Sleep problems and pain represent major public health concerns. In addition to being highly prevalent, both conditions have been shown to be persistent and recurrent,17,31 resulting in substantial societal costs.1,5,15,20,26,45 The link between sleep and pain has been investigated extensively over the past few decades. Evidence from both clinical and epidemiological studies shows that individuals with chronic pain are also likely to have a range of sleep problems.19,32,44 Although the direction of causality is not entirely clear, and is most likely bidirectional, several lines of evidence point to sleep problems as the primary antecedent factor. This includes evidence that insomnia exacerbates existing pain and predicts new-onset pain,5,25,35,46 as well as studies demonstrating that sleep quality predicts pain severity the next day.

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

Abstract
Sleep problems and pain are major public health concerns, but the nature of the association between the 2 conditions is inadequately studied. The aim of this study was to determine whether a range of sleep measures is associated with experimental increased pain sensitivity. A cross-sectional large population-based study from 2007 to 2008, the Tromsø 6 study, provided data from 10,412 participants (age: mean [SD], 58 [13] years; 54% women). Self-reported sleep measures provided information on sleep duration, sleep onset latency (SOL), and sleep efficiency, as well as frequency and severity of insomnia. The main outcome measure was pain sensitivity tests, including assessment of cold-pressor pain tolerance. We found that all sleep parameters, except sleep duration, were significantly associated with reduced pain tolerance. Both the frequency and severity of insomnia, in addition to SOL and sleep efficiency, were associated with pain sensitivity in a dose–response manner. Adjusting for demographics and psychological distress reduced the strengths of the hazard ratios, but most associations remained significant in the fully adjusted models. There was also a synergistic interaction effect on pain tolerance when combining insomnia and chronic pain. We conclude that sleep problems significantly increase the risk for reduced pain tolerance. Because comorbid sleep problems and pain have been linked to elevated disability, the need to improve sleep among patients with chronic pain, and vice versa, should be an important agenda for future research.

Keywords: Epidemiology, Sleep, Pain sensitivity

1. Introduction
Sleep problems and pain are major public health concerns. In addition to being highly prevalent, both conditions have been shown to be persistent and recurrent,17,31 resulting in substantial societal costs.1,5,15,20,26,45 The link between sleep and pain has been investigated extensively over the past few decades. Evidence from both clinical and epidemiological studies shows that individuals with chronic pain are also likely to have a range of sleep problems.19,32,44 Although the direction of causality is not entirely clear, and is most likely bidirectional, several lines of evidence point to sleep problems as the primary antecedent factor. This includes evidence that insomnia exacerbates existing pain and predicts new-onset pain,5,25,35,46 as well as studies demonstrating that sleep quality predicts pain severity the next day.

Although there is clearly a strong relationship between pain and sleep, such that insomnia increases both the likelihood and severity of clinical pain, it is not clear exactly why this is the case. Specifically, it is not known whether insomnia increases pain by exacerbating conditions that cause pain, for instance through immunological changes causing muscle and joint soreness, or whether poor sleep quality affects pain processing more directly by sensitizing peripheral nociceptors and/or by affecting central inhibitory and facilitating mechanisms, causing a state of generalized hyperalgiesia. Attempts have been made to investigate this issue by assessing pain sensitivity with experimental pain stimuli before and after sleep deprivation. Unfortunately, these studies have all been very small (n ≤ 20) and results have been equivocal.8,12,21,24,27,28,36,39,42 To the best of our knowledge, only 1 epidemiological study has examined the relationship between sleep and experimental pain sensitivity.8 In this study of 424 subjects, pain thresholds were significantly lower among those reporting the highest level of sleep problems. However, as pain thresholds were measured with pressure stimuli applied at fibromyalgia tender points, it is not clear whether the finding reflects muscle tenderness or generalized hyperalgiesia.

Furthermore, very few studies have examined sleep parameters beyond experimental sleep restriction/deprivation. Whether pain sensitivity is also related to sleep factors such as sleep duration or symptoms of insomnia has not yet been investigated. Finally, previous studies have not controlled for potential confounding demographic factors and emotional distress. Therefore, the aims of this study were (1) to determine the association between pain sensitivity and a range of sleep parameters in a large population-based sample; and (2) to further investigate the relationship between pain and sleep by examining the joint or synergistic association of insomnia and chronic pain on pain sensitivity.
2. Methods

2.1. Participants and study procedure

This study was conducted as part of the sixth Tromsø study. The Tromso study started in 1974 and has been repeated with 5- to 7-year intervals since then. The sixth wave (Tromsø 6, 2007-2008) included a questionnaire screening of chronic pain and sleep, as well as an examination of pain sensitivity with experimental pain stimuli of adult residents in Tromsø, Norway. Details of the study protocol have been reported elsewhere. In short, a total of 12,984 participants (ages, 30-87 years; median, 58 years; 53.4% women) completed a health questionnaire (response rate 66%) and were further invited to participate in a physical and medical examination.

Before the pain sensitivity testing, participants underwent a brief screening interview and visual inspection of their hands. Participants were excluded if they (1) were unable to understand the test instructions (eg, dementia, language difficulties), (2) had health conditions that would interfere with the testing (open sores, amputations, etc), or (3) reported a lack of sensation or abnormal sensation in their hands. In addition, subjects were excluded from the pain sensitivity testing if they reported health issues in which previous experience indicated that cold exposure might lead to undesirable side effects. More details regarding the cold-pressor procedure have been reported elsewhere. The final sample included 10,412 participants with valid data on both the sleep and pain sensitivity variables.

2.2. Instruments

2.2.1. Sleep variables

Frequency of self-reported insomnia during the last year was assessed using a 4-point Likert scale with the following response options: (1) “never, or just a few times a year,” (2) “1 to 3 times a month,” (3) “approximately once a week,” and (4) “more than once a week.” Insomnia severity was assessed on a 4-point Likert scale with the following response options: (1) “no complaint,” (2) “little complaint,” (3) “pretty much,” and (4) “very much.” A dichotomous variable (labeled “insomnia disorder”) was created using both the frequency and severity items. Participants were classified as positive for insomnia disorder if they reported either “very much” or “pretty much” on the insomnia severity item and also reported their insomnia frequency to be “more than once a week.” If the responses did not meet these criteria, they were coded negative for insomnia disorder.

Self-reported bedtime and rise time were indicated in hours and minutes and were reported separately for weekend and weekdays (only weekdays sleep data were used in this study). Time in bed (TIB) was calculated by subtracting bedtime from rise time. Sleep onset latency (SOL) was indicated in hours and minutes, and in addition to being used continuously, a 4-point categorical variable was also created: (1) “less than 15 minutes,” (2) “15 to 29 minutes,” (3) “30 to 59 minutes,” and (4) “greater than 60 minutes.” Time from last awakening to getting out of bed (GOB) in the morning was also reported. Sleep duration was defined as TIB minus (SOL + GOB). For the purpose of this study, sleep duration was also split into 5 categories (less than 5 hours, 5:00-5:59 hours, 6:00-6:59 hours, 7:00-7:59 hours, greater or equal to 8 hours). Sleep efficiency was calculated as sleep duration divided by TIB multiplied by 100 (reported as percentage). Sleep efficiency was split into 3 categories based on recommended cutoffs: (1) <85%, (2) 85% to 90%, and (3) >90%.

2.2.2. Pain sensitivity testing

2.2.2.1. Cold-pressor test

A 3°C circulating water bath (Julabo PF40-HE; JULABO Labortechnik GmbH, Seelbach, Baden-Württemberg, Germany) connected to a 13-L external Plexiglas container with a flow of 22 L/min was used in the cold-pressor test. The participants submerged their dominant hand and wrist in the cold water of the Plexiglas container as long as they were able to, up to a maximum of 106 seconds. Time to withdrawal of the hand from the cold water was recorded. Pain intensity was recorded 4 seconds after the start of the test and every 9 seconds thereafter on an 11-point numeric rating scale, with 0 = “no pain” and 10 = “the most intense pain imaginable” as the anchors.

2.2.3. Psychological distress

Anxiety and depression symptoms were recorded with the Hopkins Symptom Check List, 10-item version (HSCL). The HSCL is an epidemiological screening tool for detecting negative affect and has been validated against clinical diagnostic depression and anxiety tools. The mean HSCL score was calculated for participants who had responded on 7 or more of 10 HSCL questions, otherwise their data were coded as missing. Participants with a score of 1.85 or higher were classified as having psychological distress. This cutoff has previously been shown to have a sufficient sensitivity and specificity (80% and 98%, respectively) with respect to detecting anxiety or depression compared with the more extensive 25-item HSCL version.

2.2.4. Chronic pain

Comorbid chronic pain was assessed by the following question (yes/no): “Do you have persistent or frequently recurring pain that has lasted for 3 months or more?”

2.2.5. Education

Self-reported level of education was assessed using the following 5 response options: (1) “primary/secondary school” (2) “technical/vocational school” (3) “high school diploma,” (4) “college/university less than 4 years,” and (5) “college/university 4 years or more.” For the purposes of this study, this variable was dichotomized, with the 2 latter categories comprising “college education.”

2.3. Statistical analysis

SPSS version 22 was used for statistical analysis. Pearson χ² and independent samples t-tests were used in univariate comparisons of categorical and continuous variables, respectively. Nonparametric tests (Mann–Whitney U test) were used for univariate comparisons of nonnormal distributed data. Because of a nonlinear relationship between age and pain sensitivity, age was also treated as a categorical variable in the analysis, with the categories 30 to 49 (reference group), 50 to 59, 60 to 69, and 70 to 87 years. Sex, age (groups), education, and psychological distress were included as independent covariates or cofactors in the model.

Cox proportional hazard regression was used to analyze the effect of sleep variables (exposure) on pain sensitivity (outcome). For cold-pressor endurance time, hand withdrawal was defined as an event and individuals enduring the full 106 seconds were treated as censored in the analysis. Group comparisons of sleep...
variables were performed in a stepwise manner, including sex, age, and education as covariates in the first step and psychological distress in the second. Results were considered significant if values were $P < 0.05$.

We also explored the synergistic interactions of sleep and pain by examining whether being classified as having “insomnia disorder” and reporting chronic pain had a synergistic effect on pain tolerance. This was calculated using the algorithm suggested from earlier research\(^3\) in which the synergy index (SI) is equal to calculations of \(\frac{\text{HR (AB) - 1}}{\text{[HR (Ab) - 1]} + \text{[HR (aB) - 1]}}\), where A and B denote the presence of 2 risk factors (insomnia and chronic pain) and a and b are designated as the absence of these risk factors. An SI of 1.0 implies perfect additivity and 1 indicates synergistic interaction, ie, suggests that the joint effects of insomnia and pain on pain tolerance are more than additive.

### 2.4. Ethics

This study was approved by the regional ethical board for medical research and participants gave written informed consent before inclusion in the study.

### 3. Results

3.1. Sample characteristics

The mean age of the 10,412 participants was 57.5 (SD, 12.6; median, 59), and the sample included more women (53.4%) than men (46.6%). The proportion of individuals fulfilling the criteria for insomnia disorder was 10.5%, with a higher prevalence among women (14%) than men (6.5%, $P < 0.001$). Participants with insomnia were also older and had lower levels of education than those without insomnia, but these differences were only

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographical and clinical characteristics among men and women with and without insomnia disorder.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Insomnia disorder (n = 793)</strong></td>
<td><strong>No insomnia (n = 9619)</strong></td>
</tr>
<tr>
<td></td>
<td>Women</td>
</tr>
<tr>
<td><strong>Sex, %</strong></td>
<td>72.1***</td>
</tr>
<tr>
<td><strong>Median age (IQR)</strong></td>
<td>62 (52-70)***</td>
</tr>
<tr>
<td><strong>Education (college education), %</strong></td>
<td>23.4***</td>
</tr>
<tr>
<td><strong>Psychological distress (HSCL &gt; 1.85), %</strong></td>
<td>44.1***</td>
</tr>
<tr>
<td><strong>Comorbid chronic pain, %</strong></td>
<td>70.7***</td>
</tr>
<tr>
<td><strong>Cold-pressor tolerance &lt; 106 s, %</strong></td>
<td>47.4***</td>
</tr>
<tr>
<td><strong>Cold-pressor intensity rating (mean NRS)</strong></td>
<td>7.2 (2.5)***</td>
</tr>
</tbody>
</table>

Univariate analysis of Insomnia disorder (insomnia severity = “very much” or “pretty much,” and insomnia frequency = “more than once a week”) vs no insomnia (Pearson $\chi^2$ test of categorical variables, t test of means, and Mann–Whitney U test of medians). HSCL, Hopkins Symptom Checklist 10-item version; IQR, interquartile range; NRS, numeric rating scale.

\(*P < 0.05; **P < 0.01; ***P < 0.001.\)

### Table 2

Stepwise Cox regression of the cold-pressor test results (among 10,412 women and men).

<table>
<thead>
<tr>
<th>% (n)</th>
<th>Model 1: crude</th>
<th>Model 2: adjusted for age, sex and education</th>
<th>Model 3: adjusted for age, sex, education, and psychological distress</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Insomnia frequency</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never, or just a few times a year</td>
<td>63.3 (8007)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>1-3 times a month</td>
<td>17.2 (2177)</td>
<td>1.24***</td>
<td>1.12-1.36</td>
</tr>
<tr>
<td>Approximately once a week</td>
<td>6.6 (836)</td>
<td>1.39***</td>
<td>1.22-1.59</td>
</tr>
<tr>
<td>More than once a week</td>
<td>12.9 (1630)</td>
<td>1.52***</td>
<td>1.37-1.68</td>
</tr>
<tr>
<td><strong>Insomnia severity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No complaint</td>
<td>62.4 (7859)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Little complaint</td>
<td>27.1 (3411)</td>
<td>1.33***</td>
<td>1.23-1.44</td>
</tr>
<tr>
<td>Pretty much</td>
<td>7.6 (951)</td>
<td>1.47***</td>
<td>1.29-1.67</td>
</tr>
<tr>
<td>Very much</td>
<td>2.9 (369)</td>
<td>2.04***</td>
<td>1.70-2.45</td>
</tr>
<tr>
<td><strong>Sleep onset latency</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;15 min</td>
<td>54.1 (3597)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>15-29 min</td>
<td>22.9 (1523)</td>
<td>1.16*</td>
<td>1.03-1.31</td>
</tr>
<tr>
<td>30-59 min</td>
<td>18.0 (1196)</td>
<td>1.37***</td>
<td>1.21-1.55</td>
</tr>
<tr>
<td>≥60 min</td>
<td>5.0 (331)</td>
<td>1.53***</td>
<td>1.24-1.88</td>
</tr>
<tr>
<td><strong>Sleep duration</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5:00 h</td>
<td>4.9 (2947)</td>
<td>1.06</td>
<td>0.83-1.37</td>
</tr>
<tr>
<td>5:00-5:59 h</td>
<td>11.7 (714)</td>
<td>0.94</td>
<td>0.79-1.13</td>
</tr>
<tr>
<td>6:00-6:59 h</td>
<td>38.9 (2375)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>7:00-7:59 h</td>
<td>35.4 (2158)</td>
<td>1.10</td>
<td>0.98-1.24</td>
</tr>
<tr>
<td>≥8:00 h</td>
<td>9.2 (560)</td>
<td>1.50***</td>
<td>1.26-1.78</td>
</tr>
<tr>
<td><strong>Sleep efficiency</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥90</td>
<td>88.2 (6459)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>85-89.99</td>
<td>7.6 (471)</td>
<td>1.21*</td>
<td>1.00-1.45</td>
</tr>
<tr>
<td>&lt;85</td>
<td>4.1 (256)</td>
<td>1.47***</td>
<td>1.16-1.84</td>
</tr>
</tbody>
</table>

$^*P < 0.05; ^{**}P < 0.01; ^{***}P < 0.001$. CI, confidence interval.
significant among women (detailed in Table 1). Comorbid psychological distress (HSCL score > 1.85) was more frequent among participants with insomnia (33.9% vs 5%, \( P < 0.001 \)).

3.2. Sleep and pain sensitivity: the cold-pressor test

In all, 68% of the participants completed the cold-pressor test without withdrawing their hand before the test ended. Participants with an insomnia disorder were more likely to withdraw before the test ended than did the controls (42.4% vs 30.9%, \( P < 0.001 \)). Both insomnia frequency and severity were associated with pain sensitivity in a dose–response manner. As detailed in Table 2, participants reporting insomnia more than once a week had a 52% higher hazard ratio (HR = 1.52) for reduced cold-pressor pain tolerance, compared with weekly (HR = 1.39) and monthly (HR = 1.24) complaints of insomnia (reference “never”: all \( P < 0.001 \)). Insomnia severity was also associated with reduced pain tolerance, with HRs ranging from 2.04 (“very much”) to 1.33 (“little complaint”) (reference: “no complaint”). In terms of SOL, participants with an SOL of more than 1 hour had a 53% higher HR for reduced pain tolerance, compared with 37% in participants with an SOL of 30 to 59 minutes and 16% for those with an SOL of 15 to 29 minutes (reference SOL < 15 minutes). In contrast, sleep duration was not associated with reduced pain tolerance, with the exception of those sleeping 8 hours or more.

As detailed in Table 2, the pain sensitivity-sleep associations were only slightly attenuated by adjusting for age and gender. Figure 1 depicts the hazard plots for the cumulative proportion of participants withdrawing their hand during the cold-pressor test for all sleep variables. Additional adjustments for psychological distress (HSCL > 1.85) reduced the associations, but most HRs remained significant, at least for the most extreme response options.

3.3. Joint associations of insomnia and chronic pain with pain tolerance

To further explore the link between chronic pain and sleep, we examined the joint association of insomnia and chronic pain on withdrawal during the cold-pressor test. As depicted in Figure 2, the HR of reduced pain tolerance was higher when reporting both chronic pain and insomnia (combined at both “very much” levels) (HR = 2.21; 95% confidence interval = 1.79-2.73), and significantly higher than merely summing the 2 conditions, indicating a synergistic interaction effect in the crude analyses (SI = 1.334). When adjusting for all covariates, the HRs were somewhat reduced, especially for insomnia, whereas the synergistic interaction effect increased (SI = 1.444).

4. Discussion

In this large population-based study, all sleep parameters were significantly associated with reduced pain tolerance. Both the frequency and severity of insomnia, in addition to sleep onset problems and sleep efficiency, were associated with pain sensitivity in a dose–response manner. Adjusting for demographics and psychological distress reduced the strengths of the HRs, but most associations remained significant in the fully adjusted models. We also found a synergistic interaction effect on pain tolerance when combining insomnia and chronic pain.

Figure 1. Cumulative proportion withdrawing hand during the cold-pressor test (CPT): results for sleep variables. Cox regressions, adjusted for sex and age. * \( P < 0.05 \); ** \( P < 0.01 \); *** \( P < 0.001 \). HR, hazard ratio.
4.1. Comparison with previous research

This is the first large population-based study to examine the link between sleep and pain sensitivity. To date, only a handful of studies have investigated heat and cold pain stimuli, but with conflicting results. Two small studies of healthy adults found no significant association between sleep and thermal pain thresholds. Also, Busch et al. recently examined patients with somatoform pain disorder and reported that although the pain thresholds remained unchanged after 1 night’s total sleep restriction, the level of pain complaints increased. In contrast to these studies, Roehrs et al. found that loss of hours of sleep significantly decreased finger withdrawal latency after noxious thermal heat in pain-free individuals. Similarly, in a study of 20 healthy adults, Kundermann et al. found that sleep deprivation resulted in a significant decrease in pain thresholds, without altering the detection thresholds for warmth and cold. This latter study suggests that sleep problems may have a hyperalgesic effect that cannot be explained by changes in general somatosensation.

In a somewhat larger study of participants, Chiu et al. found that subjects with symptoms of insomnia had lower threshold for pressure pain. However, that study did not adjust for important confounders, and also their sample comprised participants with substantial chronic widespread pain and psychological distress, and as such were not generalizable to the general population. In contrast to these studies, this study of more than 10,000 participants from the general population found consistent significant associations between pain sensitivity and a range of sleep measures.

It is noteworthy that both the frequency and severity of insomnia, as well as SOL and sleep efficiency were related to increased pain sensitivity, whereas sleep duration was not. However, this apparent inconsistency is not surprising. An important issue when studying any consequence of sleep is to differentiate between distinct types of sleep problems; and although there is a significant overlap between those who report insomnia and those who have a short sleep duration, it is also important to distinguish between these 2 groups. In addition to the diagnostic criteria of having difficulty falling asleep and maintaining asleep, a diagnosis of insomnia also requires that the sleep problems must occur despite adequate opportunity and circumstances for sleep.

As such, voluntary or enforced sleep loss, which is a characteristic of behaviorally induced insufficient sleep syndrome, should not be misclassified as insomnia. The distinction between sleep deprivation and insomnia is also important when studying their respective consequences. Although sleep deprivation has consistently been linked to reduced neuropsychological performance, the effect of insomnia on this outcome is less clear, and at best, more subtle and qualitatively different from sleep loss.

4.2. Potential mechanisms

Although previous studies have predominantly been focused on examining whether sleep and pain are consistently associated, there is now more focus on investigating how these conditions are related. In that respect, several pathways have been proposed...
as potential candidates. First, both sleep and pain have been found to differ across demographic factors. For example, sleep problems are more common among females and older adults.\(^4^4\) However, adjusting for demographic factors (age, gender, and education) in this study only marginally attenuated the association between most sleep measures and pain sensitivity, and there is generally little evidence that such interactions may explain much of the sleep–pain link.\(^4^4\) Second, several studies have pointed to negative affect as a common factor for both sleep and pain. Consistent with this finding is the fact that depressive symptoms have been found to mediate the association between sleep and pain in both clinical and nonclinical samples.\(^4^3\) This was supported by this study, where adjusting for psychological distress explained a significant part of the association between sleep and pain sensitivity. However, it has also been shown that sleep quality mediates the relationship between pain and depression,\(^4^6\) and as such, the temporal dynamics between these 3 conditions remain uncertain.\(^4^4\) Third, with regards to which neurotransmitter systems may be involved in the pain–sleep association, dopamine has been shown to be an important contributor. It is well known that dopamine is fundamental in the sleep–wake regulation, and it has been suggested that pain may alter the signaling of dopamine, negatively affecting sleep quality.\(^4^9\) However, more research is needed to examine how sleep problems may alter dopamine functioning and how this may ultimately influence pain sensitivity, and vice versa.

### 4.3. Clinical implications

The main finding in this study was that impaired sleep was associated with increased pain sensitivity. As comorbid sleep problems and pain have been linked to elevated disability,\(^2^2\) the need to improve sleep among patients with chronic pain, and vice versa, is evident. Both pharmacological\(^4^1\) and cognitive behavioral therapy (CBT)\(^5^1\) interventions for insomnia and pain interactions have been thoroughly investigated. Regarding nonpharmacological interventions, which today are generally regarded as the treatment of choice for chronic insomnia,\(^4^3\) a CBT-based approach addressing both pain and sleep has been found to be effective.\(^5^1\) As such, future research should focus on examining low-threshold interventions of comorbid sleep and pain, as Internet-based self-help interventions have shown promising results in treating both conditions individually.\(^7^,^3^8^,^4^8\)

### Conflict of interest statement

The authors have no conflicts of interest to declare.

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