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# The interplay between sleeplessness and high-sensitivity c-reactive protein on risk of chronic musculoskeletal pain. Longitudinal data from the Tromsø Study

Eivind Schjelderup Skarpsno[1,2], Paul Jarle Mork[1], Tom Ivar Lund Nilsen[1,3], Ólöf Anna Steingrímsdóttir[4], John Anker Zwart[5,6,7], Kristian Bernhard Nilsen[5,6,8]

[1]Department of Public Health and Nursing, Norwegian University of Science and Technology (NTNU), Trondheim, Norway, [2]Department of Neurology and Clinical Neurophysiology, St. Olavs Hospital, Trondheim, Norway, [3]Clinic of Anaesthesia and Intensive Care, St Olavs Hospital, Trondheim University Hospital, Trondheim, Norway, [4]Division of Mental and Physical Health, Norwegian Institute of Public Health, [5]Department of Neurology, Oslo University Hospital, [6]Research and Communication Unit for Musculoskeletal Health (FORMI), Oslo University Hospital, Oslo, Norway, [7]Faculty of Medicine, University of Oslo, Oslo, Norway, [8]Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology (NTNU), Trondheim, Norway

Corresponding author:

Eivind Schjelderup Skarpsno, Department of Public Health and Nursing, Norwegian University of Science and Technology (NTNU), 7491 Trondheim, Norway.

E-mail: eivind.s.skarpsno@ntnu.no

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ABSTRACT

*Study Objectives* To examine independent associations of sleeplessness and high-sensitivity C-reactive protein (hsCRP) with risk of chronic musculoskeletal pain, and to explore the joint effect of sleeplessness and hsCRP on risk of chronic musculoskeletal pain.

*Methods* A population-based prospective study of 3,214 women and 3,142 men (mean age 55.4, range 32-87) without severe chronic musculoskeletal pain and with hsCRP ≤10 mg/L at baseline in 2007-2008. Modified Poisson regression was used to calculate adjusted risk ratios (RRs) with 95% confidence intervals (CIs) for any chronic musculoskeletal pain and chronic widespread pain (CWP) at follow-up in 2015-2016 associated with self-reported sleeplessness and hsCRP at baseline.

*Results* Compared to persons without sleeplessness, women and men reporting often/or always sleeplessness had RRs of CWP of 2.53 (95% CI 1.94-3.29) and 2.48 (95% CI 1.63-3.77), respectively. There was no clear association between hsCRP and risk of any chronic musculoskeletal pain or CWP. Joint effect analyses using persons without sleeplessness and with a hsCRP <1.00 mg/L as the reference gave RRs for chronic musculoskeletal pain of 1.73 (95% CI 1.26-2.37) for those with often/always sleeplessness and hsCRP <1.00 mg/L; 1.01 (95% CI 0.78-1.32) for those without sleeplessness and hsCRP ≥3.00 mg/L; and 2.47 (95% CI 1.79-3.40) if they had both often/always sleeplessness and hsCRP ≥3.00 mg/L. The corresponding RRs for CWP were 1.89 (95% CI 1.27-2.83), 0.96 (95% CI 0.68-1.37) and 2.83 (95% CI 1.1.91-4.20), respectively.

*Conclusions* These results suggest that there is an interplay between sleeplessness and hsCRP on risk of any chronic musculoskeletal pain and CWP.

Key words: sleep problems, insomnia, chronic musculoskeletal pain, inflammation, mechanisms, cohort studies, prospective, risk, epidemiology

## STATEMENT OF SIGNIFICANCE

The mechanisms underlying the association between sleeplessness and risk of any chronic musculoskeletal pain and chronic widespread pain (CWP) are not entirely clear; however, it has been suggested that elevated systematic inflammation in response to poor sleep can contribute to the development of pain. The results from this prospective study shows that low-grade systemic inflammation amplifies the adverse effect sleeplessness has on the risk of any chronic musculoskeletal pain and CWP. Thus, people with underlying systemic inflammations may be particularly vulnerable to the detrimental effects of sleeplessness. Low-grade systemic inflammation could be a mechanism linking sleeplessness to risk of chronic musculoskeletal pain, but elucidating this possible causal pathway requires data on the temporal relation between sleeplessness and inflammatory responses.

## INTRODUCTION

Chronic musculoskeletal pain and chronic widespread pain (CWP) are important causes of reduced quality of life, physical impairment, sick leave and years lived with disability[1-6] that leads to high economic costs.[2,6] Chronic pain is often defined as pain lasting more than three months during the past year, but both shorter and longer durations are used as criterion for chronicity guidelines.[7] A commonly used definition of CWP is pain located on the axial skeleton, both above and below the waist, and on the left and right sides of the body.[8,9] A recent meta-analysis reported a pooled prevalence of chronic pain of ~30% in the general population, with study-specific estimates ranging from 9% to 64%.[7] For CWP, it has been reported an overall prevalence of ~10%.[9] The high prevalence and the negative consequences of chronic musculoskeletal pain and CWP for affected individuals and society emphasize the importance of identifying modifiable risk factors and possible underlying mechanisms.

Sleep problems and chronic musculoskeletal pain are likely to be bi-directionally related,[10] i.e., chronic musculoskeletal pain is associated with risk of sleep problems[11] and vice versa.[12] Although longitudinal studies have shown that sleep problems are associated with increased risk of chronic musculoskeletal pain and CWP,[12-16] the mechanism underlying this association is not clear. Some studies have shown that sleep restriction induce an inflammatory response,[17,18] which may contribute to sensitization of the nociceptive system and thereby increase the susceptibility for developing chronic pain.[17] Inflammation can be assessed by measuring circulating levels of inflammatory markers such as tumor-necrosis-factor-α, interleukin-6 (IL-6), IL-1 , and high-sensitivity C-reactive protein (hsCRP).[19] Although clinically significant inflammation may be reflected by hsCRP levels above 10 mg/L,[20] there is a lack of studies examining whether there is an association between inflammation and chronic musculoskeletal

pain beyond the context of infectious and inflammatory diseases. Some cross-sectional studies have shown that low-grade systemic inflammation with hsCRP levels between 3-10 mg/L are associated with some chronic pain conditions[21-23] and elevated pain sensitivity.[24] However, prospective studies are needed to elucidate if a low-grade systemic inflammation increases the risk for chronic musculoskeletal pain or whether it develops secondary to pain. Exploring the long-term interplay between sleeplessness and low-grade systemic inflammation may therefore improve our understanding of the potential link between sleep problems and risk of chronic musculoskeletal pain

The aim of the current study was twofold. First, to examine the independent associations of sleeplessness and hsCRP on risk of chronic musculoskeletal pain, and second, to explore the joint effect of sleeplessness and hsCRP on risk of chronic musculoskeletal pain. We hypothesized that i) sleeplessness increases the risk of chronic musculoskeletal pain and CWP, and ii) that elevated hsCRP amplifies the adverse effect of sleeplessness on risk of chronic musculoskeletal pain and CWP. Further, since some evidence suggests that there exists sex-specific differences in the association between poor sleep and development of chronic pain,[25] we also explored the association between sleeplessness, hsCRP and risk of chronic musculoskeletal pain separately for women and men.

## METHODS

### Study population

The Tromsø Study is a longitudinal population-based cohort study carried out in the municipality of Tromsø (Norway). Based on the official population registry, residents of the municipality were invited to take part in the survey. The first survey (Tromsø 1) was conducted in 1974 and

have since then been repeated with 5- to 7-years intervals with the most recent in 2015-2016 (Tromsø 7). The aim was to include large, representative samples of the Tromsø population, with invitation of whole birth cohorts and random samples. Information on lifestyle and health-related factors was collected by questionnaires and clinical examinations. More detailed information about the Tromsø Study can be found elsewhere.[26]

Non-fasting blood samples were not included in Tromsø 1-5 and the current study is therefore based on information from Tromsø 6 (2007-2008) and Tromsø 7 (2015-2016). At Tromsø 6, 19,762 persons were invited, and 12,984 aged 30 to 87 years participated in the study. At Tromsø 7, 32,591 persons were invited and 21,083 (65%) aged 40 to 99 years participated. For the purpose of the current study, we selected 8,906 who participated at both Tromsø 6 and Tromsø 7. Of these, we excluded 2,083 persons who reported severe chronic musculoskeletal pain at baseline at Tromsø 6. Few participants had hsCRP values above 10 mg/L (n=229) and were excluded because this may indicate acute or chronic diseases. Further, we excluded participants who were underweight (n=30) or had incomplete information about frequency of sleeplessness (n=118). Of the remaining 6,446 persons, 6,356 persons (3,214 women and 3,142 men) answered relevant pain question at follow-up in Tromsø 7. Only participants with complete data on sleeplessness, hsCRP and chronic musculoskeletal pain were included in the current study.

This study was approved by the Regional Committee for Ethics in Medical Research (#2016/1997/Rek Sør-øst C and #2014/940/Rek Nord), and the Norwegian Data Protection Authority. The participants have given written informed consent. The study was carried out according to the Declaration of Helsinki.

**Chronic musculoskeletal pain**

At Tromsø 6 and Tromsø 7, chronic musculoskeletal pain was assessed by six questions, one for each of the following body regions: "neck/shoulder", "arm/hand", "upper back", "lower back", "hip/leg/feet" and "other regions". The participants were asked if they had suffered from pain and/or stiffness in muscles and joints in these body regions that lasted for at last three consecutive months the last year. The response options were: "no complaints", "mild complaints" and "severe complaints". Participants who reported "severe complaints" at baseline in Tromsø 6 were excluded from the study. At follow-up in Tromsø 7, any chronic musculoskeletal pain was defined as "severe complaints" in ≥1 body region while CWP was defined as "mild complaints" and/or "severe complaints" in all three of the following body regions: a) neck/shoulder/upper back/lower back, b) arm/hand and c) hip/leg/feet. To be defined with CWP, the participants had to answer "severe complaints" in at least one of the mentioned body regions (a, b, or c). Our definition of CWP approximates the 1990 criteria of the American College of Rheumatology,[8] i.e. pain being present in the axial skeleton, left and right sides of the body, and above and below the waist. In the current study, the participants were not asked specifically about having pain in both the left and right side of the body.

**Sleeplessness**

At Tromsø 6, frequency of self-reported sleeplessness was assessed by the question: "How often have you suffered from sleeplessness during the last 12 months?" with the response options: 1) "never, or just a few times a year", 2) "1-3 times a month", 3) "approximately once a week" and 4) "more than once a week". These response options were organized into "never/seldom" (never, or just a few times a year), "sometimes" (1-3 times a month or approximately once a week) and

"often/always" (more than once a week). The reported sleeplessness in the Tromsø 6 study may be considered a proxy for insomnia.[27] However, to avoid misunderstanding with studies using the more precise definition of insomnia, we choose to not substitute sleeplessness with insomnia in the present study.

**High-sensitivity C-reactive protein**

At Tromsø 6, non-fasting serum samples were drawn from all participants using a particle-enhanced immunoturbidimetric assay, on a Modular P autoanalyser (Roche Diagnostics, Mannheim, Germany) with reagents from the manufacturer with a detection limit of 0.12 mg/L. All analyses were analyzed at the Department of Laboratory Medicine, University Hospital of North Norway, Tromsø. We constructed a variable with three categories: "<1.00mg/L", "1.00-2.99 mg/L" and "≥3.00 mg/L", which has been associated with different levels of disease risk.[20,28] Participants with hsCRP values above 10 mg/L were excluded.

**Other variables**

Education was assessed by the question "What is your highest level of education?" with the response options "primary or 1-2 years secondary school", "vocational school", "high secondary school", "college/university <4 years", and "college/university ≥4 years". These response options were then classified as "primary or up to two years secondary school" (primary or 1-2 years secondary school), "upper secondary" (vocational school) and "college/university" (college/university <4 years, college/university ≥ 4 years). Smoking was assessed by the question "Do you/did you smoke daily?" with the response options "yes, now", "yes, previously" and "never". Standardized measurements of body height (to the nearest centimeter) and weight (to

the nearest half-kilogram) obtained at the clinical examination at Tromsø 6 was used to calculate body mass index (BMI). BMI was classified into three groups according to the cutoff points suggested by the World Health Organization[29]: normal weight (BMI: 18.5-24.9 kg/$m^2$), overweight (BMI: 25-29.9 kg/$m^2$) or obese (BMI: ≥30 kg/$m^2$). Habitual exercise level was assessed by the following three questions: 1) "How often do you exercise"? with the response options "never", "less than once a week", "once a week", "2-3 times a week", and "approximately every day", 2) "How hard do you exercise?" with the response options "no sweat or heavy breath", "heavy breath and sweat", and "push myself to exhaustion", and 3) "For how long time do you exercise?" with the response options "<15 min", "15-29 min", "30-60 min", and "more than 1 hour". These questions were then collapsed and defined according to the index developed by Nes and colleagues [30] and categorized into tertiles: "low", "moderate" and "high". To assess symptoms of anxiety and/or depression, the participants were asked a 10-items psychological health questionnaire (SCL-10) with response options on a four-points scale ranging from "not at all" to "extremely". Four items are related to anxiety while six items are related to depression. The scores were calculated as the mean value over all 10 items. As recommended, the cut-off score was set to ≥1.85 to indicate presence of anxiety and/or depression [31]. The participants were asked to answer if they worked in a shift work schedule during the past three months ("yes", "no"). To assess number of chronic somatic conditions, the participants were asked to indicate the presence (yes", "no") on the following conditions: asthma, cardiovascular conditions (stroke or angina pectoris), diabetes, hypothyroid, kidney disease, chronic bronchitis/emphysema/chronic obstructive pulmonary disease and hypertension. These answers were then summed and categorized into "zero", "one", "two", and "three or more". The participants were also asked to report use of painkillers on prescription, painkillers

on nonprescription and sleeping pills during the last 4 weeks, with the response options “not used”, “less than every week”, “every week, but not daily” and “daily”.

**Statistical analysis**

A modified Poisson regression model was used to estimate risk ratios (RRs) of any chronic musculoskeletal pain and CWP at follow-up in Tromsø 7 (2015-2016). Sleeplessness and hsCRP at baseline in Tromsø 6 (2007-2008) served as exposures. The precision of the RRs was assessed by 95% confidence intervals (CIs) using robust variance estimation. Participants who reported to have sleeplessness “sometimes” and “often/always” were compared to the reference group with sleeplessness “never/seldom”. Participants with hsCRP 3.00-10.00mg/L and hsCRP 1.00-2.99 mg/L were compared to the reference group with hsCRP <1.00 mg/L. All associations were stratified by sex and adjusted for age (continuous), education (primary or 1-2 years secondary school, upper secondary, college/university and unknown), smoking (never smoked, former smoker, current smoker, unknown), BMI (normal weight, overweight, obesity), and habitual exercise level (low, moderate, high, unknown). The independent association of hsCRP with any chronic musculoskeletal pain and CWP was also adjusted for sleeplessness (never/seldom, sometimes, often/always). Since it is more likely that sleeplessness induces an inflammatory response than vice versa, the independent association of sleeplessness with any chronic musculoskeletal pain and CWP was not adjusted for hsCRP.

We estimated the joint effect of sleeplessness and hsCRP on risk of any chronic musculoskeletal pain and CWP, using participants with hsCRP <1 mg/L who reported never/seldom sleeplessness as the reference group. The analysis of joint effect was conducted on a pooled sample adjusting for sex (women, men) in addition to all the potential confounders

described above. Potential effect modification between the variables was assessed as departure from additive effects by calculating the relative excess risk due to interaction (RERI). We calculated RERI estimates with 95% CIs from the following equation: $RERI=RR_{\text{sleeplessness (often/always) and hsCRP 3-10mg/L}} - RR_{\text{sleeplessness (often/always) and hsCRP <1mg/L}} - RR_{\text{sleeplessness (never/seldom) and hsCRP 3-10mg/L}} + 1$, i.e., RERI>0 indicates a synergistic effect beyond an additive effect.[32] For the calculation of confidence intervals, the covariance matrix for the regression coefficients was estimated. In order to obtain the correct estimates, the model was set up with indicator variables for each of the different combinations of exposure. More detailed information about the procedure can be found elsewhere.[32,33]

We conducted six sensitivity analyses to evaluate the robustness of the results. First, since several somatic conditions have been shown to be associated with inflammatory markers,[28,34-36] we repeated the main analysis adjusting for chronic somatic conditions (categorized as zero to three or more symptoms). Second, we performed an analysis including symptoms of anxiety and/or depression as a covariate in the regression model. Third, we repeated the main analysis adjusting for shiftwork. Fourth, we performed an analysis including use of painkillers and sleeping pills as covariates in the multi-adjusted models. Finally, because habitual exercise level had 9.9% missing compared to less than 1% in other covariates, we performed multiple imputations of habitual exercise level. In the multiple imputation model, we created 20 imputations and used ordered logistic regression for an ordinal variable. The predictors in the model were all variables used in the main analysis model (including the outcome variables). Furthermore, we performed complete case analyses excluding participants with missing values on physical exercise.

All statistical analyses were performed using Stata for Windows, version 15.1 (StataCorp LP, College Station, Texas).

## RESULTS

Table 1 presents the baseline characteristics of the study population stratified by sex and frequency of sleeplessness. A total of 504 (15.7%) women and 333 (10.6%) men reported any chronic musculoskeletal pain at follow-up (Tromsø 7). The corresponding numbers for CWP were 327 (10.2%) women and 198 (6.3%) men.

**Table 1.** Characteristics of the study population at baseline in 2007-2008 (n = 6,356) stratified by sex and sleeplessness

Table 2 shows the independent associations of sleeplessness and hsCRP at baseline (Tromsø 6) on risk of any chronic musculoskeletal pain and CWP at follow-up (Tromsø 7). Women and men who reported often or always sleeplessness had increased risk of any chronic musculoskeletal chronic pain, with RRs of 2.02 (95% CI 1.72-2.64) and 2.09 (95% CI 1.50-2.90), respectively, compared to women and men who reported sleeplessness never/seldom. The corresponding RRs for CWP were 2.53 (95% CI 1.94-3.29) and 2.48 (95% CI 1.63-3.77), respectively. There was no meaningful associations between hsCRP and any chronic musculoskeletal pain nor CWP.

**Table 2.** Risk of any chronic musculoskeletal pain and chronic widespread pain at follow-up (2015-2016) associated with sleeplessness and high-sensitivity c-reactive protein at baseline (2007-2008) stratified by sex

Table 3 shows the joint effect of sleeplessness and hsCRP at baseline (Tromsø 6) on risk of any chronic musculoskeletal pain and CWP at follow-up (Tromsø 7). Using persons without sleeplessness and with a hsCRP <1.00 mg/L as the reference gave RRs for any chronic musculoskeletal pain of 1.73 (95% CI 1.26-2.37) for those with often/always sleeplessness and hsCRP <1.00 mg/L; 1.01 (95% CI 0.78-1.32) for those without sleeplessness and hsCRP 3.00-10.00 mg/L; and 2.47 (95% CI 1.79-3.40) if they had both often/always sleeplessness and hsCRP 3.00-10.00 mg/L. The corresponding RRs for CWP were 1.89 (95% CI 1.27-2.83), 0.96 (95% CI 0.68-1.37) and 2.83 (95% CI 1.1.91-4.20), respectively. The RERI estimates for these association were 0.73 (95% CI -0.35 to 1.80) for any chronic pain and 0.98 (95% CI -0.45 to 2.41) for CWP. Although imprecise, this indicate interaction on an additive scale between frequency of sleeplessness and hsCRP with risk of any chronic musculoskeletal pain and CWP.

**Table 3.** Risk of any chronic musculoskeletal pain and chronic widespread pain at follow-up (2015-2016) associated with the joint effect of sleeplessness and high-sensitivity c-reactive protein at baseline (2007-2008)

*Supplementary analyses*

We also conducted several sensitivity analyses to assess the robustness of our findings. Including number of chronic somatic conditions and shift work in the regression model had negligible influence on the results. Adjusting for anxiety and/or depression had no influence on the independent association between sleeplessness and any chronic musculoskeletal pain and CWP among women, whereas the association was somewhat attenuated among men; i.e., compared to the reference group of men without sleeplessness, men who were often/always sleepless had RRs of any chronic musculoskeletal pain and CWP of 1.80 (95% CI 1.28-2.56) and 1.99 (95% CI

1.27-3.13), respectively. The joint effect of sleeplessness and hsCRP on risk of any chronic musculoskeletal pain and CWP was not influenced by the above adjustment. However, adjusting for use of painkillers and sleeping pills slightly attenuated the joint effects of sleeplessness and hsCRP. Compared to the reference group of persons without sleeplessness and hsCRP <1.00 mg/L, persons who were often/always sleepless and had hsCRP 3.00-10.00 mg/L had RRs of any chronic musculoskeletal pain and CWP of 2.04 (95% CI 1.41-2.94) and 1.96 (95% CI 1.25-3.09), respectively). Finally, complete case analyses and multiple imputations had only marginal influence on the estimated associations.

## DISCUSSION

The current study indicates a strong and positive association between self-reported sleeplessness and risk of any chronic musculoskeletal pain and CWP. The strength of the association was similar in women and men. Although we found no meaningful association between hsCRP and risk of chronic musculoskeletal pain, our analyses of joint effects show that elevated hsCRP amplify the adverse effect of sleeplessness on risk of any chronic musculoskeletal pain and CWP. Although the precision of the estimated excess risk due to interaction was low, our findings suggest that there is a synergistic effect between sleeplessness and hsCRP on risk of any chronic musculoskeletal pain and CWP that is beyond additivity.

Our finding of a strong and positive association between sleeplessness and development of any chronic musculoskeletal pain and CWP is in line with findings in other prospective studies.[12-16] For instance, a recent prospective study showed that results based on a definition which was a proxy for the 4$^{th}$ edition of the Diagnostic and Statistical Manual of Mental Disorders[37] insomnia diagnosis was strongly and positively associated with risk of CWP.[12]

Although our question on sleeplessness only allowed us to assess the frequency of experiencing sleeplessness we found a clear dose-response association. Women and men who experience sleeplessness 1-3 times a month up to once a week had ~60-80% increased risk while those who experience sleeplessness more than once a week have a more than twofold increased risk of any chronic musculoskeletal pain and CWP. Thus, our data underscore the importance of reducing both mild and severe sleeplessness in order to reduce the incidence of chronic musculoskeletal pain. One should however bear in mind that the different definitions of both sleep problems and chronic pain limit the possibility for a direct comparison with previous findings.

We are not aware of any previous study that has investigated whether individuals without chronic musculoskeletal pain along with elevated hsCRP are at increased risk of any chronic musculoskeletal pain and CWP. Cross-sectional studies have reported higher levels of hsCRP in persons with chronic pain conditions such as rheumatoid arthritis,[22] fibromyalgia[38] and chronic low back pain,[23] suggesting that hsCRP may represent a potential biomarker for increased risk of chronic pain. However, our results do not support the view that higher levels of hsCRP among persons without chronic musculoskeletal pain increase the risk of chronic musculoskeletal pain. We found a weak increased risk of CWP among men with hsCRP 3.00-10.00 mg/L but the CI was wide, and this result should therefore be interpreted with caution. It should also be noted that our definition of CWP included people with mild pain in up to two body regions.

Our analysis of joint effect showed that hsCRP may amplify the adverse effect of sleeplessness on risk of any chronic musculoskeletal pain and CWP. This result indicates an interplay between hsCRP and sleeplessness in the development of chronic pain. Although the underlying mechanism for this association is unclear, it has been suggested that an inflammatory response provides a pathway between poor sleep and increased pain.[17] Disturbed sleep and short

sleep duration may induce an inflammatory response[39,40] that sensitize sensory neurons.[41] Moreover, one study showed that people with elevated hsCRP have increased pain sensitivity.[24] However, the latter study did not examine the influence of sleep on this association. It is therefore conceivable that sleeplessness induces a low-level systemic inflammation that sensitizes peripheral and central pain processing. This hypothesis is supported by studies suggesting that up-regulation of pro-inflammatory cytokines are linked to progression of chronic pain [42-44] and pain intensity.[45] Further, people with sleep problems are more likely to develop mood disorders,[46] which in turn may increase the levels of pro-inflammatory cytokines.[47] If sleeplessness is associated with mood disruption, and in turn, mood disruption is associated with a low-level systemic inflammation, then a credible hypothesis is that mood disruption represents a downstream mediator on the association between sleeplessness and systemic inflammation. To summarize, there is a lack of studies examining the interplay between sleeplessness and low-grade inflammation on the risk of chronic musculoskeletal pain. The current study extends therefore on previous findings by showing that in pain-free people with sleeplessness, increased hsCRP may be involved in the development of chronic musculoskeletal pain. Our findings, together with previous experimental studies, therefore suggest that individuals with sleep problems and a low-graded systemic inflammation are more susceptible to develop chronic musculoskeletal pain.

Strengths of the current study include the prospective design along with available information about several potential confounders. Further, we had a sufficiently large sample to perform analyses of the joint effect of sleeplessness and hsCRP. Some limitations should be considered in the interpretation of the results. First, we were not able to classify CWP as pain in both the left and right side of the body and our classification of CWP pain is therefore different

from the 1990 criteria of the American College of Rheumatology.[8] However, diagnosis criteria of CWP remains controversial even though different diagnostic criteria have been developed.[8,48,49] Moreover, our classification of CWP includes mild pain in one or two body regions. Second, although we excluded persons with severe chronic pain at baseline, it is possible that persons with mild pain in one or more body locations at baseline were included in our study population. Third, it should be noted that our definition of chronic musculoskeletal pain includes both pain and/or stiffness in muscles and joint. Thus, differences in the pathophysiology of stiffness and pain should be considered in the interpretation of the study. Fourth, assessment of sleeplessness was based on self-report, and future studies should therefore include objective measures of sleep. Fifth, frequency of sleeplessness was assessed by a single question and we have no detailed information about actual sleep time, problems initiating sleep, nocturnal awakenings, early awakenings or daytime sleepiness. Further, our question do not capture whether sleeplessness occur regardless of the presence of a coexisting mental or medical conditions. It should be noted that sleeplessness and hsCRP were measured at the same time, and it is therefore uncertain whether elevated hsCRP is a consequence of sleeplessness or if it develops secondary to these symptoms. Unfortunately, we were unable to examine whether changes in sleeplessness and hsCRP during the follow-up influence the risk of chronic musculoskeletal pain and CWP. Longitudinal studies with repeated measurements are therefore needed to examine if sleeplessness is associated with elevated hsCRP and if inflammation due to sleeplessness is causally linked to risk of chronic musculoskeletal pain. Finally, it should be noted that some of the categories of the joint variable had low statistical power due to few people, thereby increasing the probability that random error has influenced our results.

In conclusion, this prospective study shows that sleeplessness is strongly associated with increased risk of chronic musculoskeletal pain and CWP in women and men. There was no clear independent association between hsCRP and risk of chronic musculoskeletal pain but elevated hsCRP amplified the adverse effect of sleeplessness on the risk of chronic musculoskeletal pain. These findings suggest that pain-free individuals with sleeplessness and low-grade systemic inflammation are more susceptible to develop any chronic musculoskeletal pain and CWP.

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