Original Experimental

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The potential effect of walking on quantitative sensory testing, pain catastrophizing, and perceived stress: an exploratory study

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Abstract

Objectives: Studies suggest that a range of pain mechanisms, such as poor quality of sleep, perceived stress, pain catastrophizing or pain sensitivity, are likely to enhance clinical pain. Animal studies suggest that these pain mechanisms can be modulated by increasing physical activity, but human data are needed to support this hypothesis. This exploratory study aimed to investigate the changes in pain mechanisms after a simple self-directed walking program of 8-weeks. Additionally, this exploratory study investigated the interaction between changes over time in assessments of poor quality of sleep, perceived stress, pain catastrophizing or pain sensitivity and how these changes interacted with each other.

Methods: This prospective cohort study included 30 healthy subjects who were assessed at baseline and 4- and 8-weeks after initiating the walking program (30 min walking/day for 8 weeks). Self-report outcomes included: Pain Catastrophizing Scale (PCS), the Perceived Stress Scale (PSS) and Pittsburgh Sleep Quality Index. Pressure pain thresholds, temporal summation of pain and conditioned pain modulation (CPM) were assessed using cuff algometry.

Results: Twenty-four subjects completed all the visits (age: 42.2, SD: 14.9, 16 females). PCS and PSS significantly decreased at the 8-week's visit compared to baseline ($p<0.05$). No significant differences were seen for an improvement in quality of sleep ($p=0.071$) and pain sensitivity ($p>0.075$) when comparing the 8-week's visit to the baseline visit. Changes in pain mechanisms comparing baseline and 8-weeks data were calculated and regression analyses found that an improvement in PCS was associated with an improvement in CPM ($R^2=0.197$, $p=0.017$) and that a higher adherence to the walking program was associated with a larger improvement in PCS ($R^2=0.216$, $p=0.013$).

Conclusions: The current exploratory study indicates that a simple self-directed walking program of 8-weeks can improve pain catastrophizing thoughts, perceived stress. Higher adherence to the walking program were associated with an improvement in pain catastrophizing and an improvement in pain catastrophizing was associated with an increase in conditioned pain modulation.

Keywords: walking; pain mechanisms; QST; pain catastrophizing; sleep quality; perceived stress

Introduction

Chronic pain affects approx. 20 % of the world's population and musculoskeletal (MSK) pain is the largest contributor to the high prevalence [1]. Inactivity have been suggested to maintain or worsen MSK pain [2, 3] but inactivity can also be associated with obesity [4, 5] or poor quality of sleep [6] and these factors are suggested to worsen MSK pain [7, 8]. Various forms of physical activity (often in combination with patient education) is recommended as a first-line treatment

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for many MSK pain disorders [9–11]. Walking is an easily implementable activity and walking programs with a duration of weeks has been demonstrated to improve pain and disability in patients with MSK pain [12] but the underlying mechanisms associated with pain relief are still to be explored.

Poor sleep quality is a major clinical issue for patients with chronic pain as up to 50 % of patients report poor sleep quality [13]. Poor sleep quality is also an issue in healthy pain-free individuals and epidemiological studies indicate that poor quality of sleep is associated to the development of widespread pain in the future [14, 15]. Recent evidence indicate that poor quality of sleep can negatively affect measures of pain sensitivity parameters in healthy individuals [16]. Additionally, poor quality of sleep is associated with worsening in psychological factors such as pain catastrophizing [7, 17] and higher levels of pain catastrophizing is associated with more impaired conditioned pain modulation (CPM) [18]. Finally, increased stress is associated with poor quality of sleep and vice versa [19] and this can potentially be associated with low-grade inflammation [20], which in preclinical studies are linked with increased sensitivity of both peripheral and central pain mechanisms [21, 22]. Conclusively, healthy pain-free individuals might experience increased pain sensitivity, and this could be due to impaired sleep quality or increased stress levels.

Quantitative sensory testing (QST) is utilized to assess nerve function and is used to quantify pain sensitivity in humans. Severe MSK pain is often associated with lower pressure pain thresholds (PPTs), facilitated temporal summation of pain (TSP) and impaired CPM [23–25]. PPTs assessed in a painful area can assess localized hyperalgesia whereas outside of a painful area can assess widespread hyperalgesia [26]. TSP is believed to assess the wind-up process of dorsal horn neurons [26] and facilitated TSP is therefore believed to reflect sensitization of spinal cord mechanisms. CPM is assumed to assess the balance of descending pain inhibitory and facilitatory mechanisms [27] and impairment of CPM therefore suggests an imbalance in these mechanisms [28]. Recent evidence suggests that a subpopulation of healthy pain-free individuals might be more pain sensitive than others and that these subjects experience more pain when exposed to an acute trauma [29, 30].

Studies indicate that exercise is associated with improvement in sleep quality [31, 32] and increases in PPTs and CPM [31, 33, 34]. Some exercise programs can be difficult to implement in patients with chronic MSK pain, due to pain and discomfort for weight-bearing exercise modalities. Walking is a simple exercise which can improve physical activity and is implementable for e.g. patients with osteoarthritis [12]. Studying the interaction between exercise and different dimensions of pain, including pain sensitivity and sleep quality, in individuals without chronic pain will contribute to our comprehension of these intricate systems. These findings can provide a basis for future investigations in the field of chronic pain research.

This exploratory study aimed to assess if a battery of QST assessment, pain catastrophizing, stress and sleep quality assessed in healthy pain-free individuals could be modulated by a simple self-directed walking program of 8-weeks.

Methods

Participants

The current exploratory study aimed to include 30 pain-free subjects who were in good health. Recruitment of participants was conducted through Aalborg University, Denmark. Inclusion criteria consisted of healthy, pain-free individuals, both women and men, who had access to a smartphone and were capable of using the Strava app. Exclusion criteria encompassed drug and/or alcohol addiction, previous medical history of neurological, musculoskeletal, or mental illnesses, chronic pulmonary conditions, atrial fibrillation, atrial flutter, chronic pain conditions, and current use of analgesic medication. A pre-inclusion interview was conducted to screen all subjects for these inclusion and exclusion criteria.

All subjects received detailed verbal and written information and signed prior to enrollment in the study. The study was approved by The North Denmark Region Committee on Health Research Ethics (N-20180089). The experiment was carried out in accordance with the Helsinki Declaration.

No studies have assessed the effect of an 8-week walking program on QST data and therefore the data to support a precise power calculation are not available. Based on previous studies using other exercise modalities [33, 35], the sample size calculation for the current study was based on an effect size of 0.6, with a power of 80 % and an alpha of 0.05, which yielded a sample size of 24 subjects. Longitudinal studies are known to suffer from drop-outs and therefore the current study aimed to recruit 30 subjects to account for drop-outs.

Experimental design and outcomes

The experiment consisted of three identical sessions (1) baseline, (2) 4-week follow-up and (3) 8-week follow-up. The 8-week exercise intervention consisted of 30-min walk 5 days a week, as studies has shown that exercises intervention lasting several weeks are capable of improving QST-parameters in chronic pain patients [31, 33, 34]. The daily walks were reported to the research team through the Strava app (Strava Inc, San Francisco, CA, United States). The participants were not restricted to a specific length or speed during their walks and were allowed to walk at their own pace. While the research team did not monitor the exact length of the walks, the Strava app served as a means of confirming that the subjects completed a walk of 30 min duration on a daily basis.

At each session Computer-controlled Cuff Algometry measurements were carried out and the four self-administered questionnaires: Pittsburgh Sleep Quality Index (PSQI), Pain Catastrophizing Scale (PCS), International Physical Activity Questionnaire (IPAQ) and the

Perceived Stress Scale (PSS) were completed. The measurement took place in a quiet isolated room at the Department of Health Science and Technology, Aalborg, Aalborg University, Denmark and FIXNORDIC A/S, Horsens, Denmark.

Questionnaires

The Pain Catastrophizing Scale (PCS) consists of 13 items focusing on thoughts and feelings in connection with pain [36]. The questions are rated on a 4-point scale ranging from 0 (not at all) to 3 (very much).

PQSI is a validated tool used to assess sleep quality in both clinical and non-clinical settings, as well as in young and old individuals [37–39]. The questionnaire is based on a four-point likert-scale, ranging from 0 meaning "not at all" to 3 meaning "all the time". PQSI consists of 19 items, which are used to create seven component scores evaluating sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication and daytime dysfunction. The sum of each component score makes up a global score ranging from 0 to 21, with a higher global score indicating a lower sleep quality [40].

PSS is developed to assess the degree of situations in which one's life are appraised as stressful within the last month [41]. As the questionnaire is completed continuously during this study, an overall estimation of self-estimated stress levels of 3 months was collected. In this study a 10-item version was used, as it has demonstrated to be superior to the original 14-item version [42, 43]. Participants are asked to evaluate their response upon life events and situations during the past month using a 5-point likert-scale ranging from 0 meaning "never" to 4 meaning "very often" with a total score ranging from 0 to 40 [42].

IPAQ is widely used for observing physical activity levels among 18–65 year-old adults [44]. This study used the long-lasting self-administered 27-item version which is designed to report thorough information within all domains of physical activity such as, leisure-time activity, household and yard-work activity, physical activity at work, self-powered transport and sedentary activity [44]. Total scores were calculated by summation of weighted MET-minutes per week across all activity domains [44].

Quantitative sensory testing

Deep tissue pain sensitivity was evaluated by cuff pressure stimuli using a computer-controlled cuff algometer (Cortex Technology and Aalborg University, Denmark), including a 13-cm wide tourniquet cuff (VBM, Sulz, Germany) and an electronic VAS (Aalborg University, Denmark) for the recording of the pain intensity. The cuff was placed at the head of the gastrocnemius muscle of the dominant lower leg. The electronic continuous VAS (sliding resistor) was 10 cm long and sampled at 10 Hz; 0 cm: no pain and 10 cm: worst pain imaginable. Cuff algometry is a reliable assessment for PPTs, TSP, and CPM [45, 46] and has often been utilized in studies with patients with chronic pain and healthy pain-free individuals [16, 29, 47, 48].

The pressure of the cuff was increased by 1 kPa/s and the participants were instructed to rate the pain intensity continuously on the electronic VAS until the tolerance level was reached. At this point, the participants were instructed to press a stop button. The pressure pain detection threshold (cPDT) was defined as the pressure at which the VAS score exceeded 1 cm as in previous studies [29, 48, 49]. The pain tolerance threshold (cPTT) was defined as the point at which participants indicated that their pressure tolerance level had been reached, which was signaled by pressing a stop button. The measurements were conducted once on both the dominant and non-dominant lower leg to the most affected knee.

Ten short-lasting stimuli (1 s each) at the level of the cPTT were given at the lower leg with a 1 s break between stimuli. The participants were instructed to continuously rate the pain intensity of the sequential stimuli using the electronic VAS and not return to zero during the breaks. For each cuff stimulus, a VAS score was extracted. TSP was calculated as the absolute difference between the last three stimuli and the first three stimuli as in previous studies [16, 50].

The CPM magnitude was assessed as the absolute changes in cPDT with and without a cuff conditioning stimulus. The conditioning stimulus was applied to the non-dominant lower leg, and the cPDT was assessed on the dominant lower leg as described above. The conditioning stimulus was applied as a constant stimulus with an intensity of 70 % of the pain tolerance level on the non-dominant leg [45, 48, 51]. The CPM effect was calculated as the absolute difference in conditioned and unconditioned cPDT (i.e., cPDTconditioned minus cPDTunconditioned).

Statistical analysis

Repeated measures analysis of variances (RM-ANOVAs) with a time factor (baseline, 4-week visit, and 8-week visit) were conducted for all questionnaires and QST data. The Bonferroni post hoc test was utilized to adjust for multiple comparisons. Cohen's d was used to report effect sizes. No imputations were made and only data from subjects with complete data at the three time points was used in the analysis.

Three multiple linear regression models with dependent parameters being change in (1) cPPT, (2) TSP and (3) CPM and independent parameters being change in PCS, PSS, PSQI and IPAQ were established in an attempt to understand the modulation of different study parameters and their interactions changes in pain sensitivity. Changes in study parameters were based on changes from baseline assessment to 8-week follow-up. Backwards elimination was applied to the linear regressions to identify independent predictors using cut-offs for statistical independence and inclusion of 0.05 and exclusion of 0.157, respectively, according to Akaike's Information Criterion for prognostic models [52]. The adjusted R^2 value was reported for each model. Scatterplot of standardized predicted values verses standardized residuals for all the regression analysis were plotted to test the assumptions of homogeneity of variance and linearity. For the analysis, all collinearity tolerance and variance inflation factor (VIF) levels were above 0.1 and below 10 [53], respectively, indicating no collinearity or multicollinearity among the independent variables.

Statistical tests were conducted using the IBM SPSS Statistics software version 26 (IBM, New York, USA). $p<0.05$ was considered a significant finding. All data are presented as means±standard deviation (SD) unless otherwise specified.

Results

Twenty-four participants completed all three visits, see Table 1 for demographics. The average adherence to the walking program was found to be 84 % (SD: 19 %).

The 8-weeks walking program did not significantly increase physical activity (IPAQ scores) over time ($F(2,46)=2.67$, $p=0.080$).

Table 1: Demographic information on the 24 subjects who completed the study.

Demographics	
Age, years	42.17 (SD: 14.87)
BMI, kg/m^2	27.20 (SD: 4.18)
Sex (female/male)	16/8
Baseline IPAQ score (met minutes/week)	4376 (SD: 4492)

kg, kilograms; MET, metabolic equivalent of task

Changes over time for pain catastrophizing, sleep and stress

A significant decrease in PCS scores were observed over time (F(2,44)=4.42, p=0.018) with post hoc analysis revealing significantly lower PCS scores at the 8-week visit when compared to the baseline visit (Bonferroni: p=0.013, Cohen's d: 0.57), Figure 1A. PSS scores significantly decreased over time (F(2,46)=4.28, p=0.020) with post hoc analysis revealing that scores at the 8-week visit were significantly lower when compared to the baseline visit (Bonferroni: p=0.017, Cohen's d: 0.53), Figure 1B. No significant changes over time were found for the PSQI (F(2,46)=2.06, p=0.069), Figure 1C.

Quantitative sensory testing

No significant changes were observed in cPPT (F(2,46)=2.74, p=0.075), TSP (F(2,46)=))=1.527, p=0.228) and CPM (F(2,46) =0.214, p=0.808) over time, Figure 2.

The interaction between modulation of study parameters

The scatterplot of standardized predicted values verses standardized residuals for all the regression analysis, showed that the data met the assumptions of homogeneity of variance and linearity, and the residuals were approximately normally distributed.

A regression model containing changes in study parameters were associated to a change in TSP (adjusted R^2=0.065, tolerance>0.7, VIF<1.5) and applying backwards elimination to this model identified changes in PSS as an important parameter, but not a significant independent parameter (p=0.147) for change in TSP (adjusted R^2=0.052, tolerance=1.0, VIF=1.0). Additionally, a regression model found that changes in questionnaire parameters were associated to a change in CPM (adjusted R^2=0.161, tolerance>0.7, VIF<1.5) and applying backwards elimination to this model identified changes in PCS as an independent factor (p=0.017) for change in CPM (adjusted R^2=0.197, tolerance=1.0, VIF=1.0). No associations were found to change in cPPT.

A regression analysis containing changes in questionnaire parameters were associated to a change in PCS (adjusted R^2=0.104, tolerance>0.7, VIF<1.4) and applying backward elimination to the model identified that higher adherence were independently (p=0.013) associated with larger improvement in PCS (adjusted R^2=0.216, tolerance=1.0, VIF=1.0). A regression analysis containing changes in questionnaire parameters were associated to a change in PSS (adjusted R^2=0.009, tolerance>0.7, VIF<1.5) and applying backward elimination to the model identified that larger improvement in PSQI were associated (p=0.134) with larger improvement in PSS (adjusted R^2=0.058, tolerance=1.0, VIF=1.0). A regression analysis containing changes in questionnaire parameters were associated to a change in IPAQ (adjusted R^2=0.007, tolerance>0.7, VIF<1.5) and applying backward elimination to the model identified that larger improvement in PSQI were associated (p=0.125) with larger improvement in IPAQ (adjusted R^2=0.063, tolerance=1.0, VIF=1.0). A regression analysis containing changes in

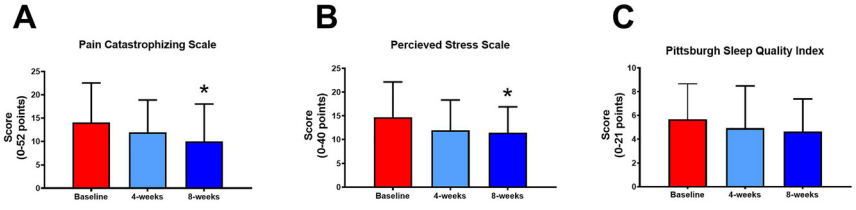

Figure 1: (A) Pain Catastrophizing Scale, (B) Perceived Stress Scale and (C) Pittsburgh Sleep Quality index scores from before (baseline) and after 4-weeks and 8-weeks of initiating the walking program. * indicated significant changes (p<0.05) when compared to the baseline visit.

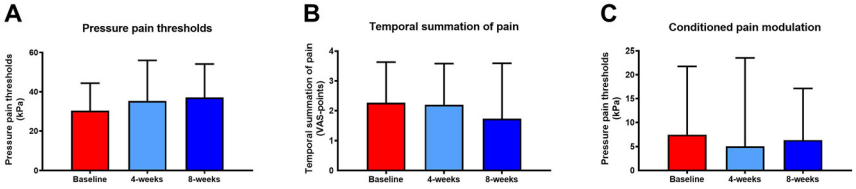

Figure 2: (A) Pressure pain thresholds, (B) temporal summation of pain and (C) conditioned pain modulation from before (baseline) and after 4-weeks and 8-weeks of initiating the walking program. * indicated significant changes (p<0.05) when compared to the baseline visit.

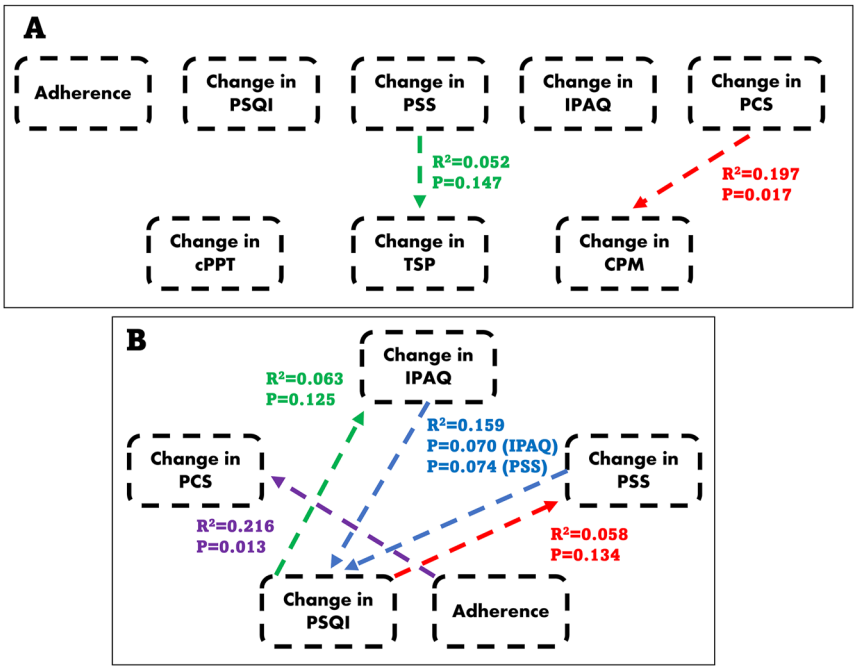

Figure 3: Multiple linear regressions were completed to understand the interaction between changes in study parameters assessed before and 8-weeks after a walking program in healthy pain-free subjects. Model A focused on understanding the changes in pain sensitivity parameters whereas model B focuses on understanding the modulation of sleep, stress, physical activity and pain catastrophizing. Both models contained adherence to the walking program. Color-coding's are linked to the specific regression analysis aiming to explain the variability. PSQI, Pittsburgh Sleep Quality Index; PSS, Perceived Stress Scale; IPAQ, The International Physical Activity Questionnaire; PCS, Pain Catastrophizing Scale; cPPT, cuff pressure pain threshold; TSP, temporal summation of pain; CPM, conditioned pain modulation.

questionnaire parameters were associated to a change in PSQI (adjusted R^2=0.109, tolerance>0.7, VIF<1.4) and applying backward elimination to the model identified that larger improvement in PSS (p=0.074) and IPAQ (p=0.070) were associated with larger improvement in PSQI (adjusted R^2=0.159, tolerance>0.9, VIF<1.1). See Figure 3 for associations between changed study parameters.

Discussion

This exploratory study found that a simple self-directed walking program of 8-weeks significantly reduced perceived stress and pain catastrophizing. This study suggests that a decrease in perceived stress was associated with a decrease in temporal summation of pain and a decrease in pain catastrophizing was associated with an increase in conditioned pain modulation. Finally, improvement in perceived stress and physical activity were associated with an improvement in sleep quality and vice versa and a higher adherence to the exercise program was associated with a decrease in pain catastrophizing.

Changes in cognitive factors after exercise

A recent systematic review and meta-analysis found that high intensity interval training could increase mental well-being, and reduce depressive symptoms and perceived stress compared to non-active control groups in non-chronic pain subjects [54]. Youngstedt and Kline [32] reported that increased physical activity was associated with better sleep quality in the general population [32] and Lyng et al., 2022 demonstrated improvements in PSQI after an 8-week exercise program for patients with shoulder pain [31]. Two randomized controlled trials demonstrated no effect of 12-weeks of high intensity interval training on sleep quality when compared to a non-active control group [55, 56]. Patients with chronic low back pain who report low levels of physical activity are more likely to report higher levels of kinesiophobia, pain catastrophizing and fear avoidance beliefs when compared to patients with higher levels of physical activity [57], indicating an association between physical activity and mental health. Less intensive exercise-modes might also improve cognitive factors, as e.g. 8-weeks of yoga exercise have been shown to improve pain catastrophizing in patients with fibromyalgia [58]. Additionally, a randomized controlled trial found that 8-weeks of low-intensity physical activity program combining talking and weightlifting (light weight) improved pain catastrophizing, perceived stress and PPTs in patients with fibromyalgia when compared to patients receiving no intervention [59]. This study distinguishes itself from previous attempts by focusing on a straightforward self-directed walking program that necessitates no specific equipment or instructions. Moreover, our study exclusively involves pain-free individuals. Despite the exploratory nature of this study, the results indicate potential improvements in certain pain-related cognitive factors after an 8-week walking program in pain-free individuals. The dose-response relationship between adherence and

larger improvement in pain catastrophizing thoughts is of interest and should be further investigated in future studies.

Changes in pain sensitivity after exercise

Pre-clinical literature suggests that inactivity is associated with a higher level of pro-inflammatory cytokines and that exercise potentially leads to a more anti-inflammatory profile [60]. Pro-inflammatory cytokines are known to sensitize peripheral [21] and central nervous system [61] and therefore, the potential anti-inflammatory profile caused by exercise could partly explain the hypoalgesia effect of exercise.

In humans, a recent systematic review of randomized controlled trails concluded that exercise could improve local and widespread pressure hyperalgesia in patients with chronic pain [62]. Additionally, Lyng et al. [31] demonstrated improvements in CPM following an 8-weeks exercise program for patients with shoulder pain and Heredia-Rizo et al. [33] demonstrated an improvement in PPTs and CPM following a 5-week exercise program for patients with neck and shoulder pain. Hansen et al. [35] demonstrated improvements in exercise-induced hypoalgesia following 7-weeks of military training in healthy individuals and specifically found that subjects with higher levels of pain sensitivity at baseline were more likely to improve in pain sensitivity following the intervention.

The current study utilized a light exercise program, which cannot be compared to the previous studies, and finds that a simple self-directed walking program of 8-weeks could not reduce pain sensitivity. Additionally, this study found that a decrease in perceived stress was associated with a decrease in temporal summation of pain and that a decrease in pain catastrophizing was associated with an increase in CPM. Randomized controlled trials are needed to confirm these results.

Limitations

The current exploratory study is limited by the absence of a control or placebo group, necessitating cautious interpretation of the results. Furthermore, the sample size used in this study was determined based on an estimated effect size of 0.6 for the walking intervention on quantitative sensory testing (QST). However, the effect sizes reported for the significant findings in this study are below 0.6, indicating that the study may be underpowered. Therefore, the results should be interpreted with caution. Additionally, it is important to note that the effect size of 0.6 was derived from studies involving patients with chronic pain [33] and interventions that differ from a walking program [35]. Consequently, the findings of the current study should be approached with caution.

The current study examined potential associations between the study parameters using multiple linear regression. However, it is important to note that the study sample size does not provide sufficient statistical power for such an analysis, and there is a high risk of overfitting the model. These multiple linear regression models should be confirmed in larger studies with sufficient power. Therefore, it is crucial to interpret the results from the model with caution.

Conclusions

The findings of this exploratory study suggest that an 8-week self-directed walking program can lead to improvements in pain catastrophizing thoughts and perceived stress among healthy individuals. Additionally, a higher adherence to the walking program was associated with an improvement in pain catastrophizing thoughts and an improvement in pain catastrophizing might be associated with an improvement in CPM. This study is exploratory in nature and non-controlled and therefore the results should be interpreted with care.

Research ethics: The study was approved by The North Denmark Region Committee on Health Research Ethics (N-20180089). The experiment was carried out in accordance with the Helsinki Declaration.
Informed consent: All subjects received detailed verbal and written information and signed prior to enrollment in the study.
Author contribution: Anna Houmøller Rasmussen, Lærke Kjeldgaard Petersen, Mette Andbæk Kaasgaard, Maria Møller Bertelsen, Michael Skovdal Rathleff, and Kristian Kjær-Staal Petersen designed the study. Anna Houmøller Rasmussen, Lærke Kjeldgaard Petersen, Mette Andbæk Kaasgaard, and Maria Møller Bertelsen collected the data under supervision of Kristian Kjær-Staal Petersen. Anna Houmøller Rasmussen, Lærke Kjeldgaard Petersen, Mette Andbæk Kaasgaard, and Maria Møller Bertelsen wrote the first draft of the manuscript. Michael Skovdal Rathleff, and Kristian Kjær-Staal Petersen critically revised the manuscript. The authors have accepted responsibility for the entire content of this manuscript and approved its submission.
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Data availability: The data can be obtained on reasonable request from the corresponding author.

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