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Associations among acute and chronic musculoskeletal pain, sleep duration, and C-reactive protein (CRP): A cross-sectional study of the UK Biobank dataset

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Abstract

Both musculoskeletal pain and sleep disturbances are major health problems worldwide. Literature suggests that the two are reciprocally related and both may be associated with changes in C-reactive protein (CRP) levels. However, the relationships among musculoskeletal pain, sleep duration, and CRP remain unclear.

In this cross-sectional study, we investigated the relationship between acute and chronic musculoskeletal pain, sleep, and inflammation using the data from the initial visit of the UK Biobank. 17,642 individuals with chronic musculoskeletal pain, 11,962 individuals with acute musculoskeletal pain, and 29,604 pain-free controls were included in the analysis. In addition, we validated the findings using data from the second visit assessment of the UK Biobank.

We found that 1) chronic pain was associated with higher CRP levels compared to both acute pain and the pain-free controls; 2) chronic pain was associated with a lower sleep score (a measurement of sleep patterns), compared to acute pain and the pain-free controls; and acute pain was associated with lower sleep scores compared to the controls; 3) there was a significant negative

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association between the sleep score and CRP; 4) CRP may partially mediate the association between chronic pain and decreased sleep score. However, the effect size of the mediation was very small, and the pathophysiological significance remains uncertain. Further validation is needed. These findings were partly replicated in the UK Biobank second visit assessment cohort with a smaller sample size. Our findings, which are based on the large UK Biobank dataset, support the interplay between musculoskeletal pain, sleep patterns, and the potential mediating role of CRP on this reciprocal relationship.

Keywords

musculoskeletal pain; sleep disturbance; C-reactive protein; acute pain; chronic pain

INTRODUCTION

Both musculoskeletal pain and sleep disturbances are major health problems worldwide, with profound negative impact on quality of life, general health, and socio-economic well-being[1–3].

Literature suggests that sleep and pain are reciprocally related and interact with each other. Pain causes sleep disruption, and sleep loss exacerbates pain[4,5]. Sleep disturbance may play an important role in pain modulation processes. Numerous studies have shown that elevation of spontaneous and evoked pain is promoted by sleep deprivation[5–12]. Epidemiological studies have shown that sleep disturbance, e.g., insomnia, is highly prevalent among people with chronic pain[13], and individuals with insomnia are more likely to report chronic low back pain[14].

Additionally, inflammatory processes are dysregulated in people with sleep disturbances and contribute to pain sensitivity[15]. Inflammation may play an important role in the development and maintenance of musculoskeletal pain as well as sleep disturbance[5]. For example, people with increased levels of inflammation are more likely to report chronic low back pain[14]. Inflammation is typically measured by inflammatory markers such as C-reactive protein (CRP), tumor necrosis factor alpha (TNFα), and interleukin 6 (IL-6). Conceptual models of relationships between insomnia, pain, and inflammation suggest that insomnia could increase basal inflammation, which could then lead to increased pain[5,16,17]. Self-reported poor sleep quality similarly is associated with elevated inflammatory markers[11,18,19].

Musculoskeletal pain is typically categorized in two states: acute pain, lasting less than three months, and chronic pain, lasting three months or longer[20,21]. While there is growing interest in understanding how acute pain develops into chronic pain, the role of inflammation and sleep in the transition from acute to chronic pain remains unclear. Although there are studies about the relationship between inflammatory markers and different states of pain, sample sizes of those studies are relatively small, which could largely affect the reliability of conclusions that were drawn from them[22].

The UK Biobank is a large-scale biomedical database, which includes many measurements and self-reported features for over 500,000 adult participants from the Great Britain

area. Recently, investigators have started using the UK Biobank to investigate chronic pain, including the contributions of genetic factors, and have produced some interesting findings[23–25].

Leveraging the rich data collected by the UK Biobank[26], the cross-sectional study reported here aims to better understand the relationship among acute and chronic musculoskeletal pain, sleep, and inflammation. We specifically focus on the associations between the presence of self-reported acute and chronic musculoskeletal pain, self-reported sleep behaviors, and CRP serum levels. We examined data from age- and sex-matched participants with no pain as controls. We first established that there were differences in CRP levels and high-risk sleep patterns between each group. We then performed a mediation analysis to investigate the potential role of CRP as a mediator of bi-directional associations between pain and sleep patterns. We hypothesize that 1) both chronic and acute musculoskeletal pain are associated with increased sleep disturbances and CRP levels, and 2) CRP mediates the association between musculoskeletal pain and sleep disturbances.

METHODS

UK Biobank

The data used in this study were obtained from the UK Biobank[26]. The UK Biobank has ethics approval from the North West Multi-Centre Research Ethics Committee (MREC). Further details on the UK Biobank Ethics and Governance framework are available at: https://www.ukbiobank.ac.uk/learn-more-about-uk-biobank/about-us/ethics. Data used in this study were obtained under application #32568.

Briefly, the UK Biobank recruited over 500,000 participants aged 40–70 years across Wales, England, and Scotland from 2006–2010. People who were identified from NHS patient registers according to being aged 40–69 and living within a reasonable travelling distance of an assessment centre were invited to participate. Around 5 million invitations were sent to recruit roughly 500,000 participants (https://www.ukbiobank.ac.uk/media/0xsbmfmw/egf.pdf). All participants provided informed consent for access to their medical records and health information for research purposes. In the initial assessment, participants provided detailed information on lifestyle, health, physical measures, and demographics, as well as blood, urine, and saliva samples. We focused primarily on three measures, including sleep behavior, CRP levels, and musculoskeletal pain. We repeated this examination using second visit data collected between 2012 and 2013 in a sample of approximately 20,000 individuals; this examination served to validate findings from the larger set of initial visit data. For more detailed information about the UK Biobank, please refer to the study website at www.ukbiobank.ac.uk.

Inclusion/exclusion criteria

We excluded participants with any psychological or neurological disorder captured by ICD-10 or ICD-9 diagnosis, a diagnosis of diabetes from a physician, or other self-reported long-standing illness, disability, or infirmity. Next, we excluded individuals who had: 1) missing data for any of the variables we analyzed or used as covariates, or 2) uninterpretable

responses (e.g. “do not know” and “prefer not to answer”) to any of the variables we analyzed or used as covariates. After these exclusions and quality control checks, we created the musculoskeletal pain and pain-free control groups.

Group assignment – musculoskeletal pain classification

The present study examined individuals with chronic musculoskeletal pain, acute musculoskeletal pain, and pain-free controls. Chronic musculoskeletal pain is defined as pain that persists or recurs for more than 3 months[21]. To define these groups, pain-related questions in the UK Biobank touchscreen questionnaire were used. Question 1: “In the last month have you experienced any of the following that interfered with your usual activites? (You can select more than one answer)”. The choices included headache, facial pain, neck or shoulder pain, back pain, stomach or abdominal pain, hip pain, knee pain, pain all over the body, none, or prefer not to answer. Question 2: for each type of pain selected, participants were then asked if they “have had that pain for more than 3 months”. We included participants in the chronic pain group if they indicated having “neck or shoulder pain”, “back pain”, “hip pain”, or “knee pain” for at least three months and selected no additional sites of pain. We included participants in the acute pain group if they reported having “neck or shoulder pain”, “back pain”, “hip pain”, or “knee pain” at the time of the initial assessment but indicated the pain was not present for three or more months. A sample of individuals who self-reported no pain was used to create a 1-to-1 control group that was matched on the sex and age of each individual in the acute pain group and then the chronic pain group, both of which were combined to create one control group. A summary of the sample size and demographics for each group can be found in Table 1.

Variables of Interest and Covariates

CRP (mg/L) was measured by immunoturbidimetric - high sensitivity analysis on a Beckman Coulter AU5800 using blood that collected from the UK Biobank initial visit.

Sleep behaviors, including sleep duration, chronotype, insomnia, snoring, and daytime sleepiness, were self-reported in a sleep-related questionnaire. The questions were as follows: “About how many hours sleep do you get in every 24 hours? (please include naps), “Do you consider yourself to be (choices of ‘Definitely a morning person’, ‘More a morning than evening person’, ‘More an evening than a morning person’, ‘Definitely an evening person’, ‘Do not know’, ‘Prefer not to answer’)?”, “Do you have trouble falling asleep at night or do you wake up in the middle of the night?”, “Does your partner or a close relative or friend complain about your snoring?”, and “How likely are you to doze off or fall asleep during the daytime when you don’t mean to? (e.g. when working, reading or driving)”. Based on previous studies[27–29], we used sleep scores to quantify healthy sleep patterns. Low-risk sleep behaviors were defined as sleeping 7–8 h/day, early chronotype (“morning” or “morning than evening”), report of never or rarely having insomnia symptoms, no self-reported snoring, and no excessive daytime sleepiness (“never/rarely” or “sometimes”). For each sleep factor, low risk was coded as 1 and high risk as 0; a five-point scale were used to generate a sleep score ranging from 0 to 5, with higher scores corresponding to a healthier sleep pattern. Participants who indicated “do not know” or “prefer not to answer” were excluded from the analysis.

Sex, age, physical activity, body mass index (BMI), smoking status, and income were included as potential confounding variables; these factors have been shown to affect CRP levels and sleep behaviors[14]. Sex and age were acquired from the central registry at recruitment, but in some cases were updated by the participant. Physical activity was measured using summed Metabolic Equivalent Task minutes per week for all activity, derived from Metabolic Equivalent Task scores data based on IPAQ (International Physical Activity Questionnaire) guidelines. BMI was calculated from body composition estimated by impedance measurements. Smoking status and average total household income before tax were self-reported.

Statistical Analysis

Descriptive statistics were used to identify the mean and standard deviation of CRP and sleep score for each group. Hedges' g was used to calculate effect size. Differences across groups in CRP levels and sleep scores were assessed using analysis of covariance (ANCOVA) with type II sum of squares, adjusting for sex, age, physical activity, body mass index (BMI), smoking status, and income. A post-hoc Tukey's HSD test was used to assess differences between specific groups. Finally, we examined the relationship between sleep scores and CRP levels across the groups, and within each group using Pearson's correlation. In addition, we repeated these analyses in the second visit assessment cohort.

To further explore the relationships between pain, sleep quality, and CRP levels, we performed a mediation analysis[30] with 1000 bootstrapping iterations to determine whether CRP mediates the association between musculoskeletal pain and sleep score when comparing chronic pain vs. controls and comparing acute pain vs. controls. Since our data is cross-sectional, we performed the analysis first using pain as the independent variable and sleep score as the response variable, and then with sleep score as the independent variable and pain as the responses, and compared these results[31,32].

We performed the mediation analysis only when the association between the independent and dependent variable, and the association between the mediator and the independent and dependent variables were significant based on the ANCOVA post-hoc analyses. The schematic representation of the mediation analyses is shown in Figure 1. We also repeated the same mediation analyses using only age and sex as covariates, as the other covariates may vary over time.

In all analyses, p values less than or equal to 0.05 ($p \leq 0.05$) were considered statistically significant. We used the programming language R for data analysis and performed statistical analyses using R studio with packages 'car', 'psych', 'mediation', 'ggpubr', and 'ggplot2'[33].

RESULTS

Participants in each group

Among 240,768 participants in the initial assessment, 17,642 individuals reported chronic musculoskeletal pain, 11,962 individuals reported acute musculoskeletal pain, and 29,604 pain-free individuals matched to the two pain groups reported no pain (Table 1). Thus, 59,208 individuals comprised the total sample with 47.1% female and a mean age of 55.77

years. Age and sex characteristics of each group can be found in Table 1. More information about the number of participants excluded can be found in Figure 2.

In the validation analysis using second visit data, 669 individuals reported chronic pain, 494 individuals reported acute pain, and the matched pain-free control group contained 1,163 individuals. The entire cohort consisted of 2,326 individuals with 43.9% female and a mean age of 60.67 years. 887 of these participants were in the initial assessment cohort, of which 44 had their acute pain in the initial assessment transition to chronic pain in the second visit.

Associations between musculoskeletal pain, CRP, and sleep patterns

Musculoskeletal pain and CRP—The data showed a significant association between pain groups and CRP levels when adjusting for sex, age, physical activity, body mass index (BMI), smoking status, and income ($p = 0.013$). Post-hoc analysis revealed that chronic pain was associated with higher CRP levels, compared to the acute pain group and the pain-free control group ($p \leq 0.001$, effect size: 0.04 and 0.07, respectively). There was no significant difference in mean CRP levels between the acute pain group and the pain-free controls ($p = 0.062$, effect size: 0.03). The mean and standard deviation of CRP levels for each group are summarized in Table 1. The CRP levels (mean and standard error of the mean) for each group are also shown in Figure 3.

In second visit cohort, the association between pain groups and CRP levels was not significant ($p = 0.426$). However, the trends and effect sizes were similar to that of the initial assessment results for the larger cohort. The effect size was 0.04 when comparing chronic vs. acute pain, 0.09 when comparing chronic pain vs. pain-free controls, and 0.05 when comparing acute pain vs. pain-free controls. The mean and standard deviation of CRP levels are presented in Table 1.

Musculoskeletal pain and sleep score—In the multivariable adjusted analysis, there was a significant group effect for sleep scores when adjusting for sex, age, physical activity, body mass index (BMI), smoking status, and income ($p < 0.001$). Tukey's tests indicated that chronic pain was associated with lower sleep scores compared to the acute pain group and the pain-free control group ($p < 0.001$, effect size: 0.10 and 0.17, respectively). Acute pain was also associated with lower sleep scores, compared to the controls ($p < 0.001$, effect size: 0.03). The mean and standard deviation of the sleep scores for each group are summarized in Table 1. The sleep scores (mean and standard error of the mean) for each group is also shown in Figure 3.

Analyses of the second visit assessment cohort confirmed a significant group effect for sleep scores when adjusting for sex, age, physical activity, body mass index (BMI), smoking status, and income ($p = 0.021$). Tukey's tests revealed that the chronic pain group had higher risk sleep patterns, as indicated by sleep scores, compared to pain-free controls ($p = 0.007$, effect size: 0.14); however, there was no significant difference between the acute pain group and the chronic pain and pain-free control groups, ($p=0.655$, effect size: 0.05; $p = 0.185$, effect size: 0.09, respectively). The mean sleep scores and standard deviations are presented in Table 1.

Association between Sleep score and CRP—Lower sleep scores were associated with higher CRP levels across groups and within each group (all groups: $p < 0.001$, $r = -0.05$; chronic pain: $p < 0.001$, $r = -0.04$; acute pain: $p < 0.001$, $r = -0.06$; controls: $p < 0.001$, $r = -0.04$), indicating that higher risk sleep patterns are associated with more severe inflammation.

The validation analysis using second visit cohort confirmed that higher CRP levels were associated with higher risk sleep patterns ($p = 0.037$, $r = -0.04$) across groups. Although correlations were not significant within the groups, the trend of the effect remained consistent (chronic pain: $p = 0.107$, $f = -0.06$, acute pain: $p = 0.269$, $r = -0.05$, controls: $p = 0.493$, $r = -0.02$).

Mediation analysis

We investigated if CRP was a mediator between pain and sleep score by comparing the chronic musculoskeletal pain group vs pain-free controls, as well as chronic pain vs acute pain groups, adjusting for sex, age, BMI, physical activity, smoking status, and income. The analysis indicated that CRP partially mediated the association between chronic pain (independent) and decreased sleep score (dependent) ($p = 0.04$). This partial mediation was also significant in the reverse direction (with chronic pain as dependent and decreased sleep score as independent) ($p = 0.02$). However, the mediation effect sizes were small (of the order of 1/1000) compared to the direct effect. When comparing the chronic and acute pain groups, CRP did not significantly mediate the relationship between sleep score and pain ($p = 0.27$). The total association, direct association, and mediation effects are presented in Table 2. Note that we did not investigate the mediation effect between acute pain and pain free controls as there was no significant difference between the acute pain and pain-free controls for CRP level ($p = 0.062$).

The results of mediation analyses adjusting for sex and age only achieved similar results. We found that CRP partially mediates the association between chronic pain (independent) and decreased sleep score (dependent) ($p < 0.001$). This partial mediation was also significant in the reverse direction (with chronic pain as dependent and decreased sleep score as independent) ($p < 0.001$). When comparing chronic and acute pain, CRP partially mediated the association between pain (independent) and decreased sleep score (dependent) ($p = 0.008$), as well as in the reverse direction (with pain as dependent and decreased sleep score as independent) ($p = 0.028$). The total association, direct association, and mediation effects are presented in Table 3.

Discussion

In this study, we investigated associations among musculoskeletal pain, CRP, and sleep patterns. We found that: 1) the chronic pain group showed higher CRP levels, compared to both the acute pain and the pain-free control groups. There was no significant difference in mean CRP levels between the acute pain and the pain-free control groups; 2) the chronic pain group produced lower sleep scores, compared to acute pain and the pain-free controls. The acute pain group also produced lower sleep scores, compared to pain-free controls; 3) the mediation analysis indicated that CRP partially mediated the association between

chronic pain (independent) and decreased sleep score (dependent). Examination of the second visit cohort assessments showed similar effect sizes and similar but non-significant differences, likely due to reduced statistical power in a smaller sample size. Our findings support the hypothesized associations among musculoskeletal pain, CRP, and sleep patterns.

Musculoskeletal pain and CRP

Recently, CRP changes in patients with musculoskeletal pain has drawn increased attention[22]. In a recent review paper[22], the authors summarized three studies that compared CRP levels in people with acute and chronic low back pain (LBP) vs. controls and found mixed results. In a study of 99 individuals having an onset of acute LBP within the past two weeks and 55 pain-free controls, the authors observed significantly higher baseline CRP levels[34]. In addition, they detected significantly higher median CRP levels in patients with high pain intensities (visual analog scale, VAS ≥ 4), compared to those with low pain intensities (VAS < 4) and pain-free controls[34].

In a subsequent study from the same group[35], the authors assessed individuals within two weeks of the onset of acute LBP (n = 109) and pain-free controls (n = 55). Levels of CRP, TNFα, IL-6 and interleukin-1β (IL-1β) as well as questionnaires related to pain, disability, sleep, and psychological status were collected. Participants repeated measurements throughout six months. Results showed that high inflammation (CRP/IL-6) was associated with good recovery, but specific elevation of TNFα along with depressive symptoms was associated with poor recovery. The early role of CRP (and perhaps IL-6) in the control of inflammation and recovery were further supported by a recent 12-month follow-up study of this sample[36].

Sample sizes of the above studies are relatively small, which significantly influences one's confidence in the reliability of findings[22]. In the present study which used a substantially larger cohort, we found that chronic pain was associated with higher CRP levels, compared to both the acute pain and the pain-free control groups. There was no significant difference in mean CRP levels between the acute pain group and the pain-free controls. However, the time since onset of pain in the acute pain group was unknown, which may contribute to the inconsistency with results from previous studies. In addition, it is worth noting that the effect size of the increased CRP level in chronic pain compared to the other groups is rather small (chronic pain compared to acute pain: 0.04, chronic pain compared to pain-free controls: 0.07).

Musculoskeletal pain and sleep

The reciprocal association / interaction between pain and sleep disturbance has been known for a long time[37]. For example, studies have shown that insomnia symptoms are associated with reduced pain thresholds[38–40]; sleep deficiency may be involved in the transition from acute to chronic pain[41]. Chronic pain has been found to be associated with greater sleep disturbance, reduced sleep duration and sleep quality, increased time taken to fall asleep, poor daytime functioning, and greater sleep dissatisfaction and distress[42]. Improved sleep quality can reduce the pain intensity and daytime symptoms associated back and neck pain[43–45], and facilitate the treatment of chronic LBP[46].

Additional studies suggest that sleep disturbance may contribute to pain development by impacting physiological and psychosocial functioning[4,45]. For example, sleep loss triggers inflammation[47], impairs adaptive immune function[48], disturbs emotion regulation[49,50] and interferes with cognitive function[51]. These processes produce a range of physiological and psychological consequences[52] that can exacerbate pain and make its management more difficult[53].

With a large sample size, we found that individuals with acute and chronic pain produce lower sleep scores, compared to pain-free controls; chronic pain was associated with a lower sleep score than acute pain. These results are consistent with previous findings[37,42].

Sleep, CRP, and musculoskeletal pain

We also found that lower sleep scores were associated with higher CRP levels in all the groups, combined and when individually examined, indicating that higher risk sleep patterns correlate with greater inflammation. These results are consistent with previous studies indicating that poor sleep behaviors, including excessive sleep duration, poor sleep quality, and sleep deprivation, are significantly associated with elevated CRP levels[11,54,55].

Recently, the relationship between sleeplessness and inflammation on the risk of musculoskeletal pain has drawn research attention. A recent population-based prospective study of 3,214 women and 3,142 men[56] detected an association between sleeplessness and CRP on the increased risk of any form of chronic musculoskeletal pain. In a subsequent study[57], investigators found that preventing or reducing sleep problems among patients with chronic low back pain, including those with several additional pain sites, may have the potential to improve long-term prognosis of this condition.

To further explore the role of CRP in the interaction between musculoskeletal pain and sleep, we performed a mediation analysis. Our results showed that when comparing musculoskeletal pain and control groups, CRP partially mediated the association between chronic pain and decreased sleep score. This result suggests that CRP may be involved in the interaction between chronic pain and poor sleep patterns, but the mediation effect is rather mild. This partial mediation remained significant in both directions (pain as the dependent variable and sleep score as the independent variable; pain as the independent variable and sleep score as the dependent variable), consistent with the bi-directional relationship of pain and sleep disturbances. It is worth noting that the interpretation of mediation analyses should be performed with caution in cross-sectional data[31,32], so further studies are required to validate our findings. In addition, the small effect size of the mediation may be driven by the large number of participants, so we cannot conclude pathophysiological significance. Further validation is needed.

To confirm our findings, we performed an identical set of analyses using second visit assessment data of the UK Biobank cohort. As only a portion of the individuals from the initial visit participated in the second visit, the sample size was relatively small. As a result, we could only partially replicate our findings. Nevertheless, the effect sizes and trends observed for the initial and second visit cohorts are similar.

In this study, we excluded individuals with psychiatric comorbidities because 1) depression can also increase CRP levels[58,59]; and 2) studies[60] suggests that chronic pain alone and chronic pain comorbid with depression may be associated with different mechanisms. Thus, our findings may not be generalizable, i.e. not reflect the sleep and CRP alteration associated with musculoskeletal pain in the general population, but we believe it is reasonable to study a homogeneous subpopulation in order to obtain more readily interpretable results. In addition, for those who cannot obtain an adequate number of musculoskeletal pain patients without psychiatric comorbidities, an alternative method may be to include the psychiatric measurements in the model to adjust for their effects. Nevertheless, the interpretation of regression or other similar statistical analyses are conditional on the model being correct, and any statistical model is an imperfect reflection of reality. Therefore, even if we include these covariates in the analysis, we still would not fully account for the effects of these potential confounders. The UK Biobank is sufficiently large for enough subjects to remain after excluding these patients. Thus, we believe our decision to impose inclusion criteria is reasonable.

In this study, we used BMI calculated by bioelectrical impedance analysis (BIA). BIA is a non-invasive technique to measure body composition suitable in epidemiological research[61] but can be influenced by many factors that make it less accurate for certain subpopulations[62]. Both BMI measurements, calculated through BIA or traditionally using height and weight measurements, are widely used, but neither measure body fat directly. We chose to use BIA because it has been shown to be closely correlated with and as valuable as traditional BMI in regard to detection of obesity in groups[61,63].

Limitations

There are several limitations in this study. As a cross-sectional study, we cannot investigate the causal relationships amongst pain, sleep, and CRP. The UK Biobank did not collect pain intensity ratings at the same time blood samples were collected. Therefore, we cannot explore the relationships amongst pain intensity, sleep score, and CRP. Previous studies on the association between pain intensity and CRP levels were not consistent. For example, a prospective longitudinal study with a follow-up of 6 months[64] found no statistically significant differences in mean CRP levels between patients with chronic low back pain and those in a control group. CRP remained approximately constant throughout the study period; there was no correlation with pain or function. Furthermore, our sample of musculoskeletal pain is heterogeneous due to the impossibility of defining the exact cause and subtype of musculoskeletal pain for each patient. In addition, the only inflammation marker the UK Biobank collected was CRP, and thus, we could not analyze other inflammation markers such as TNFα, IL-6, and IL-1β to have a more comprehensive picture of the role of inflammation in chronic pain and sleep disturbances. We were also not able to consider the diurnal fluctuation pattern of CRP. We did not include the depression, anxiety, and other mental measurement as covariate in this study, as we have excluded participants who were diagnosed with mental disorders. Another limitation that could introduce bias to the results is that we don’t know whether the participants were receiving therapy for their pain that might affect inflammation levels and sleep behaviors.

Summary

In this large-scale cross-sectional study, we used data from the UK Biobank to investigate the association among pain, sleep, and the inflammation marker CRP. Our findings suggest that compared with pain-free controls: 1) chronic musculoskeletal pain, but not acute musculoskeletal pain, was associated with higher CRP levels; and 2) both chronic and acute musculoskeletal pain were associated with lower sleep scores (with chronic pain producing a lower score than acute pain). CRP may partially mediate the interaction between chronic pain and decreased sleep score. However, the effect size of the mediation was very small, and the pathophysiological significance remains uncertain. Further validation is needed. Our study may provide further evidence about the interaction between sleep and musculoskeletal pain, and the involvement of CRP in their interplay.

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Highlight

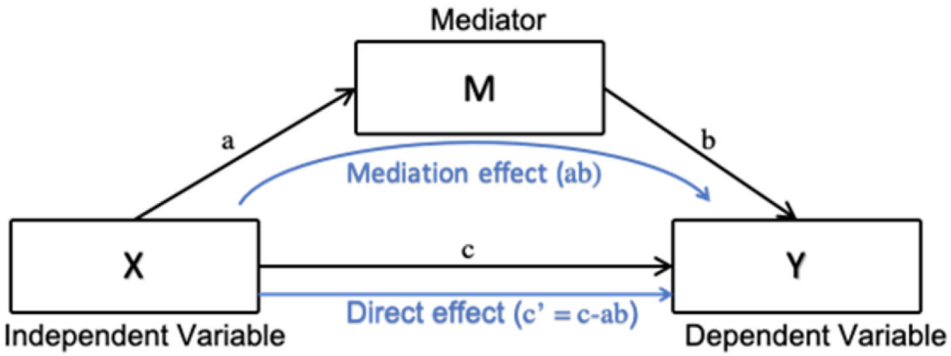
We investigated the association among acute and chronic musculoskeletal pain, sleep, and inflammation

Chronic pain was associated with higher CRP levels compared to both acute pain and the pain-free controls

Both acute and chronic pain was associated with a lower sleep score

CRP may partially mediate the association between chronic pain and decreased sleep score.

A



B

Groups of comparison	Independent variable (X)	Mediator (M)	Dependent Variable (Y)
Chronic Pain vs Controls	Pain	CRP	Sleep Score
Acute vs Chronic Pain	Pain	CRP	Sleep Score
Chronic Pain vs Controls	Sleep Score	CRP	Pain
Acute vs Chronic Pain	Sleep Score	CRP	Pain

Figure 1.

The schematic representation of mediation analysis (A), and the four mediation analyses we performed on sleep, pain, and CRP variables (B).

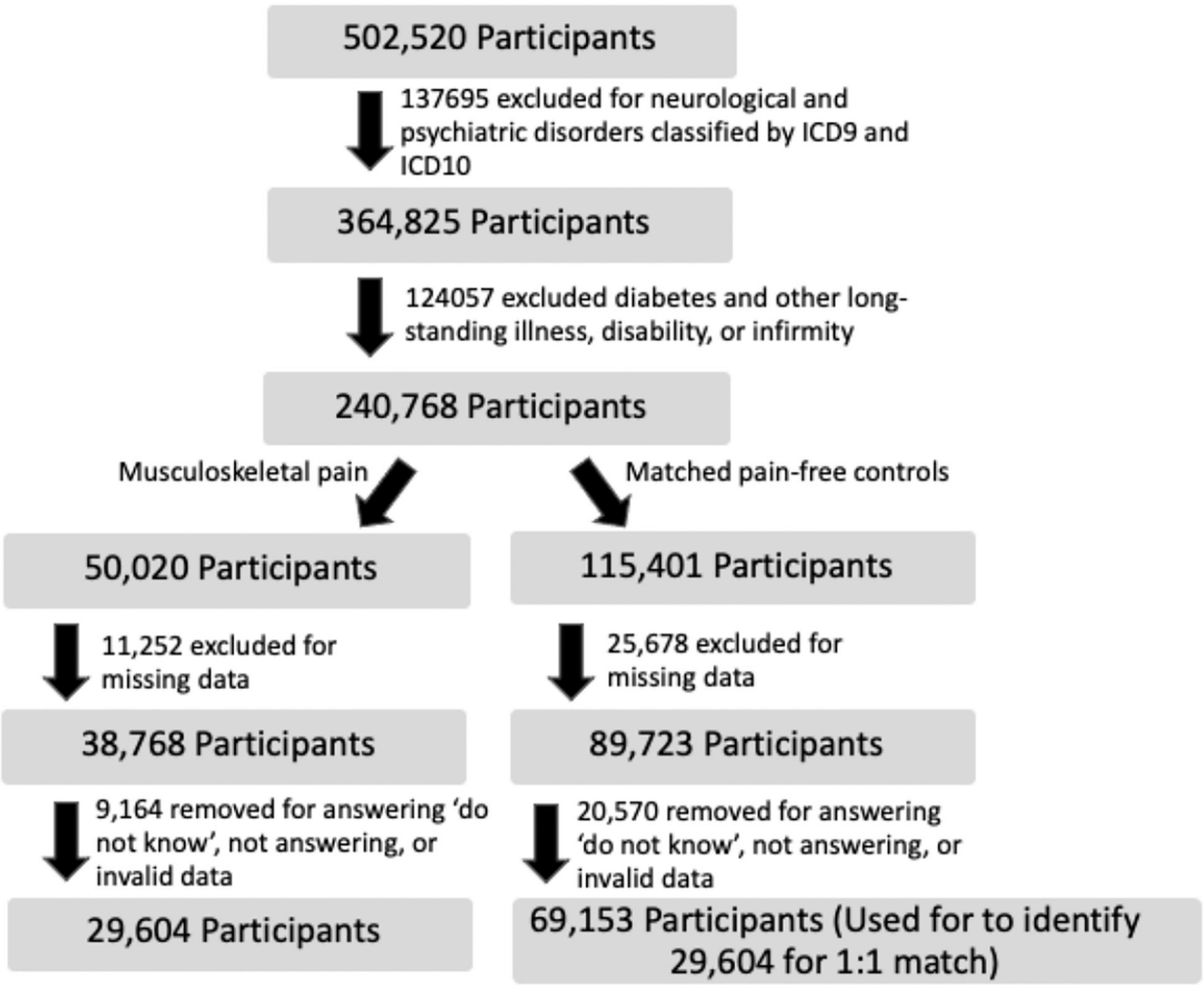


Figure 2.
Flow Chart of dropout and exclusion numbers

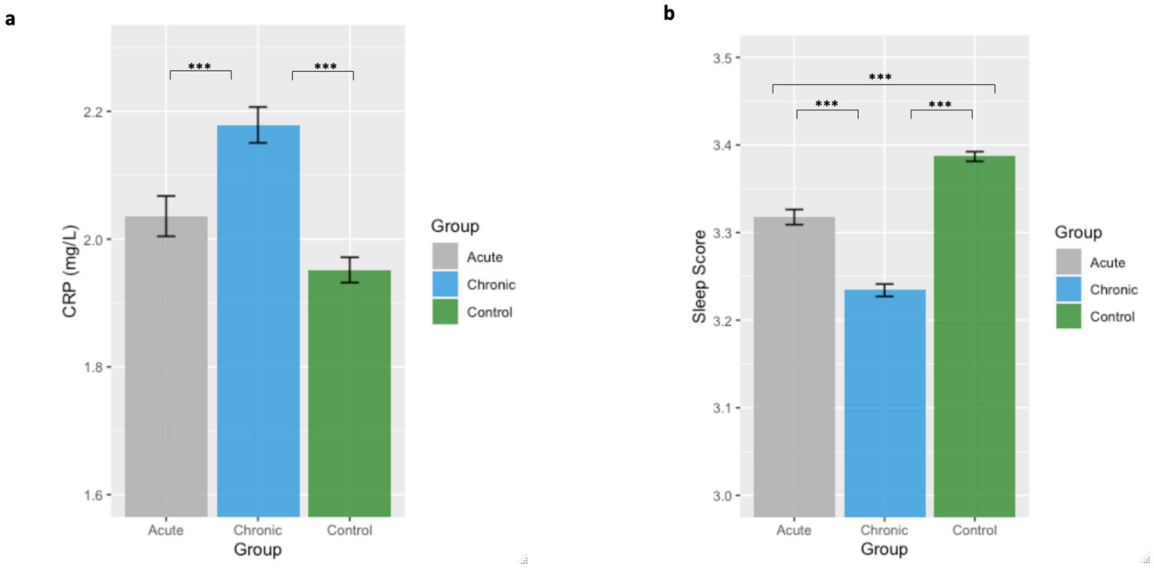


Figure 3.

Mean and standard errors of the mean for CRP (a) and sleep score (b) values for each group. Pain and control groups in each plot represent participants with the corresponding type of pain and their matched controls, respectively. Significance codes are: '***' ≤ 0.001; '**' ≤ 0.01; '*' ≤ 0.05.

Table 1

Group Characteristics. (mean ±SD)

Group	n	Age	Sex (female)	CRP (mg/L)	Sleep score
Chronic pain -initial assessment cohort	17642	56.24 ± 8.04	8586 (48.7%)	2.18 ± 3.73	3.23 ± 0.94
Acute pain -initial assessment cohort	11962	55.08 ± 8.21	5348 (44.7%)	2.04 ± 3.45	3.32 ± 0.95
Pain-free controls -- initial assessment cohort	29604	55.77 ± 8.13	13934 (47.1%)	1.95 ± 3.42	3.39 ± 0.94
Chronic pain – second visit assessment cohort	669	61.10 ± 7.40	303 (45.3%)	2.26 ± 4.98	3.25 ± 0.98
Acute pain – second visit assessment cohort	494	60.08 ± 7.84	207 (41.9%)	2.07 ± 4.56	3.30 ± 0.91
Pain-free controls – second visit assessment cohort	1163	60.67 ± 7.60	510 (43.9%)	1.85 ± 3.99	3.38 ± 0.91

Table 2

Mediation Analysis Results adjusting for sex, age, BMI, physical activity, smoking status, and income

Groups of comparison	Independent variable (X)	Mediator (M)	Dependent variable (Y)	Total effect (c)	Direct effect (c')	Mediation effect (ab)
Chronic Pain vs Controls	Pain	CRP	Sleep Score	0.129 [0.112, 0.15] ***	0.128 [0.111, 0.15] ***	2.65e-4 [9.31e-6, 0] *
Chronic Pain vs Controls	Sleep Score	CRP	Pain	0.035 [0.03, 0.04] ***	0.035 [0.03, 0.04] ***	7.23e-5 [6.63e-6,0] *
Acute vs Chronic Pain	Pain	CRP	Sleep Score	−0.074 [−0.095, −0.05] ***	−0.074 [−0.095, −0.05] ***	0.000 [−0.001, 0]
Acute vs Chronic Pain	Sleep Score	CRP	Pain	−0.021 [−0.003, −0.01] ***	−0.020 [−0.003, −0.01] ***	−5.25e-5 [−1.7e-4, 0]

Significance codes are:

*'***'* < 0.001;

*'**'* < 0.01;

''* < 0.05.

Table 3

Mediation Analysis Results adjusting for sex and age

Groups of comparison	Independent variable (X)	Mediator (M)	Dependent variable (Y)	Total effect (c)	Direct effect (c')	Mediation effect (ab)
Chronic Pain vs Controls	Pain	CRP	Sleep Score	0.153 [0.136, 0.17] ***	0.151 [0.133, 0.17] ***	0.002 [0.001, 0] ***
Chronic Pain vs Controls	Sleep Score	CRP	Pain	0.040 [0.036, 0.04] ***	0.04 [0.035, 0.04] ***	5.52e-4 [3.37e-4,0]
Acute vs Chronic Pain	Pain	CRP	Sleep Score	−0.084 [−0.107, −0.06] ***	−0.083 [−0.105, −0.06] ***	−0.001 [−0.002, 0] **
Acute vs Chronic Pain	Sleep Score	CRP	Pain	−0.023 [−0.028, −0.02] ***	−0.022 [−0.028, −0.02] ***	−2.98e-4 [−5.7e-4, 0] *

Significance codes are:

*'***'* < 0.001;

*'**'* < 0.01;

''* < 0.05.