Clinical Pain Research

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Standing time and daily proportion of sedentary time are associated with pain-related disability in a one month accelerometer measurement in adults with overweight or obesity

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Abstract

Objectives: The association between the subjective experience of pain-related disability (PRD) and devicemeasured physical activity (PA) and sedentary behavior (SB) in overweight and obese adults is not well known. The aim of this study was to investigate the associations of pain markers with accelerometer-measured SB duration and different intensities of PA among physically inactive middle-aged adults with overweight or obesity.

Methods: This cross-sectional analysis included 72 subjects (27 men) with mean age of 57.9 (SD 6.7) years and mean BMI of 31.6 (SD 4.1) kg/m². SB and standing time (ST), breaks in sedentary time, light physical activity

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Ilkka H. A. Heinonen, Turku PET Centre, University of Turku and Turku University Hospital, Turku, Finland; and Rydberg Laboratory of Applied Sciences, University of Halmstad, Halmstad, Sweden (LPA) and moderate-to-vigorous physical activity (MVPA) were measured for four consecutive weeks (mean 25 days, SD 4) with a hip-worn triaxial accelerometer. Headache, musculoskeletal pain, back pain, and PRD were assessed by visual analog scales (VAS) and using the Oswestry disability index (ODI). RAND-36 questionnaire was applied to assess health-related quality of life. The associations were studied by linear models.

Results: ST was positively and SB proportion was negatively associated with PRD when adjusted for age, sex, BMI, accelerometry duration, MVPA, pain medication use, and general health perceptions assessed by RAND-36. No associations were found between ST and back pain. SB or different PA intensities were not associated with pain experience at specific sites.

Conclusions: Longer daily ST, but not LPA or MVPA is associated with higher level of PRD. Correspondingly, higher proportion of SB is associated with lower level of PRD. This suggests that individuals with PRD prefer to stand, possibly to cope with pain. These results may highlight the importance of habitual standing behaviors in coping with experienced PRD in adults with overweight or obesity.

Keywords: accelerometry; functional performance; overweight; pain; sedentary behavior (SB).

Introduction

Pain is a complex phenomenon, with a wide variation in experience of pain across individuals. A third (ranging from 9 to 64%) of working-aged adults experience chronic pain [1]. Pain has been associated with multiple issues, including decreased quality of life [2] and increased healthcare and societal economic burden [3]. At the same

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time, a large proportion of the population is at least overweight, the prevalence being 53% in Europe [4]. Excess body weight has previously been linked to multiple pain conditions (e.g., back pain, upper and lower extremity pain, widespread pain, and headache) and pain-related disability (PRD) [5].

Excessive body mass alters joint and tissue loading, which has been suggested as a possible mechanism for pain progression in populations with overweight or obesity [6]. Additionally, overweight and obesity have been linked to low-grade inflammation, which suggests an inflammatory mechanism to be a cause for pain in individuals with overweight or obesity [7]. Coexisting depression and sleep disturbances can also affect pain development in individuals with excess weight [7]. Additionally, physical inactivity (i.e., not meeting the current physical activity [PA] guidelines) is associated with overweight and obesity [8]. Large questionnaire-based cross-sectional studies have shown an inverse dose-response relationship between PA and pain [9, 10]. Furthermore, the evidence from exercise interventions in the treatment of different pain conditions indicates small-to-moderate exercise-induced effects for reducing pain and disability [11]. Similarly, sedentary behavior (SB) defined as sitting or reclining activities with an energy consumption of <1.5 metabolic equivalents (METs) has been studied as a risk factor for pain [12-24]. However, the results are mixed: some studies have found a positive association between SB and back pain [12–17], whereas others have found no association [18-22]. In the study by Lunde et al. back pain and SB assessed by accelerometers for 3-4 days were negatively associated in healthcare workers [23]. Furthermore, Kopec et al. found that usual daily activity of walking or standing, lifting light loads, and heavy work were associated with higher risks of diagnosed chronic back pain than sitting for most of the day [24]. Additionally, standing is associated with a higher amount of back pain [25].

Questionnaires have often been used to estimate daily SB time. However, questionnaires have some weaknesses, e.g., they may underestimate SB time by 1.74 h/day, on average, compared to accelerometry-based measures [26]. In the studies assessing the associations between pain and accelerometer-measured SB, the data collection time has generally been only 4–6 days [16, 21, 23], but a longer data collection may produce more reliable mean estimates of habitual SB [27, 28].

In the field of pain research, studies on the associations of PAs and body postures measured by accelerometers, and pain markers in people with overweight or obesity are scarce. Therefore, we investigated the associations of PA and body postures, and pain markers in middle-aged adults with overweight or obesity. We used a four week accelerometer measurement and visual analog scales (VAS) as well as the Oswestry Disability Index (ODI).

Methods

This was a cross-sectional study consisting of screening and baseline data of a randomized controlled trial (NCT03101228, 05/04/2017). The study was conducted at the Turku PET Centre, Turku, Finland between April 2017 and August 2019. All participants gave their informed consent before entering the study. The study was approved by the Ethics Committee of the Hospital District of Southwest Finland (16/1810/2017) and conducted according to the Declaration of Helsinki.

Participants

The participants were recruited using newspaper advertisements and leaflets. All the screened participants with valid accelerometer data during the screening phase and adequately completed questionnaires were included in this study. Inclusion criteria for this study included body mass index (BMI) 25–40 kg/m², self-reported physical inactivity (<120 min of moderate-to-vigorous PA/week) and high sedentary time (sitting a major proportion of the day). Exclusion criteria were previous cardiac events, diagnosed diabetes, abundant alcohol use (exceeding the Finnish national limits for high-risk use), consumption of tobacco products, use of narcotics, inability to communicate in Finnish, and any chronic diseases or conditions that would be hazardous for the participant. No specific limitations regarding pain were used.

Measurements

Pain was rated with four questions and subsequent 10 cm VAS lines. The participant was asked to mark on separate VAS lines the worst headache, musculoskeletal (MSK) pain, back pain, and PRD during the previous month. MSK-pain included pain in any body region (e.g., neck, back, shoulders, hips, or knees). PRD was defined as self-reported disability or difficulty in functioning at work or in everyday tasks due to any pain. The VAS line marks were measured manually with a ruler with 1 mm accuracy. In addition, back PRD was assessed with the ODI questionnaire. ODI is a validated tool for back PRD assessment [29], providing a score between 0 and 100% (0% meaning no disability, 100% meaning highest disability). RAND-36 was used for health-related quality of life assessment. RAND-36 is a profile measure that yields eight scale scores and two summary scores (physical and mental health) [30]. Body mass was measured on a scale (Seca 797, Vogel & Halke, Hamburg, Germany) in light clothing. Body height was measured barefooted with a wall-mounted stadiometer. BMI was calculated using the formula body mass (kg)/body height $(m)^2$.

Light physical activity (LPA), moderate-to-vigorous physical activity (MVPA), steps, breaks in sedentary time, standing time (ST), and SB were measured by a hip-worn triaxial accelerometer (UKK AM30, UKK-institute, Tampere, Finland) over a four week period. Participants were instructed to wear the accelerometer on the right hip during waking hours. Daily wear time of 10–19 h and a minimum of four days of measurement were considered valid. Accelerometry data was collected with 100 Hz sampling frequency, ±16 G measurement range and four milligravity (mg) resolution. The data was analyzed in 6 s epochs using a validated mean amplitude deviation (MAD) method [31]. MAD values were further converted into METs [31]. LPA was defined as 1.5-2.9 METs (MAD 22.5-91.5 mg), MVPA as ≥3.0 METs (MAD >91.5 mg), and SB as <1.5 METs (MAD <22.5 mg) during sitting or lying. Additionally, the proportion of SB out of daily wear time of the accelerometer was calculated and presented as percentage of wear time. Body posture was defined in <1.5 MET (MAD <22.5 mg) activities by comparing the accelerometer position with the Earth's gravity vector during walking by the angle for posture estimation (APE) method. According to APE <11.6° deviation from the reference vector is defined as standing and >11.6° as SB [32]. A break in sedentary time was defined as a clear vertical acceleration (i.e., standing up) or movement (MAD ≥50.0 mg) with simultaneous measured posture change to standing after at least 1 min of sedentary time. The accelerometry variables have been explained in more detail elsewhere [33].

Statistical methods

Participant characteristics are reported as mean (standard deviation [SD]) unless otherwise stated. Sex differences were assessed by t-test for normally distributed variables, Mann–Whitney U test for non-normally distributed variables, and Fisher's exact test for categorial variables. Spearman's rank correlation was used to examine associations between the accelerometry and pain variables.

Linear models were used to further assess associations between the accelerometer and pain variables. Out of the accelerometry data we included ST or SB proportion of wear time, which were correlated to at least one of the pain variables. First, we used a crude, non-adjusted, model including only the ST or SB proportion as the independent variable and the pain variable as the dependent variable. Secondly, we adjusted the ST model for sex, pain medication use, and the total measurement time (derived from measurement days × hours). Finally, in the fully adjusted model, we included sex, age, BMI, pain medication use, total measurement time, MVPA time, and general health perceptions from RAND-36. The SB proportion model was first adjusted for sex and pain medication use. Finally, the SB proportion model was adjusted for sex, age, BMI, pain medication use, MVPA time, and general health perceptions from RAND-36. To assess sex differences, we replicated the analyses separately for men and women. Natural logarithmic transformation was performed for headache, back pain, and PRD, and square root transformation was performed for MSK-pain and ODI, to ensure normal distribution of the residuals. Residuals were visually inspected for normal distribution. Multicollinearity was assessed using correlation matrices as well as variance inflation factors (<5 was considered adequate). Results from the linear models are reported as regression coefficient B and 95% confidence interval (95% CI). Statistical significance was set at p<0.05 (two-tailed). All analyses were conducted using IBM SPSS Statistics (version 24.0 for macOS, IBM, Armonk, NY).

Results

Out of 263 volunteers 151 participants fulfilled the inclusion criteria, and valid questionnaire and accelerometer data were successfully acquired from 72 participants (38% men) (Table 1). All participants responded to the pain questionnaires except for headache (n=71), back pain (n=70), and PRD (n=71). The mean accelerometry duration was 25.4 (SD 4.1) days and mean daily accelerometer wear time was 14.6 (SD 1.0) h. The participants spent majority of the waking hours being sedentary (men 71%, women 67% of wear time). The mean reported pain experiences were 1.4 (SD 2.1) cm for headache, 3.0 (SD 2.6) cm for MSK-pain, 1.8 (SD 2.2) cm for back pain, 1.6 (SD 2.1) cm for PRD, and 8.5 (SD 8.2) % for ODI. No men and seven women used pain medication.

Table 1: Sample characteristics by sex. Unless otherwise stated, the results are presented as mean (SD).

	Men	Women	p- Value
n, %	27 (38)	45 (62)	
Age, years	58.6 (6.0)	57.5 (7.2)	0.633
BMI, kg/m ²	31.6 (4.5)	31.6 (3.9)	0.981 ^a
Uses pain medication, n, %	0	7 (16)	0.041 ^b
Physical activity			
Sedentary time, h/day	10.20 (1.08)	9.86 (1.10)	0.206 ^a
Sedentary proportion, %/day	71.2 (6.6)	66.7 (6.6)	0.007 ^a
LPA, h/day	1.63 (0.50)	1.84 (0.40)	0.014
MVPA, h/day	1.03 (0.39)	0.98 (0.31)	0.860
Standing, h/day	1.47 (0.44)	2.10 (0.69)	0.001
Steps/day	5,329	5,312	0.720
	(2083)	(1770)	
Sedentary breaks, times/day	26.0 (6.6)	31.2 (8.5)	0.006
Measurement, days	25.4 (3.7)	25.3 (4.3)	0.449
Measurement, h/day	14.3 (1.1)	14.8 (0.87)	0.040
Pain measures			
Headache, VAS 0–10 cm	0.73 (1.00)	1.73 (2.42)	0.053
MSK-pain, 0–10 cm	2.16 (2.50)	3.54 (2.52)	0.011
Back pain, 0–10 cm	1.06 (1.87)	2.24 (2.26)	0.022
Pain-related disability,	1.27 (2.24)	1.82 (2.02)	0.026
0–10 cm			
ODI, 0–100%	5.52 (6.53)	10.38 (8.53)	0.007
RAND-36 dimensions			
Physical functioning	89.2 (12.5)	82.0 (15.6)	0.022
Physical role functioning	87.0 (27.2)	83.3 (26.1)	0.346
Emotional role functioning	87.7 (22.9)	83.0 (31.5)	0.697
Vitality	73.5 (19.8)	62.6 (19.2)	0.005
Mental health	85.6 (9.2)	80.5 (13.2)	0.144
Social role functioning	94.4 (10.0)	88.9 (14.2)	0.083
Bodily pain	81.8 (18.7)	70.8 (19.7)	0.018
General health perceptions	68.3 (14.3)	65.4 (17.9)	0.595

BMI, body mass index; LPA, light physical activity; MVPA, moderateto-vigorous physical activity; MSK, musculoskeletal; ODI, Oswestry disability index. Sex difference assessed by Mann–Whitney U test (exact, two-tailed) for non-normally distributed variables, t-test for normally distributed variables^a, or Fisher's exact test for categorical variables^b.

Correlations between accelerometry and pain markers

ST was positively correlated with headache (p=0.020), MSK-pain (p=0.047), and PRD (p=0.007) (Table 2). SB and SB proportion of the wear time were negatively correlated with PRD (p=0.042 and 0.020, respectively). No correlations between pain markers and LPA, MVPA, SB, breaks in sedentary time or steps were observed.

Linear models between accelerometry and pain markers

The linear models showed a positive association between ST and PRD (Table 3). The association remained similar after adjustments in model 2 and model 3. ST and MSK-pain showed a positive association in the model 1, but the association was lost in models 2 and 3. Similarly, a positive association was present between ST and headache in model 1, but the association was lost in models 2 and 3. Furthermore, we found a negative association between SB proportion of the day and PRD (B=–7.18, 95% CI –12.83, –1.54, p=0.013). The association remained significant in model 2 (B=–6.34, 95% CI –12.09, –0.59, p=0.031) and model 3 (B=–9.39, 95% CI –16.82, –1.96, p=0.014).

Sex differences

When stratifying the linear models by sex, we found no associations between the accelerometry and pain markers in men (Supplementary Material). However, in women, ST was positively associated with PRD in all three models. ST was positively associated with MSK-pain in models 1 and 2 but the association turned borderline non-significant in model 3. In addition, ST was positively associated with ODI in models 2 and 3. Furthermore, SB proportion was negatively associated with PRD in models 2 and 3. SB proportion was also negatively associated with MSK-pain and back pain in model 3.

Discussion

In this study, we found that total daily ST, determined from accelerometer-measured data over a four week period, is positively associated with PRD in adults with overweight or obesity. Furthermore, the proportion of SB time out of daily accelerometer wear time was negatively associated with PRD. However, LPA, MVPA, steps or breaks in sedentary time were not associated with pain or PRD in this study.

Our results are in line with previous studies focusing on especially knee, hip, and low back pain. Two reports from the DPHACTO study from Denmark showed that ST is positively associated with knee and hip pain [34] as well as low back pain [25]. However, in our study, we did not find a statistically significant association between ST and specific sites of pain (i.e., headache, MSK-pain, or back pain) after adjusting for sex. Moreover, PRD might be more likely to have associations with PA measures, since disability would mean a hindrance in physical activities, whereas sitespecific pain as such might not disturb physical activities. In addition, as seen in Table 1, we found that women reported more pain and they stood more than men. However, the prevalence of back pain in both sexes in our study was similar to what previously has been reported for adults with overweight and obesity in Finland [35].

The sex difference in self-reported pain and the fact that adjustment for sex turned the association between ST and MSK-pain as well as ST and headache non-significant indicates that sex may be a stronger risk factor for pain than standing. When looking at men and women separately, we found no associations between the accelerometry results and pain measures in men. However, this could simply be due to the small sample size of men (n=27). Nevertheless, the directions of some non-significant associations were different for men and women, suggesting sex differences in pain experience. Furthermore, it has been shown previously that women are at a higher risk for experiencing pain when compared to men, as was also observed in our study. This has been explained by hormonal differences, sex differences in the endogenous opioid system responsible for pain modulation, and psychosocial mechanisms such as more catastrophizing by women, sociocultural beliefs on femininity and masculinity, and early life stress [36]. However, when PRD was used as the outcome the association remained significant even after adjusting for sex in our study. A possible reason why the results were different using ODI and PRD is the fact that the ODI scores in this sample were markedly low with less variation (range 0-33.3% out of 100%) whereas PRD had a wider range (0-8.4 cm out of 10 cm). ODI is better able to differentiate between levels of functioning at higher levels of disability [29], and therefore it would not be the optimal tool to assess this particular sample with a low prevalence of PRD. Furthermore, ODI assesses only back PRD whereas our PRD question did not differentiate between specific sites of pain.

As this is a cross-sectional study, one can only speculate on causality. Standing itself could be the cause of

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	BMI, kg/m ²	Sedentary time, h	dentary Sedentary time, h proportion, %/day	LPA, h/day	MVPA, h/day	Steps/ day	Sedentary breaks, Standing time, Headache ^c MSK-pain ^c times/day h/day	Standing time, h/day	Headache ^c	MSK-pain ^c	Back pain ^c	PRD℃	0DI, 0-100%
Age, years	-0.03	-0.12	0.12	-0.06	–0.33 ^b	-0.29 ^a			-0.24 ^a	1	0.03	-0.05	0.07
BMI, kg/m ²		0.11	0.19	-0.05	-0.24 ^a	-0.31 ^b	-0.33 ^b		0.02	0.12	0.01	-0.02	0.15
Sedentary time,			0.79 ^b	–0.38 ^b	–0.34 ^b	–0.37 ^b	-0.12	-0.52 ^b	0.02	-0.09	-0.09	–0.24 ^a	-0.04
h/day Sedentary propor-				-0.68 ^b	–0.60 ^b	–0.60 ^b	-0.37 ^b	-0.79 ^b	-0.16	-0.17	-0.12	-0.28 ^a	-0.08
tion, %/day													
LPA, h/day					0.39 ^b	0.35 ^b	0.42 ^b	0.43 ^b	0.05	0.15	0.15	0.12	0.07
MVPA, h/day						0.95 ^b	0.37 ^b		0.02	-0.05	-0.10	0.05	-0.19
Steps/day							0.37 ^b		0.06	-0.03	-0.07	0.05	-0.17
Sedentary breaks,								0.35 ^b	0.07	0.15	0.13	0.17	-0.01
times/day													
Standing time,									0.28 ^a	0.24 ^a	0.18	0.32 ^b	0.18
h/day													
Headache ^c										0.28 ^a	0.24 ^a	0.33 ^b	0.25 ^a
MSK-pain ^c											0.70 ^b	0.64 ^b	0.76 ^b
Back pain ^c												0.66 ^b	0.73 ^b
PRD ^c													0.72 ^b
BMI, body mass index; LPA, light physical activity; MVPA, mod- significant coefficients are bolded. ^a Significant at the level of	x; LPA, light ts are bolde	physical activ d. ^a Significan	BMI, body mass index; LPA, light physical activity; MVPA, moderate-to-vigorous physical activity; MSK, musculoskeletal; PRD, pain-related disability; ODI, Oswestry disability index. Statistically significant coefficients are bolded. ^a Significant at the level of p<0.01. ^c Measured by visual analog scale 0–10 cm.	o-vigorous . ^b Significa	physical ac nt at the le	ctivity; MS vel of p<0	erate-to-vigorous physical activity; MSK, musculoskeletal; PRD, pain-related disability; p<0.05. ^b Significant at the level of p<0.01. ^C Measured by visual analog scale 0–10 cm.	PRD, pain-related visual analog scal	l disability; (le 0–10 cm.	DDI, Oswestry	/ disability	' index. St	atistically

	Model 1			Model 2			Model 3		
	В	95% CI	р	В	95% CI	р	В	95% CI	р
PRD	0.89	0.33, 1.46	0.002	0.81	0.19, 1.44	0.012	0.78	0.12, 1.44	0.021
ODI	0.51	-0.02, 1.03	0.058	0.28	-0.27, 0.83	0.313	0.38	-0.17, 0.92	0.173
MSK-pain	0.32	0.04, 0.59	0.025	0.21	-0.010, 0.51	0.181	0.24	-0.09, 0.57	0.148
Back pain	0.61	-0.01, 1.24	0.055	0.41	-0.29, 1.11	0.245	0.51	-0.23, 1.25	0.172
Headache	0.58	0.05, 1.12	0.033	0.42	-0.16, 0.99	0.156	0.34	-0.27, 0.95	0.266

Table 3: Linear analysis for predicting pain from standing time in a crude model and two adjusted models.

Model 1: non-adjusted. Model 2: adjusted for sex, pain medication use, and total measurement time (days \times hours). Model 3: adjusted for sex, pain medication use, total measurement time (days \times hours), age, body mass index, MVPA, and general health perceptions. MVPA, moderate-to-vigorous physical activity; PRD, pain-related disability; ODI, Oswestry disability index; MSK, musculoskeletal. Statistically significant (p<0.05) results are bolded.

pain, especially so in an overweight population. For lower extremities, the increase in weight-bearing load from sitting to standing is obvious, but for the lower back the issue of changes in posture-specific strain has been discussed [37]. According to a review by Claus et al. the mechanical disc loading might not differ much between sitting and standing [37]. They concluded that intradiscal pressure is likely not the mechanism for posture related back pain [37]. The opposite could also be true: people with pain might prefer to stand to limit pain exacerbation by sitting or doing physically straining tasks. For example, sitting has been found to provoke short-term back pain acutely [38]. This could indicate that people might prefer standing over sitting in order to not provoke back pain. Indeed, studies on sit-stand desks have found that some people prefer to relieve back pain by standing up [39]. An interventional study on sit-stand desk use concluded that increasing ST does not cause pain - in fact, a trend towards pain relief from standing was present [40]. Controlling for work status would be justified in future studies, because the work setting likely influences the freedom of choosing between postures. Moreover, possibly some disabilities will not actualize when sitting, and this could explain the negative association between PRD and SB proportion. For example, one cannot experience difficulties in stair climbing if one doesn't climb stairs. Nonetheless, prospective trials are needed to assess causality.

We defined SB as sitting, lying, or reclining activities with an energy consumption of <1.5 METs as recommended by the Sedentary Behavior Research Network [41]. However, it is noteworthy that standing can have an energy consumption of <1.5 METs, especially so in adults with overweight or obesity [42]. Thus, the posture itself might be more relevant than the energy consumption when studying the association between PAs, body postures and pain markers in a physically inactive group of adults with overweight or obesity.

To our best knowledge, this is the first study to investigate the associations between pain-related outcomes and accelerometer-measured SB, ST and different intensities of PA in adults with overweight or obesity. In our study SB and PA habits were measured for four weeks, whereas in previous accelerometer studies the measurement period has generally been only 4–6 days [16, 21, 23]. As previously stated by Hart et al. increasing the number of measurement days increases the probability of measuring the actual habitual SB and PA [27]. Five days of measurement were needed to reliably estimate SB and three days to estimate PA (intraclass correlation coefficient ICC 0.80) compared to 21 days of monitoring. To reach full agreement (ICC 0.95) the whole 21 day period was needed to estimate SB whereas 13 days were adequate for estimation of PA. Thus, it is still unclear how many days of measurement are required to reach full agreement with habitual SB of a longer period. It is noteworthy that more days may be needed for reliable SB measurement compared to PA measurement. Furthermore, the sufficient duration of data collection needed for reliably estimating ST has not been evaluated. Therefore, it is conformational to perform a longer measurement than the <7 days used in most accelerometer studies to date. Moreover, we recently found that at least three weeks of accelerometry may be needed to find associations between PA, SB, and health outcomes [28].

Limitations

Our study has some limitations. First, the cross-sectional setting limits the interpretation of causality of the study results. Additionally, we used hip-worn accelerometers to assess PA, SB, and body posture, although the thigh has been proposed to be the optimal position for reliable recognition of SB and posture [43]. A problem with thighworn devices, however, is the use of tape which could

irritate skin and be loosened, especially so during a longer measurement period (i.e., four weeks). This could reduce the wear time and thus affect the results. To minimize these problems, we used hip-worn accelerometers with validated methods for assessing SB and posture [32]. Furthermore, we did not take different weekdays into account in the analyses of this study. However, by having a four week accelerometer measurement the possible differences between weekdays and weekends were most likely dissipated when using the mean values.

Conclusions

We found that standing for a longer time during the day is associated with higher PRD in physically inactive workingaged adults with overweight or obesity. Correspondingly, higher proportion of time spent sedentary is associated with less PRD. Instead of assuming that increasing sedentariness would alleviate PRD, we see standing as a possible coping mechanism for pain. In conclusion, this study suggests that people with PRD prefer to stand, possibly to cope with pain. Further studies should investigate whether interventions on increasing daily ST are feasible for alleviating PRD.

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Ethical approval: Research complied with all relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration (as amended in 2013) and has been approved by Ethics Committee of the Hospital District of Southwestern Finland

(16/1810/2017). The trial is registered at ClinicalTrials.gov (NCT03101228), registered 5.4.2017.

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