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The role of sleep problems in a chronic pain group compared to a control group, with respect to the response in pressure pain thresholds before and after a physical activity- a pilot study

Degree Project in Medicine

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Abstract

Background

Chronic pain is usually defined as pain lasting more than three months. Chronic pain has a prevalence of 20% in the population and one in five of the pain patients have neck or shoulder pain. Chronic pain is more common among women than men and persons with chronic pain are more likely to have sleep problems, such as insomnia, than the general population. It is also more common with symptoms of anxiety and depression among pain patients. It has been shown that physical activity can reduce pain intensity and enhance the quality of life.

Aim

To investigate whether symptoms of sleep disorder are effect modifiers of the association between either the levels of Pressure Pain Thresholds (PPT) or the change in PPT due to physical activity and chronic pain.

Method

An experimental pain study was implemented at Occupational and Environmental Medicine Clinic, Sahlgrenska University Hospital, Gothenburg, Sweden, consisting of 26 persons (21 women, 5 men) with chronic neck pain and 12 healthy controls (7 women, 5 men), all between 18-65 years old. Pressure pain thresholds (PPT) were measured in a standardized way along both trapezius muscles and tibialis anterior muscle. Measurements were made before and after a physical activity (arm cycling).

The study participants filled in a sleep diary and a sleep questionnaire (Karolinska Sleep Questionnaire) before the pain threshold measurements, which led to five sleep variables; mean sleep hours during a week (*Mean Sleep),* sleep hours the night before the examination *(Sleep Before)* and sleep quality indices regarding the presence of insomnia, awakening

problems and tiredness referred to as *Sleep Quality* (*Insomnia), Sleep Quality (Awakening)* and *Sleep Quality* (*Tiredness)*.

Results

Sleep Quality (Awakening) had significant associations with levels of PPT at both right and left trapezius ($p<0.05$), with lower sleep quality associated with higher PPT. *Sleep Quality* (*Tiredness)* was statistically significant associated with change in PPT after physical activity, where a decrease in PPT was seen after exercise among controls with higher *Sleep Quality (Tiredness)*. Change in PPT after physical activity had tendencies of association with *Sleep before* that seemed different between the groups, for both right and left trapezius. These tendencies show that more hours slept the day before the examination predict an increase in PPT at the pair of trapezius muscles after physical exercise among controls, but not among pain subjects. An increase in levels of PPT after a physical activity among both pain and control group at tibialis anterior without any difference between groups.
No statistically significant associations or tendencies were found in other variables.

Conclusion

Higher *Sleep Quality (Awakening)* predicted for lower levels of PPT in the pain group, there was a difference between the groups with a reversed pattern among the controls. Low *Sleep Quality (Tiredness)* among controls predicted for an increase in PPT after a physical activity and this pattern was not seen in the pain group. No clear causal factors behind these unexpected associations can be seen in the data, but confounders or a small sample size and thereby low power can contribute to the associations.

Key words

Pain, chronic pain, sleep, sleep disorders, physical activity

Background

Pain is a complex, subjective phenomenon defined as “An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” by the International Association for the Study of Pain (IASP). A common classification is acute and chronic pain, where acute pain is transitory and chronic pain is long lasting. Another type of classification is a pain classification according to the following pathophysiological cause: nociceptive pain (tissue damage), neuropathic pain, psychogenic pain and idiopathic pain. However the pathophysiological event of dysfunctional pain modulation is not mentioned in this classification and dysfunctional pain modulation seems to be one of the mechanisms behind chronic musculoskeletal pain.(1)

Chronic pain

Chronic pain is usually defined as pain lasting more than three months, which is beyond the normal length of tissue healing.(2) Chronic pain is common and affects approximately 20% of the adult European population.(3) The level of occurrence makes chronic pain more frequent than asthma or diabetes in the same population.(3) The leading cause of the commonly occurring chronic pain is musculoskeletal pain.(3) Localized musculoskeletal pain is most common in the back, where almost 50% of the pain patients have pain, followed by joint pain, then head, neck and shoulder pain.(4) Most of the patients (70%) are being managed in the primary care by their general practitioner.(3, 4) In fact pain is one of the most common reasons to have an appointment with the doctor.(5) However only 2% of the patients with chronic pain are treated by a pain specialist. The lack of specialist treatment could be a part of the fact that 40% of the patients feel that they have inadequate management for their pain.(4)

A survey made in Europe showed that people in the group between 40-61 years appeared to suffer more from chronic pain than people below 40 years of age.(4) Among women, the peak prevalence of chronic pain seems to be at age 65-69.(6) People with chronic pain often live many years with their pain, for example, 60% have had pain 2 to 15 years and over 20% have suffered with chronic pain over 20 years.(4) The majority of people with chronic pain report a moderate pain intensity as their last pain experience, however up to 34% report severe pain as their last pain experience.(4) Barely half the group of chronic pain patients suffer from constant pain, the remaining patients suffer from intermittent pain.(4)

Sex difference

Chronic musculoskeletal pain is more common among women, (4) women report chronic pain in more regions than men(6) and the prevalence of chronic widespread pain is higher among women than men.(7) Women tend to seek healthcare for pain management to a greater extent than men. (3) Moreover studies have shown that women have lower levels of pressure pain thresholds, but most studies have shown no difference in pain tolerance between male and female study participants.(8)

Consequences of chronic pain

Chronic pain leads to decreased physical functioning, sleep problems, anxiety and depression symptoms.(9, 10) The negative impact is greater with more severe pain.(9) Pain and mental health seem to have a bidirectional aetiology, where pain causes poor mental health and vice versa.(3) As an example treatment of depression in chronic pain patients has a more favourable outcome if the depression is treated alongside with the pain.(3) Chronic pain does not only affect the mental health, it also has a major impact on quality of life, with suffering and lost income.(3, 4) Nearly a quarter of people affected by chronic pain report that they are

less able to maintain relationships with family and friends, have a sexual relationship or maintain an independent lifestyle.(4) Thirty-two per cent of people affected by chronic pain report that they are no longer able to work outside the home.(4) Almost 20% have lost their job because of the pain, 13% have changed jobs and 16% have changed responsibilities at their present job due to their chronic pain.(4) However, it is not only the individual that gets affected economically due to the pain, the individuals' eventual inability to maintain equal work ability as previously in their lives also affects the society.(11) Each pain patient costs the society approximately 6,400 EUR annually in Sweden (data from 2008), which leads to a total national cost of 32 billion EUR.(12) This is not an isolated economical issue in Sweden only, for example it is estimated that chronic pain costs $560 to 635 billions in America every year.(13)

Treatment

The most commonly prescribed medicines for chronic pain in Europe are NSAIDs, paracetamol and opioids. NSAIDs may have an effect on chronic back pain in the short term compared to placebo.(14) No difference has been shown between NSAIDs and paracetamol.(14) It is today recommended to optimize nonpharmacological therapy and non-opioid pharmacotherapy before trial of opioids.(15) Opioid therapy for chronic non-cancer pain is a controversial medical practice which has increased the last decades. (16, 17) Morphine has been shown to increase pressure pain tolerance under experimental conditions.(18) Clinical studies have shown significant analgesic effect on chronic pain in the short term, however opioid treatment in chronic pain has not showed to improve the pain or the level of the functioning in a long term perspective.(19) The long-term perspective on opioid use in non-cancer pain has been debated considering eventual drug abuse and effects. A long term study from Denmark has shown alarming results where long term opioid therapy

is associated with negative changes in quality of life, pain interference and physical capacity.(20)

Dysfunctional pain modulation

Persistent pain seems to relate to dysfunctional pain modulation. The dysfunctional modulation is a combination of defect pain inhibition and central sensitization. Central sensitization is an enhancement of the function in the nociceptive neuron in the central nociceptive pathway caused by increase in the membrane excitability and synaptic efficacy along with reduced inhibition.(21, 22) This reaction is normally reversible and completely physiological after an acute trauma when the body should prevent further movement and damage, but the central sensitization can become persistent and cause chronic pain.(23) Central sensitization seems to play a key role in unilateral shoulder pain.(24) Treatment aiming to decrease the hyperexcitability of the central nervous system in the affected population could therefore be of interest.(24)

The other type of dysfunctional pain modulation, defect pain inhibition, seems to be the main cause of generalized pain, for example chronic widespread pain or fibromyalgia. The most important clinical risk factor to develop chronic pain is pain itself, either acute pain or chronic pain at another site. The more severe and widespread the acute pain is, the more likely it is that the previous acute pain will become chronic pain.(3) Even pain-related fear and expectation for persistent pain predicts for future pain.(25)

Pain and sleep

Patients with chronic pain are more likely to have sleep problems than the general population(9, 26, 27) and as many as two thirds of patients with chronic pain report concomitant sleep disturbances.(28) In a study from Australia, 75% of the patients with

chronic pain met the criteria for insomnia(29), which is comparable with 20% in the general population(30). The other way around, in a study group of persons with insomnia, 50% had chronic pain, which made chronic pain the most common medical problem among people with insomnia.(31) Among patients with chronic pain and clinical depression, 97% suffers from insomnia.(26)

It has been demonstrated that sleep deprivation increases pain sensitivity and decreases pain thresholds.(32) Reduced time in bed, specifically reduced REM-sleep, has been shown to have a hyperalgesic effect in healthy controls.(33) Moreover, sleep duration has been shown to have a greater independent association with pain than sleep quality.(29) However another study has shown that poor sleep quality is associated with pain, but excessive daytime sleepiness or obstructive sleep apnoea are not.(34)

It seems that pain and sleep deprivation have a bidirectional interaction.(11) Pain interferes with sleep, but disturbances in sleep also contribute to the extent of pain.(35) Sleep loss seems to be a predictor for development of chronic pain, because of the increase in neural excitability.(11) Impaired sleep quality is a predictor for chronic pain.(7) Bad sleep quality predicts more attention to the pain during the following day.(36) Stimuli that disrupt slow-wave sleep decrease delta and sigma waves, whereas alpha and beta waves increase.(35) Noise stimuli that interferes with the slow-wave sleep result in unrefreshing sleep and diffuse musculoskeletal pain in healthy subjects. These symptoms together with an increase of alpha waves is usually seen in patients with chronic widespread pain (fibromyalgia).(35)

In a 17-year follow up study on Norwegian women, 44% of the initially pain free persons had developed chronic pain, which corresponds to an annual incidence of 2.6%. Interrupted sleep, non-restorative sleep, feeling anxious, frightened or nervous had associations with

development of chronic pain.(7) In the same study 25% of the women with chronic pain at the baseline were pain free 17 years later, while 75% still had chronic pain, which corresponds to an annual recovery rate of 1.5%. Disrupted sleep, non-restorative sleep and non-specific health complaints were associated with persistence of chronic pain.(7) Age seems to be a moderate confounder in the effect of disrupted sleep on development of chronic pain.(7)

A study made on healthy women tested the effect of partial sleep loss, which showed decrements in pain-inhibitory function and an increase in spontaneous painful symptoms. However the study did not show any change in pain pressure thresholds after total sleep deprivation.(37)

Pain and physical activity

The World Health Organisation (WHO) provides guidelines regarding physical activity, addressed to healthy adults; "Adults aged 18–64 should do at least 150 minutes of moderate-intensity aerobic physical activity throughout the week or do at least 75 minutes of vigorous-intensity aerobic physical activity throughout the week or an equivalent combination of moderate- and vigorous-intensity activity. Aerobic activity should be performed in bouts of at least 10 minutes' duration."(38)

In the past, patients were told to stay inactive whilst resting to heal from the pain.(2) The general advice today is to keep active.(2) Despite the recommendation, many patients feel that they are less able or no longer able to take part in various activities.(4) Half of those with chronic pain report that they are less able to exercise and 23% report that they are no longer able to exercise due to their pain.(4) However, according to the present evidence physical activity is not likely to cause harm in patients with chronic pain.(2) Although exercise may be

harmless, pain after physical activity has been shown to be associated with persistent chronic pain(7), but there is also evidence that physical activity reduces pain intensity, increases quality of life and improves physical function.(2) Active, specific and professionally supervised physical activity among patients with chronic pain gives 20-30% more efficient treatment then patients not treated with physical activity.(5)

Strengthening neck and shoulder exercise

A study regarding pain relief in the neck/shoulder region randomized workers into two groups, one with high intensity strength training and the other as a control group. It showed that the overall intensity of neck and shoulder pain decreased significantly in the training group (49% pain reduction) compared to the control group (17% pain reduction).(39) Furthermore it seems like stretching exercises have a significant reduction in pain intensity and strengthening neck and shoulder exercises appear to have the same ability to reduce pain.(40)

Health benefits

A very high level of physical activity during leisure time among female workers without lower back pain or with non-chronic back pain reduced their risk with almost 50% for long-term (more than two consecutive weeks) sickness absence compared to colleagues with low level of physical activity. The same risk reduction could however not be seen among workers with chronic back pain in the same study.(41) The positive health effects of physical activity can be used not only with the intention to affect the pain itself, but also to prevent comorbidities of chronic pain. It is not unlikely to have another chronic disease alongside the pain, since the prevalence of chronic pain is higher among patients with chronic diseases.(3) Nearly a third of patients with coronary heart disease suffer from chronic pain(3) and the

incidence of ischemic heart disease decreases with physical activity.(38, 42) Other than preventing coronary heart disease regular exercise furthermore prevents diabetes, hypertension, stroke, depression and osteoporosis.(38)

Aim

The aim of the study is to investigate whether symptoms of sleep disorder are effect modifiers of the association between either the levels of pressure pain thresholds or the change in pressure pain threshold due to physical activity and chronic pain.

Scientific issue

Can symptoms of sleep disorders predict the level of pressure pain thresholds before a physical activity and the change in pressure pain threshold after a physical activity among individuals with chronic neck or shoulder pain?

Specific research questions:

a. Is there an association between symptoms of sleep disorders at baseline and the level of pressure pain thresholds, and if so is the association different in a chronic pain group compared to a control group?
b. Is it there an association between symptoms of sleep disorders at baseline and the change in pressure pain thresholds after a physical activity, and if so is the association different in a chronic pain group compared to a control group?

Material and Methods

This pilot study is an experimental pain study on a pain group and a control group, consisting of people of working age. Pressure Pain Thresholds (PPT) were measured at the trapezius muscles and the tibia before and after a low intensity physical activity, arm cycling, to evaluate associations between sleep disorders, PPT and the effect of the exercise.

Participants

The study included 26 persons (21 women and 5 men) with chronic neck or shoulder pain and 12 healthy controls (7 women and 5 men), it thereby included a group of 38 persons in total. Participants in the pain group were recruited from physiotherapy clinics and the Occupational and Environmental Medicine Clinic, Sahlgrenska University Hospital, Gothenburg, Sweden. The controls were recruited by advertising on official message boards at University of Gothenburg, Sweden, in addition some of the controls were friends to the pain group. Subjects had to be between 18 and 65 years of age to participate. The controls needed to be in work or studying, while the subjects in the pain group could be working, studying, or sick-listed. Participating patients were required to have experienced long-lasting, virtually continuous, musculoskeletal pain with neck or shoulder as main pain localization by at least 3 months' duration. The controls did not have any present pain during the tests and had at most three days of any pain during the last 12 months. Each participant received 1,500 SEK as a compensation.

Exclusion criteria

Subjects who had symptoms of joint involvement or tendinitis in the shoulder joint, rheumatic or metabolic disease, neurological disease, traumatically-induced neck pain (whiplash), had been diagnosed with fibromyalgia or had had a severe mental disorder were excluded from

the study. Controls who had had pain in the neck/shoulder for more than 2-3 days during the last 12 months or had a severe mental disorder were excluded from the study.

In total seven persons were not allowed to be included in the study, six from the pain group (four had exclusion criteria and two did not show up) and one from the control group, who did not show up. One control person was excluded from the study after the study start because the person had difficulties filling in the sleep diary due to language barriers, which led to a great deal of missing values.

Study inclusion

At study inclusion, a standardized medical examination was performed, including a detailed examination of the neck, shoulders, back, and upper extremities. Each subject was interviewed regarding symptoms and examined by an occupational physician at the Occupational and Environmental clinic, Sahlgrenska University Hospital (the majority was examined by the same physician and a few by one special informed colleague). A standard procedure was followed for physical examination of the neuromuscular and skeletal systems of the upper extremities to check for and identify other diseases. After having taken the medical history and after having performed the clinical examination, the occupational physician decided who was to be included in the study. All the included patients had non-specific chronic neck or shoulder pain, where no specific pathology could be established.

Hospital Anxiety and Depression Scale (HADS)

On the day of study inclusion, the participants filled in a baseline questionnaire including pain intensity and a range of other questions regarding pain (for instance pain drawing, kinesiophobia), medication, sick leave, sleep quality, lifestyle and social support. In addition

to the questionnaire the participants filled in the Hospital Anxiety and Depression Scale (HADS)(43), a short self-assessment questionnaire that measures anxiety and depression. HADS includes two subscales comprised by seven items each and the scales range from 0 to 21. A score of 0-7 indicates a non-case (no clinical depression or anxiety), a score of 8–10 indicates a possible case, and 11-21 indicates a definite case (depression or anxiety).

Diary

During a week before and a week after the day of the experiment the subjects had to fill in a diary with information about the intensity of pain (Numeric Rating Scale; NRS)(44), pain drawing, self-reported consequences of pain, sleep (Karolinska Sleep Questionnaire)(45) medication (especially analgesics), activity and mood.(46) These outcomes were in line with consensus from the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials, IMMPACT.(44) However we have chosen to focus on Karolinska Sleep Questionnaire in our study.

Pressure pain thresholds

Pressure pain thresholds (PPT) were measured in a standardized way along the trapezius muscle at three points T1, T2, T3. The study leader set out the three points by measuring from cervical spine to acromion, mark exactly in the middle, which led to the central point T2. T1 (most proximal point on the trapezius muscle) was then set out by measuring from cervical spine seven to T2 and T3 (most distal point on the trapezius muscle) was placed out between T2 and acromion. PPT measurements were made on the right and left trapezius muscle and the tibialis anterior muscle as a control. T1, T2, T3 were used to receive mean values of the PPT for right and left trapezius muscles and these mean values were used in the calculations. Measurements were made by an algometer, which was pressed to the skin at the measurement

point of the muscle. A commercially available electronic algometer was used, Somedic AB Hörby. The pistol like algometer's square centimetre sized rubber probe was placed at the muscle belly. The study leader increased the pressure steadily at a constant rate of 40 kPa/s. The participating study subjects were instructed to push a button when the pressure hurt, which consequently relieved the pressure and the pain threshold was recorded. The increasing pressure stopped a maximum of 700 kPa, to avoid hematomas and persisting soreness induced by the measurement (the maximum was 600 kPa until March 2013). Pain thresholds were assessed before and immediately after the physical exercise.

In the analysis of levels of PPT, we have chosen to use only females, because of the small sample of male participants. Moreover women have been shown to have lower PPT than men(47), which make the male PPT levels non applicable on females. In the analysis of change in PPT we will use values from men and women since the change is essentially equal between genders.(48)

Arm cycling

Data to this study has been used from the study LoadPain, Occupational and Environmental Medicine, Public Health and Community Medicine, Sahlgrenska University Hospital, Gothenburg University. The original aim of the LoadPain study was to investigate how a working population with chronic neck and shoulder pain was affected after a low intensity exercise isolated to the neck and shoulder region in order to facilitate the estimate of working ability. Arm cycling was chosen as a physical activity to resemble a dynamic working movement. The arm cycling was thereby meant as a low intensity exercise, rather than a high intensity physical activity. Heart rate was registered through a chest belt, which was registered every second minute together with values on a pain and effort scale. The arm cycling examination was made on a Monark Cardio Rehab 891 E, an arm ergometer to test

cardio and upper body strength. The study subject performed the arm cycling during 30 min with a velocity at 25 turns per minute. The resistance was standardized; men had a resistance of 200 g and women 100 g the first ten minutes. After ten minutes the resistance increased to 400 g for men and 300 g for women. After another ten minutes the resistance increased a last time to 600 g for men and 500 g for women.

Variables

The dependent variables in this study are the levels of PPT before arm cycling and changes in PPT after arm cycling. We wanted to investigate if there were associations between the levels of PPT and sleep variables or changes in PPT and sleep variables and if the associations were different between the pain and control group.

Sleep variables

The five sleep variables in this study were collected through a sleep diary and Karolinska Sleep Questionnaire(45). The study subjects filled in the sleep diary every morning they woke up during two weeks. This diary included information about weekday, which time they went to bed and woke up and how many hours they had slept. The diary made calculations of two sleep variables possible; *Mean Sleep*: the mean value of sleep hours per night during one week and *Sleep Before*: the number of sleep hours the night before the examination. The Karolinska Sleep Questionnaire (KSQ) was used to acquire sleep quality indices regarding the presence of insomnia, awakening problems and tiredness, where low index numbers indicate bad sleep quality and high numbers indicate good sleep quality. These indices will be referred to as the variables *Sleep Quality (Insomnia)*, *Sleep Quality (Awakening)* and *Sleep Quality (Tiredness)*. The test persons were asked if they had been bothered by any sleep disorder symptoms the past three months. Precise questions about sleep disorders used to calculate the sleep quality indices are shown below. Participants responded to all the questions in a one-to-

six graded scale; 1=Always bothered, 5 times per week or more; 2=Most of the times, 3-4 times per week; 3 =Often, 1-2 times per week; 4=Sometimes, several times per month; 5=Seldom, one or a few times per year; 6=Never bothered. The indices were calculated through adding the values in the same group of questions and divide by the number of questions. The indices are therefore always between 1-6.

Have you been bothered by the following complaints during the past three months?

Sleep Quality (Insomnia)	a. Problems falling asleep
	c. Repeated awakenings with problems falling asleep again
	i. Premature awakenings
	j. Disturbed/Restless sleep
Sleep Quality (Awakening)	b. Difficulties waking up
	h. Not well rested on awakening
	m. Feelings of being exhausted at awakening
Sleep Quality (Tiredness)	n. Felt sleepy during work
	o. Felt sleepy during leisure time
	p. Involuntary dozing off during work time
	q. Involuntary dozing off during leisure time
	r. Need to work hard to stay awake

Confounders and demographics

At a population level, there are different factors known to be associated with chronic pain, including physical, psychological and social variables. Some of them are modifiable (for example pain, mental health, co-morbidities, smoking, sleep, physical activity) and some are non-modifiable (for example age, sex). (3) In our study we have chosen to adjust for these

potential confounders: age, sex, BMI ($kg*m^{-2}$), depression and anxiety. Depression and anxiety symptoms have been shown in previous studies to be associated with both chronic pain(49, 50) and sleep disorders(51). The information about age was obtained from the civil registration number, BMI was calculated from the study participant's weight in kg and height in meter. Depression and anxiety was evaluated from the Hospital Anxiety and Depression Scale (HADS).

Statistical analysis

The statistical analysis was performed with Excel version 15.33 and Statistical Package for Social Science from IBM (SPSS) version 24 for Mac.

Spearman correlations were made to search for colinearity. If any continuous variable was over 0.7 or categorical variable was over 0.3 these correlations was considered to have collinearity. Paired sample t-test were made to compare mean values of the levels of PPT and compare mean values of the sleep variables between the groups. Regression analyses were made through Analyze, General Linear model and Univariate. The regression analysis combined site of PPT measurements, pain/control group and a sleep variable. One regression analysis was made with interactions between the group and the sleep variable and one regression analysis was made without interaction between the group and the sleep variable. The regression analyses were adjusted for confounders and the confounders were included in Univariate.

Power calculation

Data has been used from the experimental study LoadPain from Occupational and Environmental Medicine (Public Health and Community Medicine, Sahlgrenska University

Hospital, Gothenburg University). Power for this study was calculated during planning and the calculation showed that to achieve power of 80% based on a minimal difference of 60 kPa between pain group and control group a total sample size of 112 individuals (84 pain group, 28 healthy controls) was needed. The significance level was set to p=0.05. The relationship 3:1 pain subject versus control because of interest to study subgroups among the pain subjects. The number of 112 participants was however not achieved in this actual study. Data was collected from April 2012 to June 2015.

Ethics

The study was approved by the Regional Ethical Review Board in Gothenburg (Dnr 956-11), and followed the Helsinki Declaration. All the data were processed according to the Personal Data Act (Personuppgiftslagen, PUL) and Sahlgrenska University Hospital was responsible for the personal data. Written study information was given to the subjects, in addition to verbal information prior to participation. Written, informed consent was given by all the study participants before the measurements started. The study subjects were given information about the right to refuse to participate or withdraw the consent to participate at any time without reprisal.

Results

Strengthening exercise were more commonly performed by the controls, where 64% exercised once or more per week, than the pain group where the same number was 33%. The average exercise time was also longer among the controls. Aerobic exercise was more common than strengthening exercise among the persons with chronic pain and 50% exercised once a week or more. In the control group 85% did aerobic exercise once a week or more. Flexibility exercise were more common in the pain group (36%) than the control group (25%). Four of the persons in the pain group (15%) have or have had physically demanding works, whereas the same value is only one person (1%) in the control group.

Confounders adjusted for in the study are shown in **Table 1a**. The pain group had a greater number of participants than the control group. The mean and median BMI were higher in the pain group, but the mean BMI was not higher in a statistically significant way ($p=0.115$ for the whole dataset and $p=0.098$ for only women). The mean and median age was higher in the pain group and the mean age was higher in statistically significant way in the whole dataset ($p=0.013$), but not in the analyses made with only women ($p=0.077$).

Table 1a. Confounders used in the study, control group and pain group presented both for the total dataset and women only.

		Total dataset			Only women		
		Control group	**Pain group**	**Total**	**Control group**	**Pain group**	**Total**
Age	**Mean**	38	49	45	37	49	46
	Median	27	51	50	26	51	51
	SD	16.2	13.4	15.4	17.1	14.6	15.9
	Min, max	21, 61	22, 65	21, 65	21, 58	22, 65	21, 65
	n	12	26	38	7	21	28
BMI	**Mean**	23	25	25	21	25	24
	Median	22	25	24	21	24	22
	SD	3.5	5.3	4.9	3.1	5.6	5.3
	Min, Max	18, 28	19, 44	18, 44	18, 28	19, 44	18, 44
	n	12	26	38	7	21	28
Depression	**Mean**	11.6	12.3	12.1	11.4	12.2	12.0
	Median	12.0	12.0	12.0	12.0	12.0	12.0
	SD	1.08	1.20	1.19	1.27	1.21	1.25
	Min, Max	9.0, 13.0	10.0, 15.0	9.0, 15.0	9, 13	10, 15	9, 15
	n	12	24	36	7	19	26
Anxiety	**Mean**	8.08	8.71	8.5	8.29	8.58	8.5
	Median	8.0	8.5	8.0	8.0	8.00	8.00
	SD	2.234	2.758	2.580	2.563	2.854	2.731
	Min, Max	5, 13	5, 14	5, 14	5, 13	5, 14	5, 14
	n	12	24	36	7	19	26

Standard Deviation referred to as SD. Number of subjects referred to as n.

Sleep variables results

Analyses were made on five different sleep variables; mean sleep hours per night during a week (*Mean Sleep*), sleep hours the night before the examination day (*Sleep Before*), *Sleep Quality* (*Insomnia)*, *Sleep Quality* (*Awakening)* and *Sleep Quality* (*Tiredness)*. All the values were taken from the sleep diary respectively the Karolinska Sleep Questionnaire. Values of sleep variables are shown in **Table 1b.** The pain group had a greater spread of values than the control group, which can reflect the greater sample size.

The difference between the mean values of *Sleep Quality (Insomnia)* in the control and pain group were statistically significant in the total dataset (p=0.012) and the data with only women (p=0.011). The difference between the mean values of *Sleep Quality (Awakening)* in

the control and pain group were statistically significant in the data with only women (p=0.034) but not in the total dataset (p=0.217). No other statistically significant differences between the groups were found among the mean sleep variables.

Table 1b. Sleep variables used in the study. The study subjects filled in a diary, from where the values were collected. Mean sleep hours during a week (Mean Sleep), sleep hours the night before the examination (Sleep before), Sleep Quality (Insomnia), Sleep Quality (Awakening) and Sleep Quality (Tiredness) according to the Karolinska Sleep Questionnaire.

		Total dataset			Only women		
		Control Group	**Pain Group**	**Total**	**Control Group**	**Pain Group**	**Total**
Mean Sleep	**Mean**	7.3	7.4	7.4	7.3	7.6	7.5
	Median	7.2	7.2	7.2	7.3	7.2	7.2
	SD	0.36	0.92	0.79	0.38	0.93	0.82
	Min, Max	6.8, 8.0	7.7, 9.2	5.7, 9.2	6.8, 8.0	5.7, 9.2	5.7, 9.2
	n	12	26	38	7	21	28
Sleep Before	**Mean**	6.7	6.4	6.5	6.3	6.5	6.4
	Median	7.0	6.5	7.0	6.8	7.0	7.0
	Standard Deviation	0.93	1.48	1.32	1.08	1.55	1.41
	Min, Max	5.0, 8.0	3.0, 8.0	3.0, 8.0	5.0, 7.50	3.0, 8.0	3.0, 8.0
	n	11	22	33	6	17	23
SQ (Insomnia)	**Mean**	4.6	3.8	4.0	4.6	3.7	3.9
	Median	4.6	4.5	4.5	4.5	4.3	4.5
	SD	0.56	1.28	1.16	0.42	1.38	1.28
	Min, Max	3.75, 5.25	1.25, 5.25	1.25, 5.25	4.00, 5.25	1.25, 5.25	1.25, 5.25
	n	12	25	37	7	20	27
SQ (Awakening)	**Mean**	4.7	4.2	4.4	4.9	4.1	4.3
	Median	5.0	4.3	4.7	5.0	4.0	4.7
	SD	1.04	1.34	1.26	0.42	1.37	1.24
	Min, Max	1.67, 5.67	1.33, 6.00	1.33, 6.0	4.33, 5.33	1.33, 6.00	1.33, 6.0
	n	12	25	37	12	25	37
SQ (Tiredness)	**Mean**	4.6	4.2	4.4	4.5	4.3	4.3
	Median	4.6	4.4	4.6	4.6	4.3	4.4
	SD	0.91	1.06	1.02	0.87	1.16	1.08
	Min, Max	3.00, 6.00	2.20, 6.00	2.20, 6.00	3.00, 5.60	2.20, 6.00	2.20, 6.00
	n	12	25	37	7	20	27

SQ =Sleep Quality. Standard Deviation =SD. Number of subjects =n.

Regression analyses were made for levels of PPT or change in PPT after physical activity, the sleep variables and site of PPT measurements. Analyses which were adjusted for cofounders had increased p-values, but parameter estimate remained essentially unchanged compared to the unadjusted analyses. This means that the adjusted values were more insecure but the result did not change due to the confounders. Results presented below are the unadjusted analyses,

since the results did not change in the adjusted models and the presented results either have a statistically significance or tendencies of significance. Results left out of presentation neither have statistically significance, nor tendencies. The sleep variables possible associations with the level of PPT before arm cycling at right trapezius, left trapezius or tibia are presented first. Secondly the sleep variables possible associations with the change in PPT after arm cycling at right trapezius, left trapezius or tibia are presented.

Pressure Pain Thresholds and Sleep Variables

Levels of PPT before a physical activity and their association with the sleep variables were tested on data from women only. Described in the table below are the mean pressure pain thresholds in kPa among women before the arm cycling at right trapezius, left trapezius and tibia. No statistically significant differences between the groups were seen at right or left trapezius, but the values differed noteworthy at tibialis anterior where the controls had a significantly higher PPT ($p<0.001$). The same pattern was found in the whole dataset (both men and women) where tibia had a statistically significant difference in the levels of PPT, but not right and left trapezius.

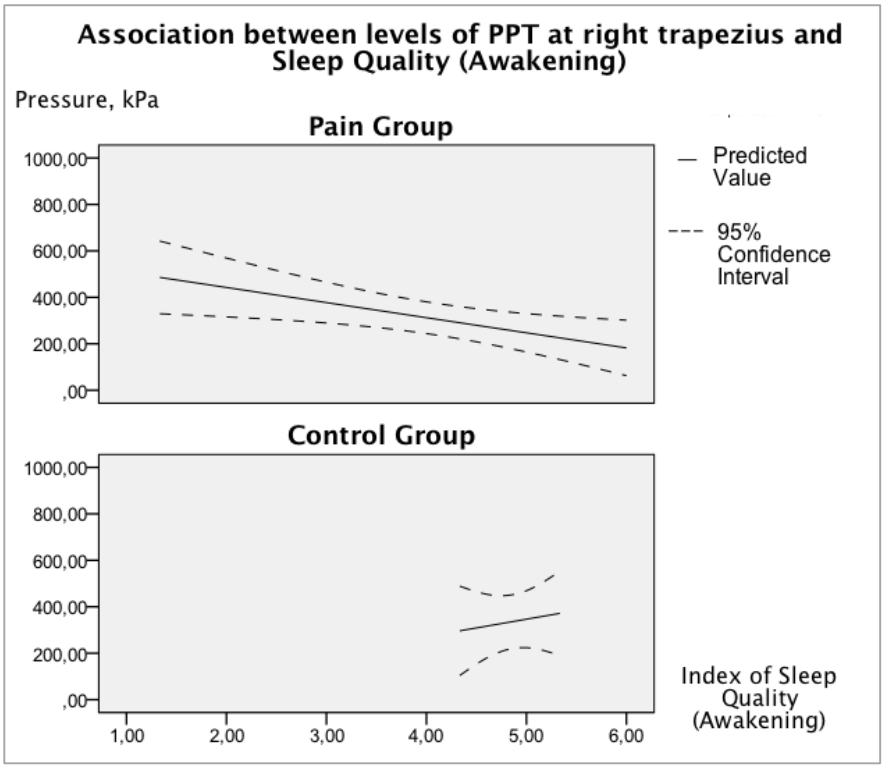
Table 2. Mean values for PPT in kPa at three sites among women; control group and pain group.

	Control group (n=7)	**Pain group (n=21)**	*p-value*
Right Trapezius	336	313	0.759
Left Trapezius	381	313	0.144
Tibialis anterior	615	384	**<0.001**

Sleep Quality (Awakening) and Pressure Pain Thresholds

There were statistically significant associations between *Sleep Quality (Awakening)* and the levels of PPT for right trapezius (**Table 3a, Graph 1**) and left trapezius (**Table 3b, Graph 2**).

At both right and left trapezius the pain group shows a pattern where better sleep quality is associated with lowered levels of PPT. For tibia only the group difference was statistically significant regarding *Sleep Quality (Awakening)* and levels of PPT **(Table 3c, Graph 3)**.

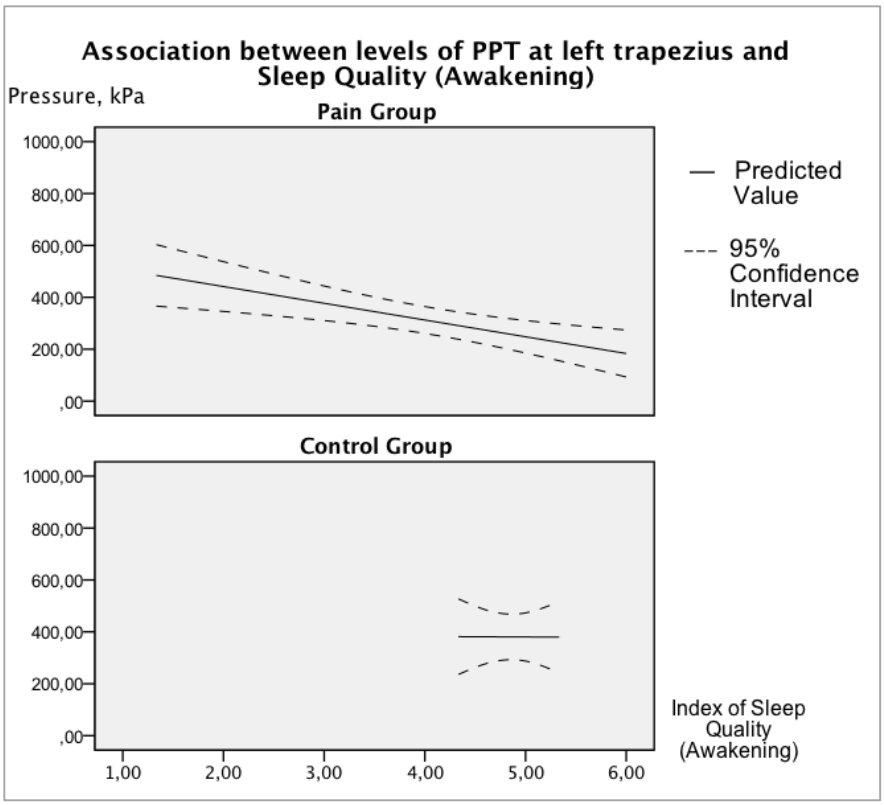


Graph 1 shows the association between the index of *Sleep Quality (Awakening)*. and level of PPT at the right trapezius. Higher *Sleep Quality (Awakening)* gives lower levels of PPT in the pain group, whereas the association seems reversed in the control group.

Table 3a Results from linear regression for pressure pain thresholds on the right trapezius, with and without interaction with *Sleep Quality (Awakening)*. Statistically significant coefficients are **bolded.**

	With Interaction			Without Interaction		
PPT Right Trapezius	Parameter estimate	Standard Error	P-value	Parameter estimate	Standard Error	P-value
Intercept	572.5	112.11	<0.001	555.6	110.26	<0.001
Control Group	-601.6	738.22	0.432	76.029	70.93	0.294
Pain Group	0[a]	.	.	0[a]	.	.
SQ (Awakening)	-65.0	26.10	**0.020**	-60.9	25.63	**0.026**
SQ (Awakening)*Group	140.2	151.99	0.366			

a. This parameter is set to zero because it is redundant.
SQ=Sleep Quality

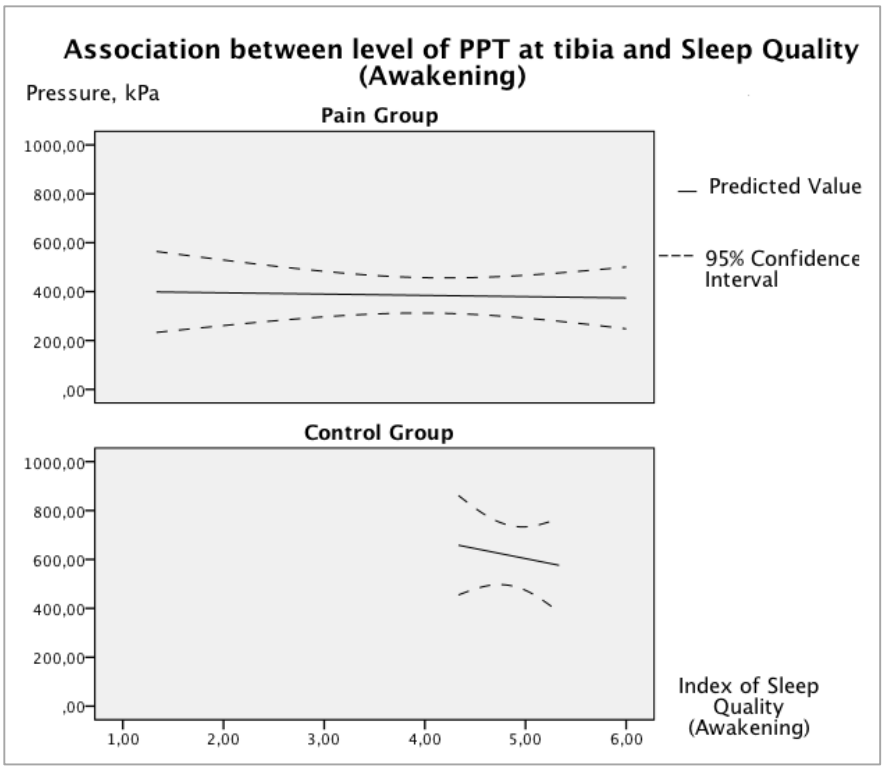


Graph 2 shows the association between the index of *Sleep Quality (Awakening)* and level of PPT at the left trapezius. Better *Sleep Quality (Awakening)* gives lower levels of PPT in the pain group, whereas in the control group the pattern is not as clear.

Table 3b. Results from linear regression for pressure pain thresholds on the left trapezius, with and without interaction with *Sleep quality (Awakening)*. Statistically significant coefficients are **bolded.**

	With Interaction			Without Interaction		
PPT Left Trapezius	Parameter estimate	Standard Error	P-value	Parameter estimate	Standard Error	P-value
Intercept	570.5	84.94	<0.001	563.0	82.56	<0.001
Control Group	-181.2	559.33	0.749	121.9	53.12	**0.031**
Pain Group	0[a]	.	.	0[a]	.	.
SQ (Awakening)	-64.5	19.78	**0.003**	-62.7	19.19	**0.003**
SQ (Awakening)*Group	62.7	115.16	0.591			

a. This parameter is set to zero because it is redundant.
SQ=Sleep quality



Graph 3. Association between levels of PPT at tibia and *Sleep Quality (Awakening)*. There is a statistical significance between the two groups.

Table 3c. Results from linear regression for pressure pain thresholds on tibia, with and without interaction with *Sleep Quality (Awakening)*. Statistically significant coefficient is **bolded.**

	With Interaction			Without Interaction		
PPT Tibia	Parameter estimate	Standard Error	P-value	Parameter estimate	Standard Error	P-value
Intercept	405.5	118.67	0.002	414.8	115.18	0.001
Control Group	608.0	781.46	0.445	236.9	74.10	**0.004**
Pain Group	0[a]	.	.	0[a]	.	.
SQ (Awakening)	-5.2	27.63	0.851	-7.5	26.78	0.781
SQ (Awakening)*Group	-76.8	160.90	0.638			

a. This parameter is set to zero because it is redundant.
SQ=Sleep quality

Sleep Quality (Insomnia) and Pressure Pain Thresholds

The association between PPT at left trapezius and *Sleep Quality (Insomnia)* had a tendency of difference between the control and pain group (**Table 4a**), whereas the association between the groups was statistically significant at tibia (**Table 4b**).

Table 4a. Results from linear regression for pressure pain thresholds on the left trapezius, with and without interaction with *Sleep Quality* (*Insomnia)*.

	With Interaction			Without Interaction		
PPT Left Trapezius	Parameter estimate	Standard Error	P-value	Parameter estimate	Standard Error	P-value
Intercept	375.6	90.45	<0.001	369.1	87.77	<0.001
Control Group	-187.5	623.13	0.766	89.7	64.29	0.176
Pain Group	0[a]	.	.	0[a]	.	.
SQ (Insomnia)	-18.8	23.24	0.428	-17.0	22.51	0.458
SQ (Insomnia)*Group	60.5	135.34	0.659			

a. This parameter is set to zero because it is redundant.
SQ=Sleep quality

Table 4b. Results from linear regression for pressure pain thresholds on tibia, with and without interaction with *Sleep Quality* (*Insomnia)*. Statistically significant coefficient is **bolded.**

	With Interaction			Without Interaction		
PPT Tibia	Parameter estimate	Standard Error	P-value	Parameter estimate	Standard Error	P-value
Intercept	363.3	106.69	0.002	367.3	103.20	0.002
Control Group	397.9	734.95	0.593	226.6	75.59	**0.006**
Pain Group	0[a]	.	.	0[a]	.	.
SQ (Insomnia)	5.7	27.42	0.837	4.6	26.47	0.864
SQ (Insomnia)*Group	-37.4	159.62	0.817			

a. This parameter is set to zero because it is redundant.
SQ=Sleep quality

Sleep Quality (Tiredness) and Pressure Pain Thresholds

The association between PPT at left trapezius and *Sleep Quality (Tiredness)* had a tendency of difference between the control and pain group (**Table 5a**), whereas the association between the groups was statistically significant at tibia (**Table 5b**).

Table 5a. Results from linear regression for pressure pain thresholds on left trapezius, with and without interaction with *Sleep Quality (Tiredness)*.

	With Interaction			Without Interaction		
PPT Left Trapezius	Parameter estimate	Standard Error	P-value	Parameter estimate	Standard Error	P-value
Intercept	412.1	120.72	0.002	421.3	109.68	0.001
Control Group	142.7	319.39	0.659	79.0	60.06	0.201
Pain Group	0[a]	.	.	0[a]	.	.
SQ (Tiredness)	-24.7	27.45	0.377	-26.9	24.79	0.289
SQ (Tiredness)*Group	-14.4	70.82	0.841			

a. This parameter is set to zero because it is redundant.
SQ=Sleep Quality

Table 5b. Results from linear regression for pressure pain thresholds on tibia, with and without interaction with *Sleep Quality (Tiredness)*. Statistically significant coefficient is **bolded.**

	With Interaction			Without Interaction		
PPT Tibia	Parameter estimate	Standard Error	P-value	Parameter estimate	Standard Error	P-value
Intercept	169.2	134.53	0.221	236.9	126.82	0.074
Control Group	693.6	355.91	0.064	223.9	69.44	**0.004**
Pain Group	0[a]	.	.	0[a]	.	.
SQ (Tiredness)	50.6	30.59	0.112	34.6	28.67	0.239
SQ (Tiredness)*Group	-106.1	78.92	0.192			

a. This parameter is set to zero because it is redundant.
SQ=Sleep Quality

Mean Sleep and Pressure Pain Thresholds

A statistically significant association was found between the control and pain group regarding levels of PPT at tibia and *Mean Sleep* (**Table 6**). However, no statistically significant association was found between *Mean Sleep* and PPT at tibia.

Table 6. Results from linear regression for pressure pain thresholds on tibia, with and without interaction with *Mean sleep*. Statistically significant coefficient is **bolded.**

	With Interaction			Without Interaction		
PPT Tibia	Parameter estimate	Standard Error	P-value	Parameter estimate	Standard Error	P-value
Intercept	340.3	303.79	0.274	311.9	291.57	0.295
Control Group	-347.8	1343.87	0.798	233.5	71.84	**0.003**
Pain Group	0[a]	.	.	0[a]	.	.
Mean Sleep	5.8	39.91	0.886	9.6	38.29	0.805
Mean Sleep*Group	79.5	183.52	0.669			

a. This parameter is set to zero because it is redundant.

Sleep Before and Pressure Pain Thresholds

A statistically significant association was found between the control and pain group regarding levels of PPT at tibia and *Sleep Before* (**Table 7**). However, no statistically significant association was found between *Sleep Before* and PPT at tibia.

Table 7. Results from linear regression for pressure pain thresholds on tibia, with and without interaction with *Sleep before*. Statistically significant coefficient is **bolded.**

PPT Tibia	With Interaction			Without Interaction		
	Parameter estimate	Standard Error	P-value	Parameter estimate	Standard Error	P-value
Intercept	507.2	184.01	0.013	483.7	167.34	0.009
Control Group	33.1	482.39	0.946	199.9	78.57	**0.020**
Pain Group	0[a]	.	.	0[a]	.	.
Sleep Before	-18.0	28.10	0.529	-14.4	25.45	0.579
Sleep Before*Group	26.3	75.03	0.730			

a. This parameter is set to zero because it is redundant.

Changes in PPT after a physical activity

Presented below are the changes in PPT after a physical activity (arm cycling). Values are taken from the total dataset, both women and men.

Mean Sleep and Change in PPT

The association between change in PPT after a physical activity at right trapezius and *Mean Sleep* had a tendency of difference between the control and pain group. (**Table 8**)

Table 8. The differences between the first measurement and the measurement after a physical activity on right trapezius adjusted to *Mean sleep*.

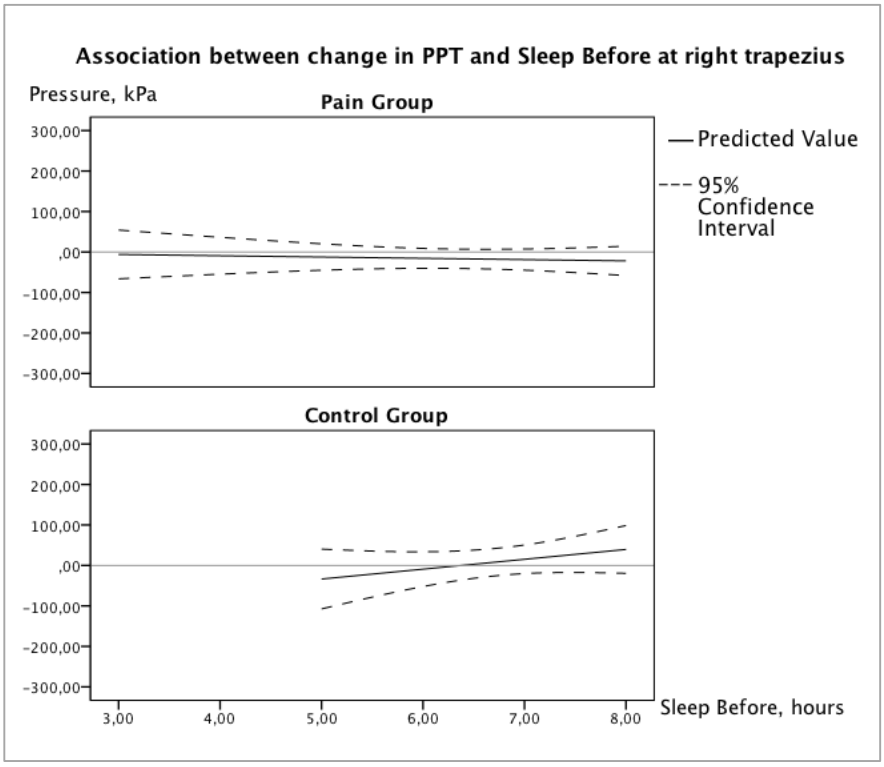
Diff Right Trapezius	With Interaction			Without Interaction		
	Parameter estimate	Standard Error	P-value	Parameter estimate	Standard Error	P-value
Intercept	-21.4	108.97	0.846	-48.4	105.43	0.649
Control Group	-367.8	420.66	0.388	46.4	23.48	0.056
Pain Group	0[a]	.	.	0[a]	.	.
Mean Sleep	0.6	14.54	0.968	4.2	14.06	0.766
Mean Sleep*Group	56.6	57.39	0.331			

a. This parameter is set to zero because it is redundant.

Sleep Before and Change in PPT

No clear statistically significance was found between *Sleep Before* and the change in PPT, but tendencies could be seen at right trapezius with interaction (**Table 9a, Graph 4**), left trapezius (**Table 9b, Graph 5**) and tibia (**Table 9c, Graph 6**). These tendencies show that

more hours slept the day before the examination predict an increase in PPT at trapezius muscles after physical exercise among controls, but not among pain subjects and an increase in levels of PPT after a physical activity among both pain and control group at tibialis anterior without any difference between groups.

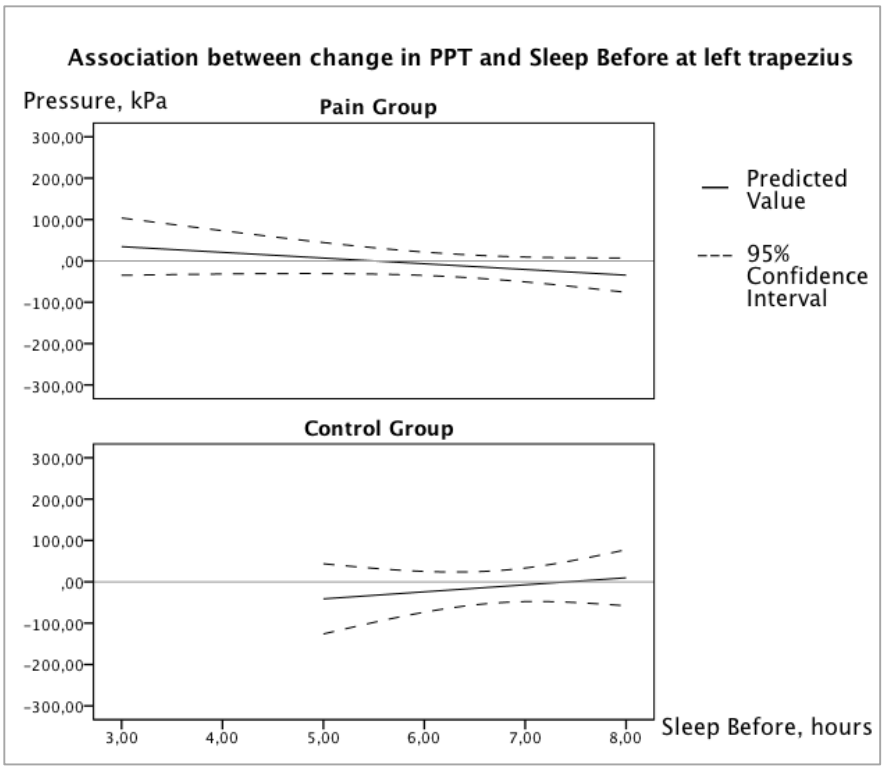


Graph 4 shows the association between *Sleep Before* and the change in PPT at the right trapezius.

Table 9a. The differences between the first measurement and the measurement after a physical activity on right trapezius adjusted to *Sleep before*.

	With Interaction			Without Interaction		
Diff Right Trapezius	Parameter estimate	Standard Error	P-value	Parameter estimate	Standard Error	P-value
Intercept	3.5	54.83	0.950	-24.3	51.11	0.639
Control Group	-158.8	142.53	0.274	24.8	21.54	0.259
Pain Group	0[a]	.	.	0[a]	.	.
Sleep Before	-3.2	8.42	0.708	1.2	7.81	0.881
Sleep Before*Group	27.5	21.14	0.203			

a. This parameter is set to zero because it is redundant.

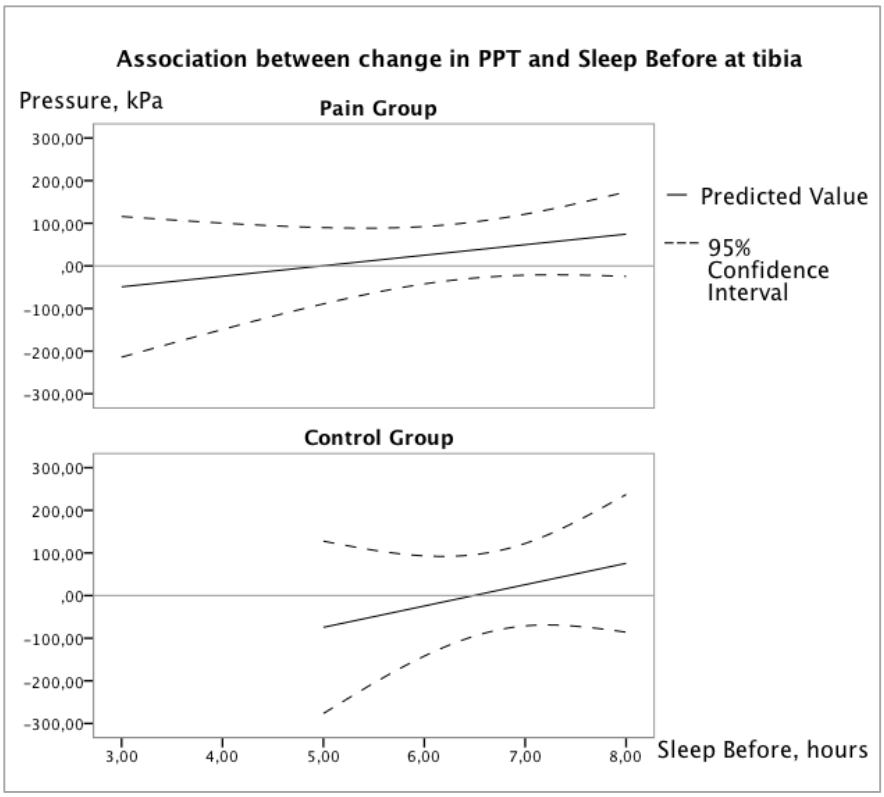


Graph 5 shows the association between *Sleep Before* and the change in PPT at the left trapezius.

Table 9b. The differences between the first measurement and the measurement after a physical activity on left trapezius adjusted to *Sleep before*.

	With Interaction			Without Interaction		
Diff Left Trapezius	Parameter estimate	Standard Error	P-value	Parameter estimate	Standard Error	P-value
Intercept	75.8	63.02	0.239	44.8	58.66	0.451
Control Group	-202.0	163.83	0.227	3.3	24.72	0.895
Pain Group	0[a]	.	.	0[a]	.	.
Sleep Before	-13.8	9.67	0.164	-8.9	8.96	0.328
Sleep Before*Group	30.8	24.30	0.215			

a. This parameter is set to zero because it is redundant.



Graph 6 shows the association between *Sleep Before* and the change in PPT at tibia.

Table 9c. The differences between the first measurement and the measurement after a physical activity on tibia adjusted to *Sleep before*.

	With Interaction			Without Interaction		
Diff Tibia	Parameter estimate	Standard Error	P-value	Parameter estimate	Standard Error	P-value
Intercept	-123.3	150.16	0.418	-148.8	136.50	0.284
Control Group	-201.4	390.35	0.610	-32.5	57.53	0.576
Pain Group	0[a]	.	.	0[a]	.	.
Sleep Before	24.7	23.05	0.292	28.7	20.84	0.178
Sleep Before*Group	25.3	57.89	0.665			

a. This parameter is set to zero because it is redundant.

Sleep Quality (Insomnia) and Change in PPT

The association between change in PPT after a physical activity at right trapezius and *Sleep Quality (Insomnia)* had a tendency of difference between the control and pain group without interaction. (**Table 10**)

Table 10. The differences between the first measurement and the measurement after a physical activity on right trapezius adjusted to *Sleep Quality (Insomnia)*.

	With Interaction			Without Interaction		
Diff Right Trapezius	Parameter estimate	Standard Error	P-value	Parameter estimate	Standard Error	P-value
Intercept	12.9	43.40	0.768	5.5	41.44	0.894
Control Group	-59.7	176.18	0.737	51.0	25.22	0.051
Pain Group	0[a]	.	.	0[a]	.	.
SQ(insomnia)	-8.0	10.90	0.469	-6.0	10.36	0.565
SQ(insomnia)*Group	24.5	38.58	0.530			

a. This parameter is set to zero because it is redundant.
SQ=Sleep quality

Sleep Quality (Awakening) and Change in PPT

The association between change in PPT after a physical activity at right trapezius and *Sleep Quality (Awakening)* had a tendency of difference between the control and pain group without interaction. (**Table 11**)

Table 11. The differences between the first measurement and the measurement after a physical activity on right trapezius adjusted to *Sleep Quality (Awakening)*.

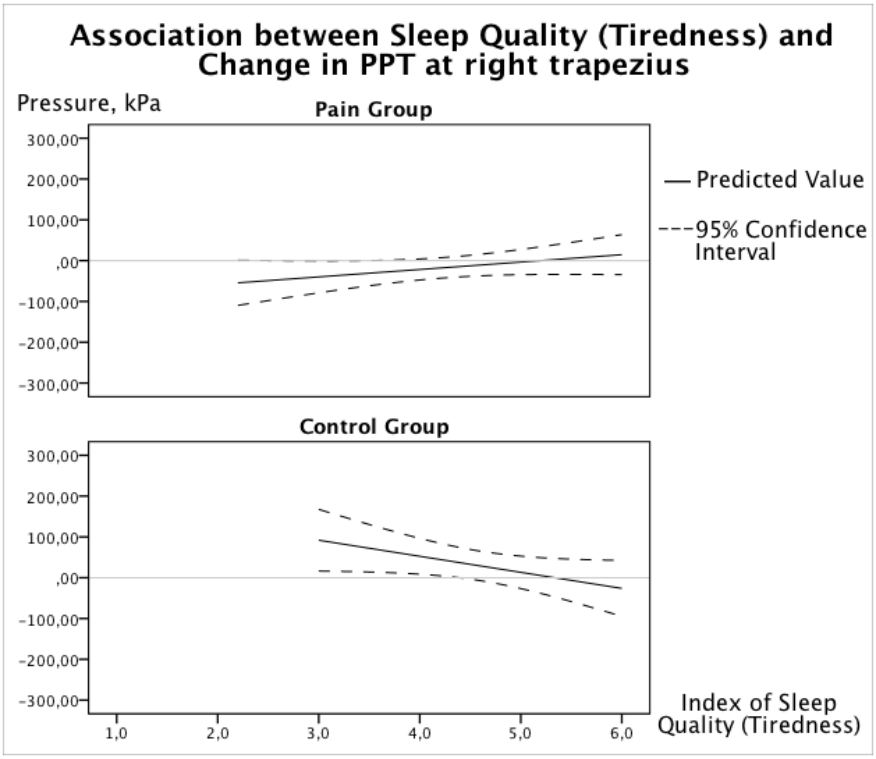
	With Interaction			Without Interaction		
Diff Right Trapezius	Parameter estimate	Standard Error	P-value	Parameter estimate	Standard Error	P-value
Intercept	-140.2	45.64	0.385	-20.1	40.87	0.627
Control Group	147.3	105.29	0.171	45.8	24.38	0.069
Pain Group	0[a]	.	.	0[a]	.	.
SQ(awakening)	5.5	10.40	0.602	0.7	9.21	0.942
SQ(awakening)*Group	-22.1	22.34	0.329			

a. This parameter is set to zero because it is redundant.

Sleep Quality (Tiredness) and Change in PPT

The association was statistically significant between the change in PPT after a physical activity at right trapezius and *Sleep Quality (Tiredness),* moreover a statistically significant difference between the control and pain group was seen. (**Table 12, Graph 7**) Among the controls a higher index of *Sleep Quality (Tiredness)* predicted a decrease in PPT after a physical activity and a lower index led to an increase in PPT after physical activity. A sleep quality index below 5 among the pain group gives negative values in the change of PPT,

which means a decrease in PPT after a physical activity compared with baseline if the test person in the pain group had low sleep quality. A higher index of *Sleep Quality (Tiredness)* in the pain group at the right trapezius lead to an increase of the PPT level compared to baseline.



Graph 7 shows the association between *Sleep Quality (Tiredness)* and change in PPT at right trapezius.

Table 12. The differences between the first measurement and the measurement after a physical activity on right trapezius adjusted to *Sleep Quality (Tiredness)*. Statistically significant coefficients are **bolded.**

	With Interaction			Without Interaction		
Diff Right Trapezius	Parameter estimate	Standard Error	P-value	Parameter estimate	Standard Error	P-value
Intercept	-94.4	53.73	0.088	-32.8	49.93	0.516
Control Group	304.3	112.72	**0.011**	44.9	24.22	0.073
Pain Group	0[a]	.	.	0[a]	.	.
SQ (Tiredness)	18.2	12.29	0.149	3.7	11.31	0.748
SQ (Tiredness)*Group	-57.5	24.47	**0.025**			

a. This parameter is set to zero because it is redundant.
SQ= Sleep Quality

Discussion

Sleep Quality (Awakening) had significant associations with levels of PPT at both right and left trapezius ($p<0.05$), with lower sleep quality associated with higher PPT in the pain group. The opposite pattern was found among the controls, where lower *Sleep Quality (Awakening)* was associated with lower PPT. The controls association pattern was more expected since previous studies have shown associations between lower sleep quality and lower pain thresholds.(33, 34, 52, 53) The unexpected result in the pain group where high *Sleep Quality (Awakening)* led to a low PPT and low *Sleep Quality (Awakening)* led to high PPT could be due to numerous reasons, among them temporal summation. Temporal summation occurs when action potentials in the presynaptic neuron arrive to the postsynaptic neuron at such a high frequency that the potentials summate each other to a higher potential. Temporal summation of pain responses has been shown to be reduced in insomnia subjects when compared to a control group.(54) Suggestively pain-inhibitory circuits in persons with low sleep quality or insomnia are fully active in an attempt to control subclinical pain. When the pain-inhibitory circuits are challenged and a painful stimulus would cause a summation of action potentials in a healthy individual, this inhibitory system cannot further increase its activity because it is already working at its maximum. This could partly explain the result in our study where low sleep quality was associated with higher PPT.

The two lowest values of PPT in the association with *Sleep Quality (Awakening)* in the pain group came from two older women (>60 years old) with a high amount of high intensity exercising and high values of *Sleep Quality (Awakening)*. Since exercise can promote higher sleep quality(55, 56), a hypothesis is that these women had high sleep quality because of their physical activity, but lower levels of PPT due to their age, sex or high pain sensitivity.(47, 57, 58) Patients with high pain sensitivity has been shown to have a more pronounced temporal summation than patients with low pain sensitivity, furthermore the temporal summation in the

high sensitivity group is further facilitated after aerobic exercise, which could suggest a change in the balance between excitatory and inhibitory descending control.(58) In comparison with their younger counterparts, older people will rate their sleep quality progressively better at any given level of objectively measured sleep efficiency.(59)

Change in PPT after physical activity was associated with *Sleep Quality* (*Tiredness)* and there was a statistically significant difference between the pain group and the control group at the right trapezius. Among the controls a higher index of *Sleep Quality (Tiredness)* predicted a decrease in PPT after a physical activity and a lower index led to an increase in PPT after physical activity. The result was somewhat surprising, especially since the pain group did not show the same association pattern as the control group. Previous studies have shown a connection between fibromyalgia and decrease in pain thresholds after exercise, probably due to central sensitization(60), but in our study the healthy controls and not the pain group showed this type of pattern. We can only speculate about the reasons of this result. The level of PPT did not differ in a statistically significant way at trapezius between the pain group and the control group, which could mean that specifically these controls had lower values of PPT at trapezius than the expected from healthy controls, since healthy controls more commonly have higher pressure pain thresholds than people with pain(61).

Controls with the lowest values of *Sleep Quality (Tiredness)* were young (<25 years) and exercised at minimum twice a week. Studies on general population has shown that the risk of excessive daytime sleepiness increase with time spent on a computer and lower leisure-time physical activity and time spent watching television or reading appeared protective against sleepiness.(62, 63) Furthermore younger age and depressive symptoms have been shown to predict daytime sleepiness.(64) Theoretically our young controls with low *Sleep Quality (Tiredness)* could spend a greater amount of their daytime in front of a computer screen and read less books than the other study persons, which would lead to the low indices of *Sleep*

Quality (Tiredness). The association between lower *Sleep Quality (Tiredness)* and higher PPT after physical activity can hypothetically be explained by the young age among the controls with lower *Sleep Quality (Tiredness)* since they reasonably the have higher pressure pain thresholds due to their young age, health and physical activity.

The tendency of association between *Sleep Before* and change in PPT among controls is comparable to the pattern seen in the literature where sleep restriction leads to a decrease of PPT in a healthy study population. (65-67)

Statistically significant associations were not found in other variables than the variables presented above, which could at least partly be due to low power with this small sample size.

Studies have shown that sleep problems are more common among persons with pain (9, 26, 27) and our study showed a statistically significant difference between the pain and the control group (among both men and women) in the mean value of *Sleep Quality (Insomnia),* where insomnia was more common in the pain group. However, the absence of more differences in sleep variables between the two groups could be due to a small sample size and thereby low power.

Methodological considerations

The PPT measurements were made only by two trained examiners and all the measurements at a test person were made by the same examiner. The continuality in the measurements is considered as a strength since experienced and trained examiners that perform all the measurements at the same test person repeatedly is suggested to increase the reliability of the measurements(68, 69). In our study test persons were not forced to reduce sleep time, which makes our study more clinically applicable since the test persons slept in their habitual way. The majority of studies that have investigated the connection between sleep and pain have been disrupting sleep by using total sleep deprivation(32, 70, 71), sleep restriction(65-67, 72),

selective sleep deprivation(32, 53), or a combination of these protocols.(32, 37, 53) In our study, we wanted to investigate if there is a similar connection between sleep loss and pain, but without actively disrupting the subjects sleep. We have adjusted for clinically relevant confounders: sex, age, BMI, depression, anxiety.

A weakness with our study is that it has a small sample size, which thereby leads to low power. The small sample size led to a smaller variance among the control group than the pain group. Due to the small sample size the p-values increased in the adjusted analyses, which made the results in less reliable, but parameter estimates were essentially the same in the adjusted analyses as in the unadjusted analyses.

Since the controls mainly were recruited from official message boards there is a possible risk of bias where people with a special interest in sleep disorders and pain are more likely to apply as controls. The interest could possibly come from previous experience in their lives of sleep disorders or tenderness in the trapezius, which thereby could mean that the controls trapezius are not totally unaffected, which could explain the unexpected result where higher *Sleep Quality (Tiredness)* was associated with lower PPT after physical activity among controls in the right trapezius.

There are different ways to report sleep, either subjectively with for example a self-reported diary or questionnaire, or objectively using polysomnography. In our study we used a self-reported diary and questionnaire, which both are subjective ways to measure sleep disturbance. The use of diaries or questionnaires in studies means that the person can have as normal sleep habits as possible. The negative effect is that the measurement is subjective, not as reliable as an objective measurement. By using polysomnography, we can measure the sleep as objectively as possible. A problem is that the measurements must be done in a sleep laboratory, quite different from how the person normally sleeps. Objective measurement of

sleep through polysomnography however shows limitations in predicting subjectively sleep quality, but the sleep efficacy and continuity have the most consistent association with subjectively reported sleep quality.(59, 73)

Conclusion

Higher *Sleep Quality (Awakening)* predicted for lower levels of PPT in the pain group, there was a difference between the groups with a reversed pattern among the controls. Low *Sleep Quality (Tiredness)* among controls predicted for an increase in PPT after a physical activity and this pattern was not seen in the pain group. No clear causal factors behind the unexpected associations can be seen in the data, but confounders or a small sample size and thereby low power can contribute to the associations. Larger studies are recommended to follow up this study with adjustments for relevant confounders.

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Populärvetenskaplig sammanfattning på svenska

Sömnstörningars roll hos en grupp med kronisk smärta jämfört med en kontrollgrupp, med hänsyn till responsen av trycksmärttrösklar före och efter fysisk aktivitet

Kronisk eller långvarig smärta, det vill säga smärta som varat mer än tre månader, är ett mycket vanligt problem i befolkningen. Var femte person (20%) lider av långvarig smärta. Även sömnproblem är vanligt förekommande och två av tre personer med långvarig smärta har någon typ av sömnstörning. Både sömnstörningar och långvarig smärta påverkar livskvaliteten negativt. Därför ville vi titta på sambandet mellan kronisk smärta i nacke och skuldror och sömn, samt se om fysisk aktivitet kunde påverka smärttrösklar. För att undersöka detta samband samt eventuell ändring av smärttrösklar tittade vi på två grupper, där en grupp bestod av personer med långvarig smärta i nacke och skuldror och den andra gruppen bestod av friska kontrollpersoner utan smärta. Testpersonerna fick fylla i en sömndagbok med information om hur många timmar de sovit i snitt under en vecka, hur många timmar de sovit dagen innan experimentet samt värdering av deras egen sömnkvalitet med avseende på sömnsvårigheter (insomni), problem med uppvaknande (att ha svårigheter att vakna, inte känna sig utvilad vid uppvaknande, samt känna sig utmattad vid uppvaknande) och problem med trötthet under vaken tid. Smärttrösklar mättes med tryck på sju mätpunkter.

Vår studie visade något oväntat att hos personer med långvarig smärta finns det ett samband mellan höga smärttrösklar på skuldrorna och sömnstörningar som innebär problem med uppvaknande, vilket skulle kunna bero på en annorlunda smärtreaktion hos de som haft smärta under en lång tid. Hos friska kontrollpersoner utan långvarig smärta gav sämre sömnkvalitet lägre smärttrösklar, vilket var ett förväntat resultat som setts i tidigare studier. Vår studie visade också att smärttrösklarna sänktes efter fysisk aktivitet hos kontrollgruppen som hade problem med dagtrötthet, men det kunde inte ses i smärtgruppen. Anledningen till

att kontrollgruppen reagerar på ett sätt, som vanligen personer med långvarig smärta gör, går bara att spekulera kring. Eftersom vår studie var liten finns det en risk att det föreligger samband som missas eller bildas trots att sambanden egentligen inte föreligger på grund av att för få försökspersoner deltog. Vår rekommendation är därför att göra fler, större studier där man tittar på samband mellan kronisk smärta, sömn och fysisk aktivitet.

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Appendices

Karolinska Sleep Questionnaire 1

Karolinska Sömnformulär

Namn/bet:.....

Har du haft känning av följande besvär de senaste tre månaderna?

	Aldrig	**Sällan** *Någon, några ggr/år*	**Ibland** *Flera ggr/mån*	**Ofta** *1-2 ggr /vecka*	**För det mesta** *3-4 ggr /vecka*	**Alltid** *5 ggr eller mer /vecka*
a) Svårigheter att somna	☐	☐	☐	☐	☐	☐
b) Svårigheter att vakna	☐	☐	☐	☐	☐	☐
c) Upprepade uppvaknanden med svårigheter att somna om	☐	☐	☐	☐	☐	☐
d) Kraftiga egna snarkningar	☐	☐	☐	☐	☐	☐
e) Kippar efter andan, "frustar" under sömnen	☐	☐	☐	☐	☐	☐
f) Andningsuppehåll under sömnen	☐	☐	☐	☐	☐	☐
g) Mardrömmar	☐	☐	☐	☐	☐	☐
h) Ej utsövd vid uppvaknandet	☐	☐	☐	☐	☐	☐
i) För tidigt uppvaknande	☐	☐	☐	☐	☐	☐
j) Störd/orolig sömn	☐	☐	☐	☐	☐	☐
k) Ofrivilliga ryckningar i benen som stör sömnen	☐	☐	☐	☐	☐	☐
l) För lite sömn (minst två timmar för lite per huvudsömn)	☐	☐	☐	☐	☐	☐
m) Känsla av att vara utmattad vid uppvaknandet	☐	☐	☐	☐	☐	☐
n) Sömnig under arbete	☐	☐	☐	☐	☐	☐
o) Sömnig under fritid	☐	☐	☐	☐	☐	☐
p) Ofrivilliga sömnperioder (tillnickning) under arbetet	☐	☐	☐	☐	☐	☐
q) Ofrivilliga sömnperioder (tillnickning) under fritid	☐	☐	☐	☐	☐	☐
r) Behov av att kämpa mot sömnen för att hålla sig vaken	☐	☐	☐	☐	☐	☐

Vilken tid går Du normalt till sängs (släcker lampan)?

Under arbetsveckan: kl._____

Under ledighet: kl._____

Vilken tid stiger Du normalt upp?

Under arbetsveckan:kl._____

Under ledighet:kl._____

Hur lång tid ligger Du vaken innan Du somnar

Under arbetsveckan:_____min

Instruktioner för användande av Karolinska Sleep Questionaire

När vi analyserar frågorna så brukar vi ge ”aldrig” värdet 6, ”sällan” värdet 5, ”ibland” värdet 4 och så vidare. Med andra ord är höga värden bra.

Frågorna a-r kan slås samman för att bilda fyra olika index:

- Sömnkvalitetsindex (insomniindex): a, c, i och j
- Uppvaknandebesvärsindex: b, h och m
- Snarkbesvärsindex: d, e och f
- Sömnighets/trötthetsindex: n, o, p, q och r

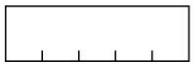
Sömnkvalitetsindex mäter om man lider av insomni. Regelbundna uppvaknandebesvär är relativt vanliga hos unga och korrelerar ofta med långvarig stress och utmattningstillstånd (men också med depression). Man kan dock ha uppvaknandebesvär i andra sammanhang t ex om man har tidigt morgonarbete och måste stiga upp tidigt. Regelbundna snarkbesvär uppträder oftast hos medelålders och äldre män – och korrelerar med övervikt och andra tecken på osund livsstil. Sömnighetsindex mäter förekomsten av trötthet och ger en uppfattning om sömnstörningen är förenad med allvarlig trötthet. Det är i allmänhet ett illavarslande tecken om ihållande trötthet förekommer. Övriga frågor är också intressanta men kan inte slås samman till ett index. T ex kan ofta förekommande mardrömmar vara en indikation på posttraumatisk stress.

Värden som är 3 eller lägre indikerar för det mesta att det föreligger besvär som är värda att utreda. Om man istället vill använda kliniska kriterier t ex på insomni eller kronisk snarkning ska patienten ha angivit en 1 eller 2 på minst en av frågorna i indexen samt dessutom ha angivit en 1 eller 2 på minst en av frågorna i sömnighetsindex. Dessutom ska man ha markerat svarsalternativ ”ganska dåligt” eller ”mycket dåligt” för frågan ”Hur tycker du att du sover på det hela taget?”. Om man vill kan man också ta hänsyn till hur mycket man sover (att regelbundet sova bara 5 timmar eller mindre kan vara ett tecken på insomni), när man stiger upp (tidigt uppstigande kan vara ett tecken på insomni) samt om det tar lång tid att somna (>30 minuter är ett tecken på insomni).

Frågorna om tupplur, sömnbehov samt om man är morgon/kvällsmänniska är inte så viktiga för den kliniska bedömningen men kan vara värdefull ur ett behandlingsperspektiv (t ex kan en extrem kvällsmänniska drabbas av insomni om man har tidig start på arbetsdagen). Även onödigt långa tupplurar på dagtid kan vara en orsak till insomnandebesvär.

Hospital Anxiety and Depression Scale (HADS)

Detta formulär innehåller frågor om hur du har känt dig under den senaste veckan.
Besvara frågorna genom att markera det svarsalternativ du tycker stämmer bäst.
Obs fyll i hela cirkeln, så här ○ ⇒●.
Om du är osäker, markera det alternativ som känns riktigast.



1. Jag känner mig spänd eller "uppskruvad"

- ○ För det mesta
- ○ Ofta
- ○ Då och då
- ○ Inte alls

2. Jag uppskattar samma saker som förut

- ○ Precis lika mycket
- ○ Inte lika mycket
- ○ Bara lite
- ○ Knappast alls

3. Jag får en slags känsla av rädsla som om någonting förfärligt håller på att hända

- ○ Alldeles bestämt och rätt illa
- ○ Ja, men inte så illa
- ○ Lite, men det oroar mig inte
- ○ Inte alls

4. Jag kan skratta och se saker från den humoristiska sidan

- ○ Lika mycket som jag alltid kunnat
- ○ Inte riktigt lika mycket nu
- ○ Absolut inte så mycket nu
- ○ Inte alls

5. Oroande tankar kommer för mig

- ○ Mycket ofta
- ○ Ofta
- ○ Då och då men inte så ofta
- ○ Bara någon enstaka gång

6. Jag känner mig glad

- ○ Inte alls
- ○ Inte ofta
- ○ Ibland
- ○ För det mesta

7. Jag kan sitta i lugn och ro och känna mig avspänd

- ○ Absolut
- ○ Oftast
- ○ Inte ofta
- ○ Inte alls

8. Jag känner mig som om jag gick på "lågt varv"

- ○ Nästan jämt
- ○ Mycket ofta
- ○ Ibland
- ○ Inte alls

9. Jag får en slags känsla av rädsla som om jag hade "fjärilar i magen"

- ○ Inte alls
- ○ Någon gång
- ○ Rätt ofta
- ○ Mycket ofta

10. Jag har tappat intresset för mitt utseende

- ○ Absolut
- ○ Jag bryr mig inte så mycket om det som jag borde
- ○ Jag kanske inte bryr mig om det riktigt så mycket
- ○ Jag bryr mig precis lika mycket om det som förut

11. Jag känner mig rastlös som om jag måste vara på språng

- ○ Verkligen mycket
- ○ En hel del
- ○ Inte så mycket
- ○ Inte alls

12. Jag ser fram emot saker och ting med glädje

- ○ Lika mycket som förut
- ○ Något mindre än jag brukade
- ○ Klart mindre än jag brukade
- ○ Nästan inte alls

13. Jag får plötsliga panikkänslor

- ○ Verkligen ofta
- ○ Rätt ofta
- ○ Inte så ofta
- ○ Inte alls

14. Jag kan njuta av en bra bok, ett bra radio eller TV-program

- ○ Ofta
- ○ Ibland
- ○ Inte så ofta
- ○ Mycket sällan

Adjusted regression analyses p values

P-values confounders level of PPT

		Right Trapezius	Left Trapezius	Tibia
Age	*Mean Sleep*	**0.039**	0.067	0.237
	Sleep Before	0.068	0.089	0.757
	SQ (Insomnia)	**0.024**	**0.032**	0.452
	SQ (Awakening)	0.141	0.311	0.320
	SQ (Tiredness)	**0.041**	**0.045**	0.865
BMI	*Mean Sleep*	0.221	0.566	0.057
	Sleep Before	0.250	0.570	0.081
	SQ (Insomnia)	0.140	0.368	0.081
	SQ (Awakening)	0.243	0.781	0.087
	SQ (Tiredness)	0.198	0.486	**0.021**
Depression	*Mean Sleep*	0.449	0.881	0.543
	Sleep Before	0.483	0.956	0.789
	SQ (Insomnia)	0.442	0.933	0.550
	SQ (Awakening)	0.221	0.321	0.262
	SQ (Tiredness)	0.268	0.613	0.726
Anxiety	*Mean Sleep*	0.197	0.425	0.850
	Sleep Before	0.076	0.102	0.346
	SQ (Insomnia)	0.287	0.498	0.901
	SQ (Awakening)	0.386	0.970	0.909
	SQ (Tiredness)	0.309	0.731	0.534

Change in PPT P-values

		Right Trapezius	Left Trapezius	Tibia
Sex	*Mean Sleep*	0.587	0.177	0.705
	Sleep Before	0.693	0.149	0.460
	SQ (Insomnia)	0.707	0.271	0.903
	SQ (Awakening)	0.498	0.188	0.856
	SQ (Tiredness)	0.762	0.224	0.776
Age	*Mean Sleep*	0.064	0.120	0.661
	Sleep Before	0.428	0.102	0.435
	SQ (Insomnia)	0.210	**0.044**	0.693
	SQ (Awakening)	0.159	0.084	0.915
	SQ (Tiredness)	0.185	0.122	0.778
BMI	*Mean Sleep*	0.649	0.091	0.249
	Sleep Before	0.515	0.270	0.303
	SQ (Insomnia)	0.781	0.322	0.117
	SQ (Awakening)	0.816	0.195	0.142
	SQ (Tiredness)	0.836	0.184	0.133
Depression	*Mean Sleep*	0.597	0.562	0.313
	Sleep Before	0.664	0.977	0.246
	SQ (Insomnia)	0.543	0.785	0.262
	SQ (Awakening)	0.634	0.488	0.412
	SQ (Tiredness)	0.562	0.335	0.344
Anxiety	*Mean Sleep*	0.312	0.589	0.980
	Sleep Before	0.192	0.576	0.830
	SQ (Insomnia)	0.238	0.987	0.850
	SQ (Awakening)	0.276	0.552	0.808
	SQ (Tiredness)	0.245	0.345	0.841

Table Left trapezius change in PPT Sleep Quality (Tiredness)

	With Interaction			Without Interaction		
Diff Left Trapezius SQ (Tiredness)	Parameter estimate	Standard Error	P-value	Parameter estimate	Standard Error	P-value
Intercept	-53.597	56.054	0.346	-47.325	48.251	0.334
Control Group	26.041	117.586	0.826	-0.384	23.405	0.987
Pain Group	0[a]	.	.	0[a]	.	.
SQ (Tiredness)	10.580	12.817	0.415	9.103	10.929	0.411
SQ (Tiredness)*Group	-5.858	25.528	0.820			