Occupational Medicine 2021;**71:**422–428
Advance Access publication on 22 September 2021 https://doi.org/10.1093/occmed/kqab133

Shift work, inflammation and musculoskeletal pain—The HUNT Study

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Background	Studies have indicated that shift work, in particular night work, is associated with chronic musculoskeletal pain but the mechanisms are unclear. It has been suggested that sleep disturbance, a common complaint among shift and night workers, may induce low-grade inflammation as well as heightened pain sensitivity.
Aims	Firstly, this study was aimed to examine the cross-sectional associations between shift work, C-reactive protein (CRP) level and chronic musculoskeletal pain, and secondly, to analyse CRP as a mediator between shift work and chronic musculoskeletal pain.
Methods	The study included 23 223 vocationally active women and men who participated in the HUNT4 Survey of the Trøndelag Health Study (HUNT). Information was collected by questionnaires, interviews, biological samples and clinical examination.
Results	Regression analyses adjusted for sex, age and education revealed significant associations between shift work and odds of any chronic musculoskeletal pain (odd ratio [OR] 1.11, 95% confidence interval [CI] 1.04–1.19), between shift work and CRP level (OR 1.09, 95% CI 1.03–1.16) and between CRP level 3.00–10 mg/L and any chronic musculoskeletal pain (OR 1.38, 95% CI 1.27–1.51). Shift work and CRP were also associated with number of chronic pain sites. Mediation analysis indicated that shift work was indirectly associated with any chronic musculoskeletal pain through CRP (OR 1.03, 95% CI 1.01–1.06).
Conclusions	The results support the hypothesis that shift work is associated with chronic musculoskeletal pain, and that systemic inflammation may be a biological mechanism linking shift work to chronic pain.
Key words	C-reactive protein; HUNT; inflammation; musculoskeletal pain; shift work.

Introduction

The Global Burden of Disease Study has documented that musculoskeletal disorders (MSDs) are among the most significant contributors to disability with low back and neck pain being the leading causes [1]. The unfavourable consequences of MSDs for both individuals and society underscore the importance of identifying modifiable risk factors for these conditions. This can inform the development of evidence-based interventions and preventive measures that target factors known to cause chronic musculoskeletal pain.

Approximately one in four Norwegians are shift workers (working regularly outside daytime) and 1 in 10 have worked at night during the last 3 months [2]. However, few studies have examined the relationship between work schedule and chronic musculoskeletal pain. No clear trends were identified in a >10-year old review [3]. Shift work was, however, associated with development of low back pain in a longitudinal study [4].

Key learning points

What is already known about this subject:

- Shift work increases the risk of sleep disturbance, which in turn may increase the level of inflammatory markers.
- Some recent evidence supports the notion that inflammatory markers may play a role in the development of chronic musculoskeletal pain.
- Whether a low-level systemic inflammation mediates the association between shift work and chronic musculoskeletal pain remains to be studied.

What this study adds:

- Shift work is associated with chronic musculoskeletal pain and elevated systemic inflammation.
- Low-level systemic inflammation may be a biological mechanism linking shift work to chronic pain.

What impact this may have on practice or policy:

- Shift work should be considered as a potential risk factor for chronic musculoskeletal pain.

Furthermore, cross-sectional studies indicate that shift work is associated with common pain conditions, such as back pain [5].

The putative causal path between adverse working hours and chronic musculoskeletal pain may be through sleep disturbance [6], as night work and early-morning shifts disrupt the normal sleep–wake cycle [7]. It has been suggested that sleep disturbance increases the level of inflammatory mediators as well as pain sensitivity [8]. Such inflammatory mediators include C-reactive protein (CRP), which is associated with systemic inflammation [9,10]. Recent studies have documented a synergistic effect of insomnia and CRP on risk of chronic musculoskeletal pain [11,12], supporting the notion that inflammatory markers may play a role in the development of chronic musculoskeletal pain.

The aim of this study was to investigate the putative association between shift work, chronic musculoskeletal pain and inflammation in a general working population. First, we examined the cross-sectional associations between shift work, CRP level and chronic musculoskeletal pain. Second, we determined whether data were consistent with an effect of shift work on pain being mediated by CRP. We hypothesized that (i) both shift work and CRP level are associated with chronic musculoskeletal pain and (ii) that an elevated CRP level mediates the association between shift work and chronic musculoskeletal pain.

Methods

All inhabitants aged 18 years or older residing in Nord-Trøndelag County in Norway were invited to participate in the Trøndelag Health Study (The HUNT Study), conducted in 2017–2019. A total of 103 800 people were invited to participate in the HUNT4 Survey. Information on lifestyle and health-related factors were collected by questionnaires, interviews, biological samples and a clinical examination. More detailed information about the HUNT Study can be found at http://www.ntnu.edu/hunt. The study was approved by the regional ethical committee (REK sør-øst A, approval no. 10950).

In the interview, participants reported their work schedule by answering an initial question and two conditional follow-up questions: 'Do you work shifts?' with response options 'Yes', 'No' and 'Do not know'. If 'Yes', participants were asked 'How many hours is a regular working day/shift?' (reported on a continuous scale), and 'Does your shift sometimes start between 04 and 06 in the morning?', with response options 'Yes' and 'No'. Based on this information, we constructed three binary variables: one primary shift work variable (response 'Yes') and two secondary shift work variables—long shift (regular working day/shift ≥12 h) and early start (response 'Yes').

The questionnaire about musculoskeletal symptoms was adopted from the Standardized Nordic Questionnaire [13]. Participants were defined to have any chronic musculoskeletal pain if they answered 'Yes' to the following question: 'During the last year, have you had pain in your muscles and/or joints that lasted for at least 3 consecutive months?' This was the primary outcome variable. Participants answering 'Yes' were also asked to indicate the affected body area(s), i.e. neck, jaw, shoulder, chest, upper back, elbow, lower back, wrist/fingers, thighs, legs, hips, knees and ankles/feet. We included number of pain sites (NPS) as a secondary outcome variable. We opted not to perform separate analyses for each pain site, as this was the outside the scope of the study.

Non-fasting serum samples were obtained from all participants and high-sensitivity CPR (hsCRP) was analysed by latex immunoassay methodology reagent kit 6K26-41 MULTIGENT CRP (Abbot, Clinical Chemistry, USA). The measurement range was from 0.1 to 160 mg/L, after automated dilution 1:10 up to 1600 mg/L. Detection limits: 0.1–160 mg/L. Analytical coefficient of variation (CV): 2.4% in the low range and 1.1% in the high range. The continuous variable hsCRP was used to construct a variable with three categories: hsCRP < 1.00 mg/L,

hsCRP 1.00–2.99 mg/L and hsCRP ≥ 3.00 mg/L. These levels have been associated with different levels of disease risk [14]. Categorization of CRP was done to assess effects at each of the three clinically relevant levels of CRP and to highlight any potential non-linear associations.

As covariates, we included age (continuous), sex (male/female) and education, which was assessed by the question 'What is your highest level of education?' with the following response options: 'Primary or secondary school', '1−2 years Senior high school', 'High school', 'Technical school, vocational school', 'University/university college <4 years' and 'University/university college ≥4 years'. Education was analysed as an ordinal variable.

Associations were analysed with binary logistic regression when any chronic musculoskeletal pain was the dependent variable, with ordinal regression when hsCRP category was the dependent, and with negative binomial regression when NPS was the dependent. Negative binomial regression was chosen over Poisson regression, since NPS was over-dispersed (variation higher than mean). For binary logistic regression and ordinal regression models, the estimates were presented as odds ratios (ORs). For negative binomial regression, the estimates were presented as incidence risk ratios (IRRs). The precision of the estimates was presented as 95% confidence intervals (CIs). The proportional odds assumption was met for ordinal logistic regression (Brant test in R).

Mediation analysis was performed on the primary shift work variable, to test the hypothesis that an association of shift work with pain is associated with hsCRP. It should be noted that mediation analysis in cross-sectional data cannot infer causality, and interpretations of the results should take this into account. Using the statistical tests described above, a four-step procedure was followed [15]. First, we tested the association between shift work and pain, second between shift work and hsCRP category. Third, we tested the association between hsCRP category and pain, and finally the association between shift work on pain, while controlling for hsCRP. Hence, a comparison was made between the indirect effect (the association between shift work and pain through CRP) and the direct effect (the association between shift work and pain after controlling for CRP). Analyses are presented as age-adjusted and multi-adjusted (age, sex and education). Excluding participants with CRP level >10 mg/L may be criticized [16]. Therefore, a sensitivity analysis was performed, running all analyses also including the 750 participants with CRP level >10 mg/L.

All statistical analyses were performed in R (version 3.6.3).

Results

Of the invited participants, 56 042 (54%) took part. In the current study, we used data from the 31 401 participants aged 18–70 years who reported to be working full-time. Firstly, we excluded participants with incomplete information on chronic musculoskeletal complaints (n = 8074), shift work (n = 27) or education (n = 109). No participants had missing measurements of hsCRP. Secondly, we excluded participants with hsCRP values >10 mg/L (n = 785), i.e. participants who were likely to suffer from an acute inflammatory condition. The analysis was therefore based on information from 23 223 participants. Table 1 shows the characteristics of the study population, stratified by shift work. The proportion of participants reporting shift work was 22%. The shift work group had a higher proportion of women, approximately 3 years lower mean age, and lower proportion with higher education. The proportion of shift workers regularly working ≥12 h/day was 11% and the proportion regularly starting work between 04 and 06 in the morning was 80%. The proportion of participants reporting any chronic pain was 48% in the group without shift work and 51% in the group with shift work.

Table 2 shows the associations between shift work, CRP and pain from separate regression analyses. The primary analyses showed that shift work was associated with increased risk of any chronic musculoskeletal pain (OR 1.11, 95% CI 1.04–1.19) and increased NPS (IRR 1.07, 95% CI 1.01–1.12). Shift work was also associated with CRP level (OR 1.09, 95% CI 1.03–1.16), not shown in table. CRP levels 1.00–2.99 and 3.00–10.00 mg/L were associated with an elevated risk for any chronic musculoskeletal pain (OR 1.12, 95% CI 1.05–1.20 and OR 1.38,

Table 1. Characteristics of the study population (N = 23 223), by shift work group

	No shift work group	Shift work group
N (%)	18 132 (78)	5091 (22)
Female, n (%)	9923 (55)	3183 (63)
Age, mean (SD)	48.2 (12)	45.4 (12.9)
Higher education, n (%)[a]	9153 (50)	2174 (43)
Long shifts, n (%)[b]		580 (11)
Early starts, n (%)		4069 (80)
hsCRP (mg/L), mean (SD)	1.67 (1.78)	1.82 (1.93)
hsCRP category, n (%)		
<1.00 mg/L	8866 (49)	2376 (47)
1.00–2.99 mg/L	6403 (35)	1790 (35)
3.00–10.00 mg/L	2863 (16)	925 (18)
Any chronic pain, n (%)	8755 (48)	2587 (51)
NPS, n (%)		
0	9392 (52)	2515 (49)
1	1945 (11)	516 (10)
2	1857 (10)	498 (10)
3	1462 (8)	483 (9)
4	1133 (6)	340 (7)
5–13	2343 (13)	739 (15)

[a]College or higher.
[b]Regularly working ≥12 h/day.

Table 2. Separate regressions with shift work and CRP level as independent variables and any chronic musculoskeletal pain or NPS as dependent variables.

			Any chronic musculoskeletal pain			NPS		
	No. persons	No cases	Age-adjusted	Multi-adjusted		Age-adjusted	Multi-adjusted	
			OR[a]	OR[b]	95% CI	IRR[a]	IRR[b]	95% CI
Primary analyses								
No shift work	18 132	8755	1.00 (ref.)	1.00		1.00 (ref.)	1.00	
Shift work	5091	2587	1.18	1.11	1.04–1.19	1.13	1.07	1.01–1.12
CRP < 1.00 mg/L	11 242	5123	1.00 (ref.)	1.00	(ref.)	1.00 (ref.)	1.00	(ref.)
CRP 1.00–2.99 mg/L	8193	4157	1.15	1.12	1.05–1.20	1.16	1.14	1.09–1.20
CRP 3.00–10.00 mg/L	3788	2062	1.49	1.38	1.27–1.51	1.42	1.33	1.25–1.43
Secondary analyses								
Shift work without long shift	4511	2424	1.00 (ref.)	1.00		1.00 (ref.)	1.00	
Shift work with long shift	580	120	0.85	0.99	0.82–1.19	0.76	0.94	0.81–1.08
Shift work without early start	1022	2080	1.00 (ref.)	1.00		1.00 (ref.)	1.00	
Shift work with early start	4069	505	0.89	0.97	0.84–1.13	0.87	1.01	0.90–1.14

[a]Adjusted for age.
[b]Adjusted for age, sex and education.

Table 3. Results from mediation analysis showing direct effects (shift work–pain) and indirect effects (shift work–CRP–pain)

			Any chronic musculoskeletal pain			NPS		
	No. persons	No cases	Age-adjusted	Multi-adjusted		Age-adjusted	Multi-adjusted	
			OR[a]	OR[b]	95% CI	IRR[a]	IRR[b]	95% CI
Direct effect	23 223	11 342	1.20	1.12	1.03–1.23	1.14	1.07	1.00–1.16
Indirect effect, CRP <1.00 mg/L	11 242	5123	1.00 (ref.)	1.00	(ref.)	1.00 (ref.)	1.00	(ref.)
Indirect effect, CRP 1.00–2.99 mg/L	8193	4157	1.02	1.01	1.00–1.03	1.02	1.01	1.00–1.03
Indirect effect, CRP 3.00–10.00 mg/L	3788	2062	1.06	1.03	1.01–1.06	1.05	1.03	1.01–1.05

[a]Adjusted for age.
[b]Adjusted for age, sex and education.

95% CI 1.27–1.51, respectively). Similarly, CRP levels 1.00–2.99 and 3.00–10.00 mg/L were associated with NPS (IRR 1.14, 95% CI 1.09–1.20 and IRR 1.33, 95% CI 1.25–1.43, respectively). The secondary analyses showed that there was no association between working long shifts or early morning starts with any chronic musculoskeletal pain or NPS.

Table 3 shows the associations between shift work and pain after adjusting for CRP (direct effects) and the associations between shift work and pain through CRP (indirect effects). Shift work was indirectly associated with any chronic musculoskeletal pain through CRP levels 1.00–2.99 and 3.00–10.00 mg/L (OR 1.01, 95% CI 1.00–1.03 and OR 1.03, 95% CI 1.01–1.06, respectively). Similarly, shift work was indirectly associated with NPS (IRR 1.01, 95% CI 1.00–1.03 and IRR 1.03, 95% CI 1.01–1.05, respectively). Shift work was also directly associated with any chronic musculoskeletal pain (OR 1.12, 95% CI 1.03–1.23) and with NPS (IRR 1.07, 95% CI 1.00–1.16), indicating partial mediation.

Excluding participants with CRP level >10 mg/L did not alter the main findings (not shown in tables).

Discussion

Shift work and CRP were independently associated with chronic musculoskeletal pain and NPS in this cross-sectional study. The mediation analysis supported the notion that CRP to some extent mediates the effect of shift work on chronic pain, although the effect sizes were small. Shift work including long working hours or early-morning shifts were not associated with pain.

This study has both strengths and limitations. A major strength is the sample size with few exclusion criteria, rendering a presumably highly representative sample of the Norwegian working population that may have relatively

high external validity in other countries with similar working life characteristics. It should be mentioned that having few exclusion criteria also may be a limitation, as musculoskeletal pain (and CRP) is sensitive also to other influences across the lifespan. When deciding not to have more strict exclusion criteria, it is under the assumption that stricter criteria also may introduce bias, e.g. by removing individuals most vulnerable for shift work. Another limitation is the study's cross-sectional nature, which may increase the risk of common method bias [17]. This seems particularly likely if the study hypothesis is not hidden from the participants. In the present study, the latter risk was potentially reduced since the shift work questions were asked in an interview separately from the remaining questions on musculoskeletal pain. Also, CRP was not measured with self-report. Another limitation is that mediation analysis in cross-sectional data cannot infer causality. A further limitation is the lack of exposure detail regarding shift work and other work characteristics, such as occupation, physical exposure or psychosocial exposure at work, that may affect the risk for musculoskeletal pain. It is not known what criteria the respondents put into the 'shift work' question, being it all non-daytime work, night shifts, etc. Also, it is possible that the relatively small effect sizes come from unknown sub-populations within the large sample size, where different effects may cancel each other out. The accumulated number of years in shift work was also unknown in the present study and thereby a possible bias in our results due to a healthy worker effect (i.e. underestimation of associations). Accumulating shift work over many years has been suggested to be associated with CRP [18], information that unfortunately was not available.

The present study found that shift work was associated with chronic pain and with NPS. This finding partly corroborates results from other cross-sectional studies of MSDs among nurses [5,19]. Also, prospective studies have indicated that shift or night work may increase the risk of low back pain [4,20]. Not only chronic, but also episodic pain seems to be affected by non-daytime working hours. After night shifts, nurses reported higher levels of headache and musculoskeletal pain in a within-subject design [21], comparing pain intensity after sleeping at night to pain intensity after night shifts. Volunteer subjects also exhibited increased experimental pain sensitivity after night shifts [22,23]. However, results from other studies conflict with our results. A recent large working-population prospective study did not find that shift work predicted chronic pain 7 years after the baseline survey [24]. Also, cross-sectional data from a nursing population indicate that headache or musculoskeletal pain complaints do not differ between shift workers and day only workers [25,26]. In summary, most of these studies found evidence of an association between shift work and pain complaints. The two studies that did not find an association were based on the same cohort. Healthy worker effects may party explain such negative findings. Other challenges in interpreting and comparing these findings may stem from differences in assessment of exposure and outcome. Neither shift work nor chronic pain are unequivocal terms.

We found modest degree of evidence consistent with an effect of shift work on chronic musculoskeletal pain being partially mediated by CRP. However, the association was stronger with higher CRP levels, potentially indicating a dose–response. An association between shift work and CRP corroborates previous cross-sectional findings among airline pilots, showing that two-shift (day and evening) and three-shift (day, evening, night) work were associated with increased systemic inflammation [27], as well as studies suggesting circadian misalignment may increase CRP levels [28]. Seemingly in disagreement with the current results, a previous study by Christensen *et al.* [24] reported no effect of shift work through CRP on chronic musculoskeletal pain measured 7 years later. However, cross-sectional analyses from the same study, and from another large working-population study [11], did find direct effects of CRP on low back pain. This finding is also supported by a recent systematic review [29]. Skarpsno *et al.* [12] did not find an association between CRP and chronic musculoskeletal pain measured 7 years later. This may suggest that an elevated CRP level does not have long-lasting consequences on risk of chronic musculoskeletal pain. The optimal time span for studying these associations prospectively is not known, which could explain some of the discrepancies of the present study with previous prospective studies.

Although the present study cannot determine a causal association between shift work and chronic musculoskeletal pain, the analyses indicate that a low-grade systemic inflammation is a potential mechanism that should be investigated further. There is also a lack of knowledge on the dose–response association, regarding shift work and pain. For this purpose, more precise exposure variables of actual working time patterns, e.g. register-based from workforce management systems, may be useful [30]. For clinicians, shift work should be considered as a potential risk factor for chronic musculoskeletal pain; knowledge that is useful also for policy makers.

The results from the current study among a Norwegian working population support the hypothesis that shift work is associated with increased odds of chronic musculoskeletal pain, and that systemic inflammation may be a biological mechanism linking shift work to chronic pain, although the effect sizes were small. Shift work with long working hours or early-morning shifts did not seem to be associated with chronic pain.

Acknowledgements

The Trøndelag Health Study (HUNT) is a collaboration between HUNT Research Centre (Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology [NTNU]), Trøndelag County Council, Central

Norway Regional Health Authority, and the Norwegian Institute of Public Health.

Competing interests

None declared.

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