 10, with higher scores indicating better quality of life [36]. The MCS and PCS of the SF12 were categorised into those with a score ≥50 and <50. Subjects were asked, "Do you currently smoke cigarettes/cigars?" and were classified accordingly as smokers or non-smokers.

2.6 Statistical analysis

Multivariable regression models were used to examine the association between PPT and CPT measures (outcome variable) with each of the 10 PA and SB measures (independent variables). For these models, PA and SB measures were parameterised as continuous variables with the exception of moderate PA and MVPA which were categorized into deciles due to left-skew distribution, and vigorous PA and MVPA accumulated in ≥10 min bouts, which were categorized into three groups with one-third of participants registering zero activity and the remaining values split at the median of the non-zero values (1.75 and 13 min/day, respectively). The analyses for all variables were adjusted for waking wear time per day (mean of daily totals on valid days, min/day, except for "Proportion of sedentary time ≥20 min") and number of days of valid wear time (>10 h/day). The analysis of breaks from sedentary time was adjusted for total sedentary time to reflect a break rate based on total sedentary time per day. All models were stratified by pain area groups in keeping with the aim of the study to estimate associations between PA and SB with pain sensitivity separately for people with "no pain areas", "single-site pain" and "multisite pain". The sample size of smallest of these groups ("single-site pain", $n = 112$) gave 80% power to detect increases in R^2 of at least 0.05 due to addition of a PA or SB variable to a base model of relevant covariates with R^2 of 0.15 at $\alpha = 0.05$. Estimates are presented with 95% confidence intervals and p-values. All models were examined for linearity of effects and absence of influential outliers, and with non-linearity modelled by addition of a quadratic

term. For PPT models, linear regression models utilising generalized estimating equations with an exchangeable correlation structure to account for the repeated measures over four sites were used. PPT models were adjusted for potential confounders [24] of sex, test site, waist-hip ratio and MCS. For CPT models, Tobit regression models were used as measures were left-censored due to the lower limit of the testing equipment being 5 °C. CPT models were adjusted for potential confounders [24] of sex, smoking and MCS. A sensitivity analysis was performed, to test if results of the main analysis were potentially biased by atypical activity levels as some participants with only a few valid days of accelerometer wear were included. Thus, the sensitivity analysis included only data from those participants with at least 3 valid weekdays and 1 valid day of weekend data in PPT and CPT regression models.

3 Results

The demographic, pain, physical, quality of life and psychological data of the 714 participants (by pain groups) are summarised in Table 1. Summary statistics for PA and SB are presented in Table 2 and for PPT (by site) and CPT

Table 1: Summary statistics for demographic, pain, physical, quality of life, psychological and smoking measures.

Variable	No pain areas ($n=438$)		Single-site pain ($n=113$)		Multisite pain ($n=163$)	
	Mean (SD) or number (%)	Range	Mean (SD) or number (%)	Range	Mean (SD) or number (%)	Range
Age (years)	22.1 (0.6)	21.0–24.4	22.1 (0.6)	20.7–24.3	22.1 (0.7)	21.0–24.2
Sex (female)	187 (42.7%)		57 (50.5%)		119 (73.0%)	
Pain chronicity						
<3 months			54 (47.8%)		46 (28.2%)	
3–12 months			23 (20.4%)		30 (18.3)	
>12 months			36 (31.8%)		87 (53.4)	
Pain frequency			4.2 (2.3)		5.4 (2.4)	
Pain intensity			4.1 (1.9)		4.8 (2.0)	
Waist-hip ratio	0.83 (0.07)	0.66–1.09	0.83 (0.07)	0.65–1.00	0.81 (0.08)	0.68–1.09
SF-12[a]						
PCS	55.3 (4.9)	24.6–66.5	52.7 (6.0)	34.8–65.4	51.1 (8.2)	14.6–70.9
PCS ≥ 50	343 (86.8%)		73 (70.0%)		104 (65.8%)	
MCS	50.0 (9.5)	11.7–62.5	47.7 (9.2)	24.4–62.4	43.0 (11.4)	−0.8–62.2
MCS ≥ 50	201 (50.9%)		55 (50.4%)		51 (32.3%)	
Smoking[b] (yes)	66 (15.1%)		20 (17.9%)		29 (17.9%)	

Missing data (all participants): [a]52; [b]4; PCS = physical component summary; MCS = mental component summary.

Table 2: Summary statistics for physical activity and sedentary behaviour measures.

Variable	No pain areas ($n=438$)		Single-site pain ($n=113$)		Multisite pain ($n=163$)	
	Mean (SD) or median (IQR)	Range	Mean (SD) or median (IQR)	Range	Mean (SD) or median (IQR)	Range
Valid days	5.3 (2.5)	1–15	5.3 (2.3)	1–10	5.4 (2.5)	1–9
Moderate PA (min/day)	28.5 (17.8, 46)	0–214.0	31.8 (19.0, 49.1)	2.3–175.0	25.6 (14.5, 37.8)	1–112.9
Vigorous PA (min/day)	0.3 (0, 2.5)	0–31.2	0.3 (0, 1.4)	0–33.0	0 (0, 1.4)	0–25.0
MVPA (min/day)	30.4 (19.0, 48.9)	0–243.2	35.0 (19.5, 53)	2.3–175.5	28.0 (15.2, 41.5)	1.0–114.3
MVPA in ≥10 min bouts (min/day)	9.2 (1.3, 20.0)	0–170.7	9.3 (1.5, 23.2)	0–99.5	6.6 (0, 14.7)	0–77.6
Sedentary time per day (min)	547.4 (94.0)	201.0–775.6	553.0 (99.9)	112.5–794.0	562.4 (96.1)	279.8–815
Sedentary time as percentage of non-MVPA time	63.6 (9.7)	28.7–87.4	63.8 (10.0)	23.0–82.5	64.6 (9.4)	29.2–83.8
Sedentary time ≥20 min (min/day)	185.3 (80.2)	0–480.0	203.0 (85.4)	30.5–445.6	193.5 (81.8)	41.0–488.0
Sedentary time ≥30 min (min/day)	115.3 (66.9)	0–406.0	130.1 (72.4)	10.3–364.6	120.5 (68.0)	0–389.0
Proportion of Sedentary time ≥20 min (percent)	32.9 (11.6)	0–80.3	35.8 (11.6)	10.8–64.8	33.6 (11.1)	11.0–73.7
Number of breaks from sedentary time per day	96.8 (18.7)	27.0–152.5	93.8 (17.6)	34.0–139.1	97.8 (18.4)	42.0–138.0

PA = physical activity; MVPA = moderate vigorous physical activity.

in Table 3. The participants' were asked to wear the accelerometer for 1 week, but the number of valid days wearing the accelerometer ranged from 1 to 15 with a mean (SD) of 5.3 (2.4).

Multivariable regression models for the association of PA and SB measures with PPT stratified by number of pain areas are shown in Table 4. For the "Single-site pain", those categorized with median amounts of MVPA accumulated in ≥10 min bouts greater than 13 min/day were associated with more pressure pain sensitivity ($p = 0.035$), with PPT estimated to be 95.0 kPa (95% CI: –171.0, –19.9, $p = 0.013$) lower compared with participants with a value between >0 and ≤13 min/day and 75.3 kPa (95% CI: –160.8, 10.3, $p = 0.085$) lower than those

Table 3: Summary statistics for pressure and cold pain threshold measures.

Variable	No pain areas ($n = 438$)		Single-site pain ($n = 113$)		Multisite pain ($n = 163$)	
	Median (IQR)	Range	Median (IQR)	Range	Median (IQR)	Range
PPT lumbar spine (kPa)	421.7 (288.7, 606.0)	69.3–1000	389.3 (280.3, 600.3)	85.3–1000	338.0 (247.2, 511.2)	82.0–1000
PPT tibialis anterior (kPa)	415.5 (284.0, 577.0)	74.0–1000	392.3 (325.0, 566.0)	86.6–1000	362.7 (275.7, 528.3)	84.0–1000
PPT upper trapezius (kPa)	261.0 (185.7, 384.3)	44.3–1000	260.3 (179.0, 392.7)	61.0–1000	228.7 (165.7, 332.7)	25.0–1000
PPT wrist (kPa)	390.7 (281.3, 530.3)	91.7–1000	398.3 (288.3, 527.0)	105.3–1000	363.0 (274.3, 532.3)	40.3–1000
CPT (°C)	9.2 (5, 20.3)	5–28.9	9.2 (5, 22.7)	5–30.3	11.5 (5, 22.7)	5–29.8

PPT = pressure pain threshold; CPT = cold pain threshold.

Table 4: Multivariable regression models for PPT (kPa) measures.

Variable	No pain areas ($n = 438$)		Single-site pain ($n = 113$)		Multisite pain ($n = 163$)	
	Regression coefficient (95% CI)[d]	*p*-Value	Regression coefficient (95% CI)[d]	*p*-Value	Regression coefficient (95% CI)[d]	*p*-Value
Moderate PA (min/day)[a,b]						
Linear term	0.7 (–23.7, 25.1)	0.998[e]	10.7 (–35.8, 57.2)	0.179[e]	–18.6 (–48.1, 10.8)	0.121[e]
Quadratic term	–0.1 (–2.6, 2.5)		–2.2 (–7.0, 2.6)		3.0 (–0.5, 6.5)	
Vigorous PA (min/day)[a,b]						
Zero	Ref.	0.669[e]	Ref.	0.854[e]	Ref.	0.543[e]
<1.75 min/day	–17.7 (–64.4, 28.9)	0.455	–23.6 (–109.0, 61.8)	0.588	28.1 (–32.9, 89.2)	0.367
≥1.75 min/day	–19.4 (–66.1, 27.4)	0.417	–15.7 (–99.7, 68.2)	0.713	28.5 (–32.6, 89.5)	0.361
MVPA (min/day)[a,b]						
Linear term	–5.6 (29.8, 18.5)	0.897[e]	10.4 (–35.4, 56.2)	0.204[e]	–16.4 (–46.1, 13.3)	0.172[e]
Quadratic term	0.6 (–1.9, 3.1)		–2.1 (–6.9, 2.6)		2.7 (–0.9, 6.3)	
MVPA in ≥10 min bouts (min/day)[a,b]						
Zero	Ref.	0.607[e]	Ref.[f]	0.035[e]	Ref.	0.536[e]
≤13 min/day	16.6 (–32.8, 66.1)	0.509	20.1 (–67.0, 107.3)	0.650	–0.9 (–59.8, 57.9)	0.976
>13 min/day	–3.3 (–53.0, 46.3)	0.895	–75.3 (–160.8, 10.3)	0.085	29.3 (–35.2, 93.9)	0.373
Sedentary time per day (min)[a,b]	–1.2[g] (–3.3, 0.9)	0.264	–0.4[g] (–4.3, 3.5)	0.847	–1.5[g] (–4.3, 1.3)	0.287
Sedentary time as percentage of non-MVPA time[a,b]	–12.0[h] (–31.0, 7.1)	0.217	–4.6[h] (–38.3, 29.0)	0.787	–9.7[h] (–35.1, 15.7)	0.453
Sedentary time ≥20 min (min/day)[a,b]	–1.2[g] (–3.4, 1.1)	0.298	–0.3[g] (–4.3, 3.6)	0.865	–2.5[g] (–5.4, 0.4)	0.094
Sedentary time ≥30 min (min/day)[a,b]	–1.2[g] (–3.9, 1.5)	0.375	0.0[g] (–4.7, 4.7)	0.996	–2.6[g] (–6.1, 0.9)	0.150
Proportion of sedentary time ≥20 min (percent)[b]	–8.1[i] (–23.5, 7.3)	0.302	4.0[i] (–24.6, 32.5)	0.786	–18.1[i] (–39.6, 3.4)	0.100
Number of breaks from sedentary time/day[a,b,c]	1.1[j] (–14.1, 11.9)	0.867	–4.7[j] (–30.2, 20.8)	0.718	0.2[j] (–18.5, 18.0)	0.982

[a]Adjusted for awake wear time; [b]adjusted for number of days of valid wear time; [c]adjusted for sedentary time per day; [d]Adjusted for sex, site, waist-hip ratio, SF12-mental component summary; [e]Overall *p*-value; [f]Contrast of group 2 vs. 1: –95.4 (–171.0, –19.9), $p = 0.013$; [g]Difference estimate represents the expected change for a 10 min change in sedentary or sitting time; [h]Difference estimate represents the expected change for a 10% change in sedentary time as % of non-MVPA time; [i] Difference estimate represents the expected change for a 10% change in proportion of sedentary time ≥20 min; [j]Difference estimate represents the expected change for 10 breaks in sedentary time; CI = confidence interval; PA = physical activity; MVPA = moderate vigorous physical activity.

subjects with 0 min/day. There were no other associations observed between PA and SB and PPT. A sensitivity analysis including only those participants with at least 3 valid weekdays and 1 valid day of weekend data ($n=460$, "No pain areas": $n=281$, $n=157$ excluded, "Single-site pain": $n=69$, $n=44$ excluded, "Multisite pain": $n=110$, $n=53$ excluded) returned similar strength and direction of regression coefficients (Appendix 1).

Multivariable regression models for the association of PA and SB with CPT stratified by number of pain areas are shown in Table 5. In the "Multisite pain group", higher levels of vigorous PA was associated with higher cold pain sensitivity ($p=0.011$) with CPT of participants with ≥1.75 min/day estimated to be 5.1 °C (95% CI: 0.7, 9.4, $p=0.022$) higher (more cold pain sensitivity) compared with participants with zero min/day, and 7.2 °C (95% CI: 2.4, 12.2, $p=0.004$) higher that those participants with <1.75 min/day. In the "No pain areas" group, more breaks from sedentary time (adjusted for minutes of sedentary time per day) were significantly associated with lower cold pain sensitivity, with CPT estimated to be 0.8 °C (95% CI: –1.5, –0.1, $p=0.046$) less (i.e. less cold pain sensitivity) for each 10-break increment per day. There were no other associations observed between PA and SB and CPT. A sensitivity analysis including only those participants with at least 3 valid weekdays and 1 valid day of weekend data ($n=454$, "No pain areas": $n=277$, $n=153$ excluded, "Single-site pain": $n=68$, $n=54$ excluded, "Multisite pain": $n=109$, $n=51$ excluded) returned similar strength and direction of regression coefficients (Appendix 2).

4 Discussion

To our knowledge, this study is the largest community-based, comprehensive investigation into the association of objectively measured, habitual PA and SB with tissue sensitivity to noxious pressure and cold stimuli in young adults. Overall, little was detected in the way of associations between PA and SB with pressure and cold pain

Table 5: Multivariable Tobit regression models for CPT (°C) measures.

Variable	No pain areas ($n=430$)		Single-site pain ($n=112$)		Multisite pain ($n=160$)	
	Regression coefficient (95% CI)[d]	*p*-Value	Regression coefficient (95% CI)[d]	*p*-Value	Regression coefficient (95% CI)[d]	*p*-Value
Moderate PA (min/day)[a,b]						
Linear term	0.4 (0.0, 0.8)	0.073	0.0 (–0.8, 0.8)	0.978	–0.1 (–0.7, 0.6)	0.783
Vigorous PA (min/day)[a,b]						
Zero	Ref.	0.199[e]	Ref.	0.146[e]	Ref.[f]	0.011[e]
<1.75 min/day	2.4 (–0.4, 5.1)	0.092	1.5 (–3.7, 6.6)	0.577	–2.2 (–6.6, 2.2)	0.320
≥1.75 min/day	2.0 (–0.8, 4.7)	0.162	–3.9 (–9.0, 1.2)	0.133	5.1 (0.7, 9.4)	0.022
MVPA (min/day)[a,b]						
Linear term	0.4 (0.0, 0.8)	0.059	–0.1 (–0.9, 0.6)	0.756	0.0 (–0.7, 0.6)	0.966
MVPA in ≥10 min bouts (min/day)[a,b]						
Zero	Ref.	0.118[e]	Ref.	0.835[e]	Ref.	0.383[e]
≤13 min/day	1.9 (–1.1, 4.8)	0.216	1.6 (–3.9, 7.2)	0.560	0.2 (–4.1, 4.5)	0.930
>13 min/day	3.1 (0.1, 6.1)	0.040	1.3 (–4.1, 6.6)	0.642	2.8 (–1.9, 7.4)	0.241
Sedentary time per day (min)[a,b]	0.0[g] (0.0, 0.2)	0.472	0.1[g] (–0.2, 0.3)	0.569	0.1[g] (–0.1, 0.3)	0.596
Sedentary time as percentage of non-MVPA time[a,b]	0.7[h] (–0.4, 1.9)	0.226	0.7[h] (–1.4, 2.9)	0.503	0.4[h] (–1.5, 2.2)	0.704
Sedentary time ≥ 20 min (min/day)[a,b]	0.1[g] (–0.1, 0.2)	0.267	0.0[g] (–0.3, 0.2)	0.931	0.0[g] (–0.2, 0.3)	0.742
Sedentary time ≥30 min (min/day)[a,b]	0.1[g] (–0.1, 0.2)	0.287	0.0[g] (–0.3, 0.3)	0.854	0.0[g] (–0.3, 0.3)	0.963
Proportion of sedentary time ≥20 min (percent)[b]	0.6[i] (–0.3, 1.4)	0.215	0.0[i] (–1.8, 1.9)	0.968	0.0[i] (–1.6, 1.6)	0.996
Number of breaks from sedentary time/day[a,b,c]	–0.8[j] (–1.5, –0.0)	0.046	0.4[j] (–1.2, 2.0)	0.595	0.3[j] (–1.1, 1.6)	0.684

[a]Adjusted for awake wear time; [b]adjusted for number of days of valid wear time; [c]adjusted for sedentary time per day; [d]adjusted for sex, smoking, SF12-mental component summary; [e]Overall *p*-value; [f]Contrast of group 2 vs. 1: 7.2 (2.4, 12.2), $p=0.004$: [g]Difference estimate represents the expected change for a 10 min change in sedentary or sitting time; [h]Difference estimate represents the expected change for a 10% change in sedentary time as % of non-MVPA time; [i]Difference estimate represents the expected change for a 10% change in proportion of sedentary time ≥20 min; [j]Difference estimate represents the expected change for an additional 10 breaks in sedentary time; CI = confidence interval; PA = physical activity; MVPA = moderate vigorous physical activity.

sensitivity. However, there were some interesting associations of note for the "Single-site pain" group between PA and pressure pain sensitivity, for the "Multisite pain" group for PA and cold pain sensitivity and for the "No pain areas" group for more breaks from sedentary time and cold pain sensitivity.

4.1 Strengths and limitations

Strengths of the study include sample size, age specific population, consideration of number of pain sites, control for potential correlates of pressure and cold pain sensitivity and the use of accelerometry to objectively measure PA and SB, including intensity, frequency, duration and pattern of accumulation over time [6]. The large sample at one age results in good power to estimate associations at this particular age, but the limitation is that the results may not be generalizable across age groups. Importantly, PA as measured in this study reflects habitual activity, providing a different capture of associations between pain sensitivity and PA when compared to laboratory controlled exercise protocols [14]. While previous studies using self-report measurement of PA suggest an association between higher levels of PA and decreased pressure and cold pain sensitivity [21, 22], they are limited by small participant numbers ($n < 72$), recall bias of activity by using self-report measurement [37], and the poor correlation of self-report with objective measurement of PA [38]. Previously, only one study considered objective measurement of SB and this only included pain-free participants ($n = 444$), finding no association between pressure and cold pain sensitivity and total daily sedentary time [24].

Affective factors potentially influence the relationship between PA and pain sensitivity, however a previous study reported that major depression did not moderate this relationship [39]. The multivariable regression models in our study were adjusted for mental health as previous investigations of the Raine cohort have reported an association of the MCS with PPT and CPT [24].

There were limitations in this study. Accelerometers were worn on the hip, therefore not measuring arm movement, were not worn while swimming and were insensitive to cycling and gradients while walking or running [40]. The authors acknowledge the limitations of an inclusion criteria of at least 1 valid day of wear time, however the sensitivity analysis including only participants with more valid days of wear time returned similar strength and direction of regression coefficients. Therefore, the inclusion criteria for wear time did not limit the results of this study.

The pressure and cold pain threshold measures used in this study may not be ideal to specifically capture the relationship of habitual PA and SB with pain sensitivity. PA can result in exercise induced hypoalgesia, with potential underlying mechanisms including acute recruitment of descending inhibitory control systems [41]. In this context, the use of dynamic quantitative sensory testing measures such as conditioned pain modulation or temporal summation may be more appropriate to capture evoked sensitivity modulation associated with PA [42]. However, conditioned pain modulation and exercise induced hypoalgesia have been found to be partially impaired in chronic pain patients with high versus low pressure pain sensitivity [16].

The literature suggests the number of pain sites is an important factor to consider when investigating the relationship between PA and pain sensitivity [15, 17], hence in the current study, participants were categorized according to their current pain status, so chronicity of pain was not considered, meaning the "Single-site pain" and "Multisite pain" groups contained participants with pain of varying duration. Table 1 reports the "Multisite pain" group contained participants with higher levels of pain chronicity, pain frequency and pain intensity when compared to the "Single-site pain" group.

Numerous statistical contrasts were performed without adjustment of the type I error rate, adopting the philosophy of Sterne et al. [43] of the unadjusted p-value as strength of evidence against the null hypothesis, and the 95% confidence interval as the range of credible values for the population parameter. It is possible that the few associations observed in this study occur by chance only, and the confidence intervals for these estimates indicate that differences may not be of a meaningful magnitude. Furthermore, the associations detected are only cross-sectional, and give us no information as to how PA and SB behaviours might temporally heighten or lower pressure and cold pain sensitivity. The following discussion of the associations identified by this study is therefore presented with this caveat in mind.

4.2 Pain sensitivity, physical activity and sedentary behaviour

With respect to findings regarding pressure pain sensitivity, for the "Single-site pain" group, participants with higher levels of MVPA accumulated in ≥10 min bouts (>13 min/day) demonstrated greater pressure pain sensitivity compared with those participants with ≤13 min/day MVPA accumulated in ≥10 min bouts, but not compared

to those with no MVPA accumulated in ≥10 min bouts. These findings suggest that for participants with "single site pain", how MVPA is accumulated (min accumulated in longer bouts of MVPA) may be important in the context of heightened pressure pain sensitivity. The mechanisms underlying heightened pressure pain sensitivity and PA in the "single site pain" group are likely complex, potentially involving both neuronal [44] and non-neuronal factors (e.g. immune) [45]. Given pressure pain sensitivity was measured across four sites and models were adjusted for site, this association might plausibly reflect changes in central nociceptive processing or modulation (for example, altered endogenous descending control system efficiency) [14] or facilitated spatial/temporal summation in response to PA [16], rather than primarily peripheral sensitisation (as this would manifest in a more localised site sensitivity). However, it is unclear why this association would be detected for the single-site pain group, but not multisite pain. Variable effects of PA on pressure pain sensitivity in both clinical and experimental pain populations have been reported [15], but interpretation is complicated by differences in study quality, design, exercise protocols, measurement tools, clinical populations and outcomes [14].

With respect to findings on cold pain sensitivity, for those with "multisite pain", participants falling within the highest tertile of vigorous PA (VPA) had greater cold pain sensitivity when compared with participants with lower or no vigorous PA. It is unclear what this association might reflect, as in this "multisite pain group", similar differences between VPA levels for pressure sensitivity would also be expected, given the potential for facilitated (temporal and spatial) nociception from deep tissues following exercise in multisite pain (for example in chronic widespread pain, or fibromyalgia [16, 17]. Notwithstanding this point, differences in cold sensitivity levels have been demonstrated previously in a non-clinical cohort drawn from the Raine Study (young females), with heightened cold pain sensitivity evident in those females reporting moderate to severe menstrual pain [46] and an association between low cortisol response to stress and musculoskeletal pain in females with heightened cold pain sensitivity [13]. These authors suggest that cold hypersensitivity may reflect changes in central regulatory systems linked to homeostasis (including thermosensation and thermoregulation). It is also possible that VPA in this group may differentially influence cold and pressure pain sensitivity, as these psychophysical tests are designed for nociceptors located in skin and muscle tissue, respectively [32]. Collectively, these findings allude to potentially important dose-relationships between PA/exercise and pain sensitivity, suggesting that higher amounts of VPA may not be ideal for all musculoskeletal pain conditions, particularly for clinical populations with two or more pain areas [15, 17].

The association of lower cold pain sensitivity with an increase in the number of breaks from sedentary time for participants in the "No pain areas" group also suggests the way sedentary time is accumulated may be related to pain sensitivity. Increased breaks in sedentary time, independent of total sedentary time, have demonstrated associations with lower waist circumference [47, 48], lower inflammatory marker concentration [47] and improved plasma glucose levels [47, 48]. These physiological effects may suggest mechanisms whereby more breaks from sedentary time could be associated with lower cold pain sensitivity partly through mechanisms including improved energy metabolism and lower circulating inflammatory markers. Young adults spend most of the waking day being sedentary [6] and targeted interventions for pain prevention and also for improving other life-course health trajectories, should consider the accumulation patterns of sedentary time.

5 Conclusions

This study was a comprehensive investigation into the association of pressure and cold pain sensitivity with habitual, objectively measured PA and SB in young adults. In this community-based sample of young adults with "No pain areas", "Single-site pain" and "Multisite pain" few associations between PA and SB with pressure and cold pain sensitivity were demonstrated. These findings suggest that consideration of patterns of accumulation of PA and SB are important for future research, and highlight the need for high quality longitudinal studies that would enable better characterisation of the pain sensitivity of cohorts over time, and related temporal influences of PA and SB on tissue sensitivity.

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Informed consent: Informed consent has been obtained from all individuals included in this study

Ethical approval: The research related to human use complies with all the relevant national regulations, institutional policies and was performed in accordance with the tenets of the Helsinki Declaration, Ethics approval for the Raine Study Cohort 22-year follow up was obtained from the University of Western Australia (UWA) (RA/4/1/5202).

Appendix

Appendix 1: Multivariable regression models for PPT (kPa) measures with at least 3 valid weekdays and 1 valid weekend day.

Variable	No pain areas ($n=281$)		Single-site pain ($n=69$)		Multisite pain ($n=110$)	
	Regression coefficient (95% CI)[d]	*p*-Value	Regression coefficient (95% CI)[d]	*p*-Value	Regression coefficient (95% CI)[d]	*p*-Value
Moderate PA (min/day)[a,b]						
Linear term	4.0 (−36.6, 28.7)	0.721[e]	37.6 (−16.6, 91.9)	0.091[e]	−12.2 (−49.2, 4.7)	0.441[e]
Quadratic term	0.0 (−3.4, 3.4)		−5.1 (−10.7, 0.5)		2.1 (−2.2, 6.5)	
Vigorous PA (min/day)[a,b]						
Zero	Ref.	0.582[e]	Ref.	0.527[e]	Ref.	0.544[e]
<1.75 min/day	−30.1 (−87.3, 27.1)	0.302	−55.3 (−43.1, 153.6)	0.271	38.1 (−30.0, 106.3)	0.273
≥1.75 min/day	−21.5 (−80.5, 37.6)	0.541	−19.6 (−83.2, 122.4)	0.709	20.7 (−53.7, 95.1)	0.586
MVPA (min/day)[a,b]						
Linear term	−10.2 (−42.9, 22.5)	0.560[e]	52.5 (−0.5, 105.5)	0.038[e]	−7.2 (−44.5, 30.2)	0.170[e]
Quadratic term	0.6 (−2.7, 3.9)		−6.5 (−12.0, −1.0)		1.3 (−3.1, 5.7)	
MVPA in ≥10 min bouts (min/day)[a,b]						
Zero	Ref.	0.630[e]	Ref.	0.084[e]	Ref.	0.897[e]
≤13 min/day	−0.9 (−70.7, 69.1)	0.980	83.1 (−28.4, 194.7)	0.144	−12.8 (−60.8, 86.3)	0.734
>13 min/day	−22.8 (−93.5, 47.9)	0.527	−9.7 (−118.3, 98.6)	0.858	19.3 (−62.6, 101.2)	0.644
Sedentary time per day (min)[a,b]	−0.6[f] (−3.4, 2.3)	0.702	−1.1[f] (−4.2, 6.3)	0.694	−0.5[f] (−4.2, 3.1)	0.770
Sedentary time as percentage of non-MVPA time[a,b]	−7.7[g] (−34.0, 18.6)	0.568	−2.2[g] (−43.9, 48.3)	0.926	−1.1[g] (−35.2, 33.1)	0.951
Sedentary time ≥20 min (min/day)[a,b]	−1.2[f] (−4.1, 1.8)	0.432	−0.2[f] (−5.0, 5.5)	0.928	−0.9[f] (−4.9, 3.2)	0.677
Sedentary time ≥30 min (min/day)[a,b]	−1.8[f] (−5.4, 1.7)	0.315	0.4[f] (−5.4, 6.1)	0.892	−1.4[f] (−6.5, 3.6)	0.574
Proportion of sedentary time ≥20 min (percent)[b]	−12.8[h] (−34.0, 8.4)	0.237	4.3[h] (−34.2, 42.7)	0.828	−9.9[h] (−39.4, 19.5)	0.508
Number of breaks from sedentary time/day[a,b,c]	2.4[i] (−14.3, 19.1)	0.779	−7.7[i] (−40.3, 25.0)	0.645	−1.8[i] (−25.1, 21.5)	0.878

[a]Adjusted for awake wear time; [b]adjusted for number of days of valid wear time; [c]adjusted for sedentary time per day; [d]Adjusted for sex, site, waist-hip ratio, SF12-mental component summary; [e]Overall *p*-value; [f]Difference estimate represents the expected change for a 10 min change in sedentary or sitting time; [g]Difference estimate represents the expected change for a 10% change in sedentary time as % of non-MVPA time; [h]Difference estimate represents the expected change for a 10% change in proportion of sedentary time ≥20 min; [i]Difference estimate represents the expected change for 10 breaks in sedentary time; CI = confidence interval; PA = physical activity; MVPA = moderate vigorous physical activity.

Appendix 2: Multivariable Tobit regression models for CPT (°C) measures (min 3 valid weekdays, 1 valid weekend day).

Variable	No pain areas ($n=277$)		Single-site pain ($n=68$)		Multisite pain ($n=109$)	
	Regression coefficient (95% CI)[d]	*p*-Value	Regression coefficient (95% CI)[d]	*p*-Value	Regression coefficient (95% CI)[d]	*p*-Value
Moderate PA (min/day)[a,b]						
Linear term	0.4 (−0.1, 1.0)	0.112	−0.3 (−1.3, 0.7)	0.548	−0.1 (−1.0, 0.7)	0.800
Vigorous PA (min/day)[a,b]						
Zero	Ref.	0.405[e]	Ref.	0.819[e]	Ref.[f]	0.004[e]
<1.75 min/day	2.4 (−1.1, 5.8)	0.180	−0.7 (−7.0, 5.5)	0.819	−2.9 (−8.0, 2.2)	0.267
≥1.75 min/day	1.6 (−2.0, 5.1)	0.394	−2.0 (−8.5, 4.7)	0.534	6.5 (1.0, 11.9)	0.020
MVPA (min/day)[a,b]						
Linear term	0.5 (−0.1, 1.0)	0.085	−0.4 (−1.3, 0.6)	0.451	0.0 (−0.8, 0.9)	0.954
MVPA in ≥10 min bouts (min/day)[a,b]						
Zero	Ref.	0.364[e]	Ref.	0.725[e]	Ref.	0.438[e]
≤13 min/day	1.5 (−2.9, 5.8)	0.500	1.7 (−5.7, 9.1)	0.651	0.1 (−5.5, 5.7)	0.962
>13 min/day	2.9 (−1.5, 7.3)	0.190	−0.6 (−7.6, 6.5)	0.873	3.2 (−3.0, 9.3)	0.306
Sedentary time per day (min)[a,b]	0.0[g] (−0.1, 0.2)	0.506	0.1[g] (−0.3, 0.4)	0.764	0.0[g] (−0.3, 0.3)	0.951
Sedentary time as percentage of non-MVPA time[a,b]	0.9[h] (−0.7, 2.6)	0.261	0.8[h] (−2.9, 3.0)	0.956	−0.1[h] (−2.6, 2.5)	0.991
Sedentary time ≥20 min (min/day)[a,b]	0.1[g] (−0.1, 0.3)	0.176	0.0[g] (−0.2, 0.4)	0.622	−0.1[g] (−0.4, 0.2)	0.591
Sedentary time ≥30 min (min/day)[a,b]	0.2[g] (−0.1, 0.4)	0.143	0.1[g] (−0.3, 0.5)	0.604	−0.2[g] (−0.5, 0.2)	0.427
Proportion of sedentary time ≥20 min (percent)[b]	1.0[i] (−0.3, 2.3)	0.119	1.1[i] (−1.5, 3.6)	0.402	−0.8[i] (−3.0, 1.5)	0.494
Number of breaks from sedentary time/day[a,b,c]	−1.1[j] (−2.1, −0.1)	0.032	−0.3[j] (−2.4, 1.8)	0.798	0.8[j] (−0.9, 2.5)	0.355

[a]Adjusted for awake wear time; [b]adjusted for number of days of valid wear time; [c]adjusted for sedentary time per day; [d]adjusted for sex, smoking, SF12-mental component summary; [e]Overall *p*-value; [f]Contrast of group 2 vs. 1: 9.3 (3.8, 14.9), $p=0.001$: [g]Difference estimate represents the expected change for a 10 min change in sedentary or sitting time; [h]Difference estimate represents the expected change for a 10% change in sedentary time as % of non-MVPA time; [i]Difference estimate represents the expected change for a 10% change in proportion of sedentary time ≥20 min; [j]Difference estimate represents the expected change for an additional 10 breaks in sedentary time; CI = confidence interval; PA = physical activity; MVPA = moderate vigorous physical activity.

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