Association between musculoskeletal pain at multiple sites and objectively measured physical activity and work capacity: results from UK Biobank study

Abstract

Objective: To describe the cross-sectional association between musculoskeletal pain at multiple sites and physical work capacity (PWC) and objectively measured physical activity (PA).

Design: Observational study

Methods: Data from a subsample of the UK Biobank were utilised (n=9,856; mean age 58.5 years, mean body mass index 30.2 kg/m^2, 62% female). PWC was measured by a bicycle ergometer and PA by an accelerometer. Pain experienced in hip, knee, back and neck/shoulder was collected by questionnaire. Linear regression modelling was used with adjustment for potential confounders to estimate the association between pain and PWC and PA.

Results: Increase in number of painful sites was associated with lower PWC, moderate and vigorous PA and increased low intensity PA in a dose-response relationship (all p-values for trend≤0.001) before and after adjustment for confounders. In site specific analyses, hip pain was associated with an increased low intensity PA (β 52.8 mins/week, 95% CI 2.3 to 103.2) and reduced moderate PA (β -50.1 mins/week, 95% CI -98.5 to -1.8). Knee pain was only associated with vigorous PA (β -5.7 mins/week, 95% CI -10.0 to -1.3). Pain at neck/shoulder pain and back were not independently associated with PWC and PA.

Conclusion: Greater number of painful sites is consistently associated with poorer PWC, increased low intensity PA and reduced moderate to vigorous PA. Clinicians should address

the critical role of being physically active in managing chronic musculoskeletal pain and interventions targeting musculoskeletal pain may be needed to increased PA levels.

Keywords: Musculoskeletal pain; multiple site pain, physical activity, physical work capacity

Introduction

Musculoskeletal pain is a major public health burden worldwide. It is common in western countries with a prevalence estimated as high as 70% in the general population [1], leading to restrictions in physical function and mobility impairments including decreased balance and gait speed, reduced quality of life and disability[2, 3]. Chronic musculoskeletal pain, generally defined as persistent or recurrent pain lasting more than three months, is typically represented by conditions such as low back pain, neck pain, chronic widespread pain (fibromyalgia) and osteoarthritis [4, 5]. A recent study of the global burden of the 328 diseases and injuries reported that low back pain, neck pain, other musculoskeletal disorders and osteoarthritis were ranked 1st, 6th, 7th and 12th, respectively, for years lived with disability (YLDs) [6]. Multiple risk factors have been reported to be associated with chronic musculoskeletal pain [4, 5, 7, 8]. There is a difference in pain mechanisms underlying acute and chronic pain. In addition to peripheral tissue injury, evidence is growing that central nervous system factor is of prominent importance in the development and persistence of chronic pain [9].

In pain research, the concept of 'multi-site' or 'multiple site' pain (MSP) has been proposed; defined as musculoskeletal pain occurring at more than one site, although, currently, an exact definition is still unclear. The prevalence of MSP is approximately 41-75% depending on study population and number of painful sites measured [10]. MSP has been found to be associated with poorer physical and psychological health, worse health-related quality of life, and more severe depressive symptoms as compared to single-site musculoskeletal pain in both cross-sectional and longitudinal studies [11, 12]. In addition, several studies reported the

adverse effects of MSP on other health outcomes, including risk of falls [13], cognitive impairments [14] and sleep quality [15]. There is also evidence to support more pronounced associations with these outcomes as painful sites increase. Many of these outcomes may result from and lead to reduced physical activity (PA) [16-19].

Low PA is the fourth leading cause of mortality worldwide. Lack of PA is associated with an increased risk for cardio-metabolic disorders [20] such as diabetes and heart diseases; and common mental disorders [21], such as depression and anxiety. A recent meta-analysis of eight studies found that older people with musculoskeletal pain are less likely to engage in PA than those without musculoskeletal pain [22]. All included studies have relied on a self-reported PA from which it is hard to quantify total PA across different domains. Self-reported activity levels are however poorly correlated with objective measures of PA participation, i.e. accelerometer, with self-reported PA estimates more likely to be higher than those measured by objectively measured PA [23]. This highlights the need for accurate and reliable measurements of PA in assessing the relationship between PA and health outcomes.

Pain experience is a complex and multifactorial nature with multiple domains involved including peripheral, psychological and neurological [24]. This heterogeneity leads to the variation in individual pain perception (including pain intensity, frequency and pattern) [25]. PA offers a broad range of health benefits; however, the mechanisms by which exercise exerts its effects remain unclear. There is evidence from mechanistically-orientated studies of PA and pain relief to support a variety mechanisms, including changes in both the peripheral and central components of the nervous systems [26-28], reduced level of chronic inflammation/comorbidities [27, 29-31], muscle strengthening and aerobic capacity [32, 33] and improvements in psychological and cognitive function [32, 34]. Whilst the causal direction of PA and pain is hard to discern, awareness is increasing that chronic pain is associated with brain structural change [35], psychosocial issues (e.g. fear-avoidance beliefs and behaviours, fear of

falling [32] and cognitive impairment [36]), which in turn contribute to reduced PA. To our knowledge, there are no previous studies reporting on the relationship between pain at multiple sites and objectively measured physical work capacity (PWC) and PA. Based on the relationship that chronic pain negatively affects PA and its potential mechanisms, we hypothesised that there is a relationship between pain at multiple sites and reduced physical work capacity (PWC) and PA, and that the relationship was stronger in those with greater number of painful sites. Therefore, the aim of this study was to describe the association between MSP and objectively measured levels of PWC and PA in a population-based sample from the UK biobank.

Methods

We used data from the UK Biobank which is a large, population-based and ongoing longitudinal study assessing how lifestyle, environmental, and genetic factors are linked to a wide range of health-related outcomes [37]. Detailed information about this project including scientific rationale, study design, and survey methods has been previously described [38]. A total of 502,656 individuals aged between 40-69 years were recruited in 2006-2010. This study was approved by the North West Multi-centre Research Ethics Committee and all participants provided written informed consent.

The location of sites at which the participants experienced pain was measured by self-reported questionnaire. Participants were asked whether they had pain (yes/no) at the: hip, knee, back and neck/shoulder for more than three months. The number of reported painful sites was summed to create a total number of painful sites with a range from 0 to 4, which was then categorised into four groups (0-2, 3 and 4 painful sites).

A single 7-day period PA was measured in a subsample of the UK Biobank between 2013 and 2015 using an accelerometer which is considered the ‘gold standard’ objective assessment

of PA for epidemiological studies [39]. Overall, a total of 236,519 participants of the UK Biobank were invited to wear an accelerometer in order to capture data on PA for a 7-day period. Of these, 106,053 agreed to wear an Axivity AX3 wrist-worn triaxial accelerometer (44.8%) over a 7-day period. Participants were asked to wear the accelerometer on their dominant wrist continuously while engaging in their normal daily activities, and then return the device. This study used the accelerometry scores which were calculated from the raw accelerometer data with a rigorous data processing procedure, published elsewhere [40]. This considered both the time and intensity of PA to maintain the average vector magnitude value over five seconds epochs, thereby providing a summary score representing an average PA level over a given time period. 103,578 participants were included in wear time analysis. Of them, 80.6% of participants wore the device for >150 hours out of a scheduled 168 hours. 6,978 participants (6.7% of sample) who had insufficient device wear time (<72 hours) were removed [40]. We categorised PA into low, moderate and vigorous intensity. Low intensity PA was defined as time spent in less than 100 milligravities (mg) activity. Moderate and vigorous PA were defined as time spent in 100–400 mg and >400 mg of activity, respectively [41, 42].

The UK Biobank participants underwent a cardio-respiratory fitness test which consisted of heart-rate monitoring (using a 4-lead electrocardiograph [ECG]; Cardiosoft v6.51) during cycle ergometry on a stationary bike (eBike, Firmware v1.7) with a ramp slope that is adapted to the individual based on age, gender, weight and medical history. Detailed protocol about cardio-respiratory fitness test has been previously described [43]. ECGs were recorded pre-test (15 seconds), during activity (6 minutes) and in recovery (1 minute). The participant's risk category was first calculated to determine what level of activity they should perform or have only a resting ECG performed. There were five risk categories: Category 2 consisted of participants who had a heart condition or diastolic blood pressure ≥95 mm of Hg and systolic blood pressure ≥160 mm of Hg; Category 3 had participants who had chest pain during

physical activity or missing data on height/heart rate; Category 4 consisted of participants who had chest pain at rest, who were unable to walk/cycle unaided for ten minutes, were pregnant, who had no data on weight, blood pressure, or pacemaker status, had diastolic blood pressure ≥110 mm of Hg and systolic blood pressure ≥180 mm of Hg, or weighed ≥150 kg; Category 5 comprised participants who had a pacemaker; Category 1 consisted of participants who did not belong to any of the above categories. For participants in Categories 1 and 2, their predicted absolute maximum workload was calculated according to age, height, weight, resting heart rate and sex using the following formula:

Absolute maximum workload = 105.2749 + (-0.0935 × age) + (-0.0280973 × age × age) + (2.809493 × sex) + (119.0087 × height) + (0.309456 × weight) + (-2.698067 × resting heart rate) + (0.0090985 × resting heart rate × resting heart rate) + (-0.3783405 × age × sex) + (60.72548 × height × sex) + (-0.15016 × weight × sex) + (-0.3730664 × resting heart rate × sex) + (0.0180811 × resting heart rate × age)

The percentage levels of effort during activity were then determined according to their risk category. The target-power was 50% and 30% of the absolute maximum workload for participants in Categories 1 and 2, respectively. For Category 3, participants were instructed to cycle at constant level whereas for Category 4 the protocol dictated that measurement was to be taken only at rest. Lastly, ECG was avoided for Category 5 since it was unsafe or pointless. Participants were instructed to either cycle at a constant workload for 6 minutes aiming for approximately 60 revolutions per minute, or cycle for the first 2 minutes at a constant workload, with the pedalling resistance increasing over the last 4 minutes.

The covariates included in the analyses were age, body mass index (BMI), sex, highest educational level attained, ethnicity, smoking status, number of treatments/medications and grip strength. Age and BMI was treated as continuous. Highest educational level was categorised as: College or university degree; A levels, AS levels, or equivalent; O levels,

GCSEs, or equivalent; CSE or equivalent; NVQ, HND, HNC, or equivalent; other professional qualifications; and none of the above. The ethnic group of each participant was recorded as: White, mixed race, Asian or Asian British, Black or Black British, Chinese, other ethnic group and do not know. Smoking status was assessed by the question, "do you smoke tobacco now?" for which the options were never, previous, and current. Number of treatments/medications was assessed by asking participants to list any prescription medications they regular take or short-term medications. Grip strength of both hands was measured in kilogram (kg) using a Jamar J00105 hydraulic hand dynamometer. For the analyses, we used the grip strength values of the dominant hand assessed by the question: "Are you right or left handed?" We used the maximum of the grip strength scores of both hands for participants who were ambidextrous or had not indicated their handedness.

ANOVA and $\chi 2$ tests were used to compare differences across groups by number of painful sites. Linear regression was then used to assess the association between number of painful sites and PWC and PA, before and after adjustment for age, sex, BMI, education level, smoking status, ethnicity, number of treatments/medications and grip strength. We also examined the associations between pain at each specific site (hip, knee, back, and neck/shoulder) and PWC and PA using linear regression models. All statistical analyses were performed using Stata V.12.1 (StataCorp, USA).

Results

A total of 9,856 participants who had complete accelerometer, PWC and pain information were included in this study. The mean age and BMI of this population were 58.5 years and 30.2 kg/m^2 with 62% females, respectively. Characteristics of these participants by number of painful sites are displayed in Table 1. Fifteen percent of participants reported pain at 0-2 sites, 16% at three sites, and 69% at four sites. Participants who reported a greater number of painful sites were older, female, had a higher BMI and lower educational level, were current

smokers, had a greater number of treatments/medications use and a lower grip strength, and were likely to be of white ethnicity. The levels of moderate and vigorous PA were low in all categories in this population. There was a significant decrease in PWC, moderate and vigorous PA as number of painful sites increased. Conversely, low intensity PA increased with increasing number of painful sites.

Table 2 shows the associations between number of painful sites and PWC and PA. Relative to those with 0-2 painful sites, participants having three or four painful sites had lower levels of PWC, moderate and vigorous PA and increased level of low intensity PA before and after adjustment for potential confounders. Furthermore, there was a significant linear trend between number of painful sites and PWC and PA in univariate and multivariable analyses (all p-values for trend ≤ 0.001).

We then performed further analyses to explore which specific pain site had the strongest associations by examining the associations between each specific pain site and PWC and PA. As shown in Table 3, hip, knee, back and neck/shoulder pain were negatively associated with PWC and moderate and vigorous PA, and positively associated with low intensity PA in univariate analysis. After adjustment for confounders as well as pain at other sites, hip pain was associated with an increased level of low intensity PA and decreased level of moderate PA. Knee pain was only associated with vigorous PA. However, statistically significant associations were not found for neck/shoulder and back pain.

Discussion

To our knowledge, this is the first study to describe the association between pain at multiple sites and objectively measured PWC and PA among a large sample of people from general population. The findings that people with greater number of painful sites appear to be less active and have worse PWC and that pain holds a strong dose-response relationship with

PWC and PA, suggest that MSP and physical health are clearly linked. Furthermore, pain in the hip and knee has strong associations with PA with hip pain mostly associated with low/moderate PA and knee pain with vigorous PA. This suggests that the impact of pain at different sites and its mechanisms by which different pain sites may contribute to reduced levels of PA are different.

There are a number of studies examining the association between musculoskeletal pain and PA. A recent meta-analysis including eight studies concluded that people with chronic pain were less likely to be active than controls without pain [22]. However, of eight studies included, PA was measured using self-reported questionnaires. Poor agreement between self-reported and objectively measured PA has been reported for people with chronic low back pain, questioning the usefulness of self-reported measures of PA in epidemiological studies. To date, no studies have aimed to quantify the association of pain with robust and objective measurements of PWC and PA. This is the first study to use accelerometry data (a 'gold standard' objective measures of PA for epidemiological studies [44]) showing that people with greater number of musculoskeletal painful sites have reduced levels of PWC and PA, compared to those with pain at two or less sites. Moreover, a dose-response relationship was also demonstrated. These findings are partially consistent with previous studies. Eggermont *et al* [3] reported that pain at multiple sites rather than pain severity is more strongly associated with poor mobility. Furthermore, Shah *et al* [45] also reported that people with three or more pain sites had 1.8 times increased risk of incident mobility disability compared to those without musculoskeletal pain. A longitudinal study by Leveille *et al* [46] found that people with widespread pain were more likely to develop mobility difficulties than those without or single-site pain during the 3-year follow-up. Although we cannot directly compare our study with prior studies, our study extends earlier studies by providing an objective estimate of the

association and showing that those with a greater number of painful sites had lower levels of PWC and PA.

Multiple pathways may underlie the association between number of painful sites and levels of PWC and PA. Investigation of the potential pathways is beyond the aim of this study. One possible explanation is that more painful sites reflect more severe and longer duration of underlying comorbidities, causing poorer PWC and less PA engagement. For instance, individuals with cardiovascular or joint diseases such as rheumatoid arthritis, osteoarthritis may have a significant restriction in form and intensity of PA. A vicious cycle may develop as reduced levels of PA may result in further loss of muscle strength, overweight/obesity and other adverse health outcomes which in turn lead to more intense pain and widespread pain [47, 48].

Fear-avoidance belief and behaviours may also partly explain the association between pain and reduced levels of PWC and PA in this study. Significantly higher scores in fear-avoidance beliefs and pain catastrophizing were observed in low back pain patients with low levels of PA [49]. Compared to patients with low fear-avoidance beliefs or with no pain catastrophizing, a risk of low levels of PA was about 4-8 times higher in those with high fear-avoidance beliefs or medium/high pain catastrophizing. Furthermore, widespread pain is an important contributor to falls in older people, which is a leading cause of accidental death in this population [50]. Thus, fear of falling is another explanation for lower level of PA in people with chronic pain. It is plausible to postulate that persons with a greater number of painful sites have stronger fear-avoidance beliefs. In addition, cognitive function might be another mediator involved in this association. Cognitive function has been shown to be associated with physical performance among patients with pain [36]. A recent neuroimaging study revealed that potential mechanism may be due to change in central nervous system involving white matter hyperintensities and fractional anisotropy induced by chronic pain, which in turn lead

to physical restrictions [35]. These findings suggest that pain-physical inactivity relationship is complex and mediated by multiple factors. A better understanding of interactions between these factors may facilitate the development of comprehensive management of pain and strategies motivating people with chronic pain to engage in PA.

Some implications are raised from our findings. Given the fact that physical inactivity and decreased PWC are linked to a number of adverse health outcomes, while a multitude of beneficial effects can be gained through increased levels of PA, multidisciplinary management and treatments for MSP incorporating cognitive behavioural treatment, pain education and underlying conditions treatment are beneficial for individual's health well-being and have a potential to reduce health burden. Since the pain-physical inactivity relationship is bidirectional and hard to disentangle, in general practice clinicians should address that engaging in PA is the cornerstone of non-pharmacological management of pain. There is evidence to suggest that PA is not only associated with increases in aerobic and strength capacity but also linked to reduction in fear-avoidant beliefs and increased cognitive resources [51]. Although a challenge is what optimal intensities and durations of PA are needed for individual bases to minimise pain exacerbation and discomfort, efforts are still required to encourage people with chronic pain, particularly those with pain at multiple sites to implement PA.

The strengths of the current study include a large national sample of general population and the objectively measured PWC and PA. There are several limitations in this study. First, our study cannot determine a causal relationship between musculoskeletal pain at multiple sites and PWC and PA due to the cross-sectional design. Longitudinal studies are needed to confirm these associations. Second, pain was measured by the self-reported questionnaire in this study which is relatively simple and cannot capture pain intensity, frequency and pattern. This limits the investigation of these pain features. Furthermore, pain intensity at each site is

also important but we were unable to evaluate if this influences our results. Third, although some potential confounders were considered in this study, we cannot address the influences of many possible confounders or mediators, such as comorbidity, psychological factors, cognitive function and previous exercise history.

Conclusions

Musculoskeletal pain at multiple sites is consistently associated with poorer PWC, increased low intensity PA and reduced moderate to vigorous PA. This emphasizes that developing effective management and treatments for people with chronic pain are of particular importance to promote PA engagement.

Practical Implications

- People with greater number of musculoskeletal painful sites are less active and have poorer physical fitness than those with fewer painful sites.
- Interventions targeting chronic musculoskeletal pain may have profound effects on increased levels of PA.
- Given the bidirectional relationship between chronic pain and PA, clinician should address the critical role of being physically active in managing chronic musculoskeletal pain.

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Table 1 Characteristics of participants by number of painful sites*

Variable	Number of painful sites			P-value†
	0-2 (N=1440)	**3** (N=1605)	**4** (N=6811)	
Age (years)	57.1±8.0	58.1±7.5	58.9±7.2	0.002
Female sex (%)	56	61	64	<0.001
Body mass index (kg/m^2)	28.7±4.8	30.2±6.1	30.4±6.0	<0.001
Qualification (%)				<0.001
College or university degree	8.3	6.4	6.6	
A levels, AS levels, or equivalent	5.8	6.4	5.0	
O levels, GCSEs, or equivalent	11.1	11.1	11.5	
CSE or equivalent	8.1	7.1	6.4	
NVQ, HND, HNC, or equivalent	17.0	14.9	14.7	
Other professional qualifications	27.0	25.5	22.6	
None of the above	20.7	26.8	31.8	
Smoking status (%)				<0.001
Never	49	46	42	
Previous	38	39	39	
Current	12	15	18	
Ethnicity (%)				<0.001
White	90	92	93	
Mixed Race	1	1	1	
Asian or Asian British	3	3	3	
Black of Black British	3	3	2	
Chinese	0	0	0	
Other	1	1	1	
Not Known	0	0	0	
Number of treatments/medications	3.5±0.1	4.6±0.1	5.6±0.1	<0.001
Grip strength (kg)	30.2 ±0.3	28.2±0.3	26.2±0.1	<0.001
Physical work capacity (watts)	58.7±39.7	47.8±40.6	41.4±39.5	<0.001
Physical activity (minutes per week)				
Low intensity	9366.1±388.0	9447.3±349.7	9490.4±343.4	<0.001
Moderate	685.7± 365.0	612.0±333.5	573.4±329.1	<0.001
Vigorous	28.2±34.4	20.8±29.8	16.3±23.2	<0.001

*Values are the Mean±SD except for percentages;
†P Values determined by t test or Pearson $\chi 2$ test (where appropriate).

Table 2 Associations between number of painful sites physical work capacity and physical activity

	No. of pain sites	Univariable β (95% CI)	Multivariable† β (95% CI)
Physical work capacity (watts)			
	0-2	Ref.	Ref.
	3	**-15.4 (-23.2, -7.7)**	**-8.8 (-15.5, 1.8)**
	4	**-21.9 (-28.0, -15.7)**	**-12.4 (17.9, 6.9)**
	P for trend	**<0.001**	**<0.001**
Low intensity (minutes per week)			
	0-2	Ref.	Ref.
	3	**79.7 (18.3, 141.2)**	50.9 (-5.7, 107.5)
	4	**122.9 (72.2, 173.6)**	**69.1 (21.7, 116.5)**
	P for trend	**<0.001**	**<0.001**
Moderate (minutes per week)			
	0-2	Ref.	Ref.
	3	**-73.2 (-131.8, -14.5)**	-46.8 (-101.0, 7.5)
	4	**-111.8 (-160.2, -63.3)**	**-62.4 (-107.8, 16.9)**
	P for trend	**<0.001**	**<0.001**
Vigorous (minutes per week)			
	0-2	Ref.	Ref.
	3	**-6.6 (-11.5, -1.6)**	-4.2 (-8.9, 0.6)
	4	**-11.1 (-15.2, -7.0)**	**-6.7 (-10.7, -2.8)**
	P for trend	**<0.001**	**<0.001**

Bold denotes statistically significant result. β regression coefficient; CI confidence interval; Ref reference group;
†Adjusted for age, sex, body mass index, education, ethnicity, smoking status, number of treatments/medications taken and grip strength.

Table 3 Association between specific pain site and physical work capacity and physical activity

	Physical activity measures	Univariable	Multivariable†
		β (95% CI)	β (95% CI)
Hip pain			
	Physical work capacity (watts)	**-3.3 (-4.9, -1.7)**	-0.3 (-6.5, 5.8)
	Low intensity (minutes per week)	**23.0 (8.7, 37.2)**	**52.8 (2.3, 103.2)**
	Moderate (minutes per week)	**-20.6 (-34.2, -7.0)**	**-50.1 (-98.5, -1.8)**
	Vigorous (minutes per week)	**-2.4 (-3.9, -0.9)**	-2.7 (-6.9, 1.5)
Knee pain			
	Physical work capacity (watts)	**-3.4 (-4.5, -2.2)**	-6.4 (-13.0, 0.2)
	Low intensity (minutes per week)	**13.8 (2.9, 24.6)**	45.0 (-7.4, 97.4)
	Moderate (minutes per week)	**-11.3 (-21.5, -1.0)**	-39.4 (-89.6, 10.8)
	Vigorous (minutes per week)	**-2.5 (-3.9, -1.3)**	**-5.7 (-10.0,-1.3)**
Back pain			
	Physical work capacity (watts)	**-4.2 (-5.2, -3.3)**	-3.7 (-10.7, 3.3)
	Low intensity (minutes per week)	**23.6 (14.6, 32.7)**	3.0 (-52.3, 58.4)
	Moderate (minutes per week)	**-22.6 (-31.2, -13.9)**	-1.9 (-54.9, 51.1)
	Vigorous (minutes per week)	**-1.1 (-2.1, -0.1)**	1.1 (-5.7, 3.5)
Neck/shoulder pain			
	Physical work capacity (watts)	**-2.5 (-3.5, -1.6)**	-5.5 (-11.4, 0.4)
	Low intensity (minutes per week)	**18.0 (8.8, 27.3)**	-9.5 (-60.6, 41.7)
	Moderate (minutes per week)	**-15.8 (-24.6, -7.0)**	10.1 (-38.9, 59.1)
	Vigorous (minutes per week)	**-2.2 (-3.2, -1.2)**	-0.6 (-4.9, 3.7)

Bold denotes statistically significant result. β regression coefficient; CI confidence interval;
†Adjusted for age, sex, body mass index, education, ethnicity, and smoking, number of treatments/medications taken and grip strength and pain at other sites in the table.