


# Number of Chronic Nighttime Insomnia Symptoms and Risk of Chronic Widespread Pain and Pain-Related Disability: The HUNT Study

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**Study Objectives:** To examine the association between the number of chronic nighttime insomnia symptoms and the risk of chronic widespread pain (CWP) and pain-related disability.

**Methods:** A prospective study of 10,847 participants in the Norwegian HUNT Study without chronic musculoskeletal pain at baseline in 2006–2008. We used a modified Poisson regression model to estimate adjusted risk ratios (RRs) with a 95% confidence interval (CI) for CWP and pain-related disability at follow-up in 2017–2019 associated with insomnia and number of nighttime insomnia symptoms at baseline. Chronic insomnia was defined according to the current classification system and grouped into three categories based on the number of reported nighttime symptoms (ie, difficulty initiating sleep, trouble maintaining sleep and early morning awakenings).

**Results:** Compared to the reference group of people without insomnia, people with insomnia had RRs for CWP and pain-related disability of 1.64 (1.26–2.14) and 1.63 (1.37–1.94), respectively. When people with insomnia were categorized based on the number of nighttime symptoms, people who reported one, two, or three nighttime symptoms had RRs of CWP of 1.19 (95% CI 0.80–1.78), 1.78 (95% CI 1.13–2.80) and 3.08 (95% CI 1.93–4.92), respectively, compared to people without insomnia. The corresponding RRs for pain-related disability were 1.49 (95% CI 1.17–1.89), 1.46 (95% CI 2.04–2.05), and 2.46 (95% CI 1.76–3.42).

**Conclusion:** These findings indicate that people with insomnia characterized by symptoms in all phases of the sleep period have a substantially increased risk of CWP and pain-related disability.

**Keywords:** sleeplessness, insomnia disorder, chronic insomnia, musculoskeletal, pain, chronic, widespread chronic pain, relative risk, epidemiology

## Plain Language Summary

Research shows that insomnia is associated with increased risk of chronic musculoskeletal pain. However, previous studies have not considered the complexity of the insomnia disorder in terms of the possible inter-individual differences in the number of nighttime symptoms. The aim of this prospective study was therefore to examine the influence of the number of chronic nighttime insomnia symptoms on the risk of chronic widespread pain and pain-related disability. Our results show that people with insomnia symptoms in all phases of the sleep period (difficulty initiating sleep, trouble maintaining sleep, and early morning awakenings) are particularly vulnerable to develop chronic widespread pain and pain-related disability. These findings are important because they indicate that insomnia is a heterogeneous condition and that the number of nighttime symptoms is an important factor that influences the association between insomnia and the risk of chronic pain. To fully understand the role of insomnia in the development of chronic

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musculoskeletal pain, there is a need for studies exploring if combinations of specific nighttime symptoms are particularly related to chronic pain.

## Introduction

Insomnia is the most common sleep disorder in the general population.<sup>1,2</sup> To be diagnosed with insomnia according to the current classification system,<sup>3</sup> the individual has to report at least one nighttime symptom (eg, difficulty initiating sleep, trouble maintaining sleep, or early morning awakenings), accompanied by daytime impairment in social, occupational and/or educational areas. The symptoms must also occur at least three times a week for at least three months, despite adequate opportunity and circumstances for sleep. Although these diagnostic criteria are recommended for use in clinical practice,<sup>3</sup> it has been shown that the type and the number of insomnia symptoms can vary across individuals diagnosed with insomnia,<sup>4–6</sup> and that non-restorative sleep may occur independently of other insomnia symptoms.<sup>7</sup> This heterogeneity has led to the view that insomnia is a complex disorder and that several insomnia phenotypes with different disease burden may co-exist.<sup>8,9</sup>

Despite the growing body of evidence showing a strong relation between insomnia and the risk of chronic musculoskeletal pain,<sup>10–13</sup> most studies have not considered the complexity of the insomnia disorder in terms of the possible inter-individual differences in the number of nighttime symptoms.<sup>10–12</sup> Some observational studies indicate that insomnia severity, defined by the frequency of sleeplessness or number of insomnia symptoms, is associated with an increased risk of chronic widespread pain (CWP), although questions fulfilling the diagnostic criteria of insomnia were unavailable.<sup>13,14</sup> The link between specific sleep-related characteristics and pain is further underscored by experimental studies showing that disruption of restorative sleep without reduced sleep efficiency is associated with decreased pain threshold<sup>15</sup> and that disruption of sleep continuity is more strongly associated with spontaneous pain reports, compared with restricted but continuous sleep.<sup>16</sup> However, the long-term effect of different sleep characteristics on the development of chronic musculoskeletal pain is unknown. Exploring the influence of the number of nighttime insomnia symptoms in people with insomnia can help identifying individuals at high risk for developing CWP and pain-related disability and provide further insight into the processes that link these conditions.

The aim of this population-based study was to examine the influence of the number of chronic nighttime insomnia symptoms on the risk of CWP and pain-related disability. To explore the hypothesis that the number of nighttime insomnia symptoms is dose-dependently associated with the risk of chronic musculoskeletal pain, we grouped people with chronic insomnia into three categories based on the number of reported nighttime symptoms (ie, difficulty initiating sleep, trouble maintaining sleep and early morning awakenings).

## Materials and Methods

### Study Population

This prospective study utilized data from the third (2006–2008) and fourth (2017–2019) surveys of the Norwegian HUNT Study. All inhabitants aged 20 years or older residing in the Nord-Trøndelag County (now Trøndelag County) in Norway have been invited to participate in the HUNT Study. Information on lifestyle and health-related factors was collected by questionnaires and clinical examination in both surveys. The HUNT surveys were completed with ~11-year intervals. More detailed information about the HUNT Study can be found at <http://www.ntnu.edu/hunt>.

In the third survey, 50,839 (54%) people accepted the invitation. In the fourth survey, 56,078 (55%) people accepted the invitation. For the purpose of the current study, we included 33,900 who participated in both 2006–2008 and 2017–2019. Of these, 13,326 persons reported no chronic musculoskeletal pain at baseline in 2006–2008. Furthermore, we excluded 156 persons who had incomplete information about insomnia symptoms. Of the remaining 13,170 participants, 10,847 answered relevant pain questions at follow-up in 2017–2019 and were included in the analysis.

### Insomnia Symptoms

Insomnia symptoms at baseline in 2006–08 were assessed by the following four questions: 1) “How often during the last three months have you had difficulty falling asleep at night?”, 2) “How often during the last three months have you woken up repeatedly during the night?”, 3) “How often during the last three months have you woken too early and couldn’t get back to sleep?”, and 4) “How often during the last three months have you felt sleepy during the day?”, with three response options for each question: “Never/seldom”, “Sometimes” and “Several times a

week". The information retrieved from these four questions was used to approximate the information necessary to diagnose insomnia according to current diagnostic classification systems.<sup>3</sup> Participants were therefore classified with chronic insomnia if they answered, "Several times a week" on at least one of the questions 1–3, and "Several times a week" on question 4. To examine the influence of number of nighttime insomnia symptoms, people classified with chronic insomnia were further categorized into three subgroups: 1) "Insomnia with one nighttime symptom", 2) "Insomnia with two nighttime symptoms", and 3) "Insomnia with three nighttime symptoms". The reliability (test-retest) of the summed scores of these three items has previously found to be good (kappa value 0.51; 95% CI 0.40–0.63).<sup>17</sup> It should be noted that although insomnia symptoms were obtained also at the follow-up survey, this information was not included in the analysis as it would have induced bias due to reverse causation between incident chronic pain and insomnia symptoms.

## Chronic Musculoskeletal Pain and Pain-Related Disability

Questions on musculoskeletal pain were adopted from the Standard Nordic Questionnaire.<sup>18</sup> At baseline, 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 and/or stiffness in your muscles and joints that lasted for at least three consecutive months?". Participants reporting any chronic musculoskeletal pain at baseline were excluded from the study.

At follow-up, 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 joints that lasted for at least three consecutive months?" Participants defined to have any chronic musculoskeletal pain were asked to indicate the affected body area(s), ie, neck, shoulders, upper back, elbows, low back, hips, wrists/fingers, knees, calf, and ankles/feet. Participants were also asked the following question: "Have you been suffering from pain in both left and right sides of the body?". Participants were defined to have CWP if they reported chronic pain in the axial skeleton, above and below the waist, and in both left and right sides of the body. The reliability of any chronic musculoskeletal pain and CWP has been evaluated previously, reporting kappa values of 0.63 (95% CI 0.53–0.73) and 0.48 (95% CI 0.38–0.64), respectively.<sup>19</sup>

Pain-related disability was assessed separately for work ability and leisure time activity. Participants were asked the following two questions 1) "Have the pain in muscles or joints reduced your ability to work?", and 2) "Have the pain in muscles or joints reduced your leisure activity?", with the response options "no" and "yes". Participants were classified with pain-related disability if they answered, "yes" to at least one of these questions. The questions on pain-related disability have not been validated.

## Assessment of Covariates

Possible confounders were assessed at baseline in 2006–08. Body mass index (BMI) was calculated as weight divided by the square of height ( $\text{kg/m}^2$ ) using standardized measurements of height (to the nearest centimeter) and weight (to the nearest half kilogram) from the clinical examination. Smoking status was assessed by questions about past or present use of cigarettes and were divided in three categories: "never smoked", "former smoker" and "current smoker". Leisure time physical activity was assessed by two questions on the number of hours per week of light (no sweating or heavy breathing) and/or hard (sweating and heavy breathing) physical activity. The response options for both questions were "none", "less than 1 hour", "1–2 hours", and "3 or more hours". We constructed a variable with three categories combining information on light and hard activities: "inactive", "low", and "moderate-to-high". The questions on light and hard physical activity have been validated in a relatively selected sample of young/middle-aged men<sup>20</sup> showing that light leisure time physical activity was not clearly related to objectively measured oxygen uptake, whereas hard physical activity was moderately correlated with this objective measure. Shift work was assessed by the question "Do you work shifts, at night, or on call?", with response options "no" and "yes". Alcohol consumption was assessed by the CAGE (Cut down, Annoyed, Guilty, Eye-opener) questionnaire using a cutoff score  $\geq 2$  to indicate possible alcohol abuse.<sup>21</sup> Symptoms of anxiety and depression were assessed by the validated questionnaire (Hospital Anxiety and Depression Scale, HADS) including seven questions on anxiety and seven questions on depression. As recommended, the cut-off score was set to  $\geq 8$  on both anxiety and depression and was dichotomized as the presence or no presence of anxiety and/or depression.<sup>22</sup> To assess comorbid conditions, participants were asked about current and previous disease (heart disease, lung diseases,

diabetes, cancer, fibromyalgia, rheumatic diseases or degenerative joint disease). Other possible sleep complaints such as sleep apnea and restless legs syndrome were assessed by the question: “How often during the last three months have you stopped breathing while sleeping and/or had tingling in legs during the context of sleep?”, with the response options “never/seldom”, “sometimes” and “several times a week”. People answering “several times a week” to this question were classified as having other sleep complaints.

## Statistical Analyses

A modified Poisson regression model was used to estimate risk ratios (RR) for the association between the number of chronic nighttime insomnia symptoms at baseline in 2006–08 (i.e., exposure variable) and the binary outcome variables chronic musculoskeletal pain (yes, no), CWP (yes, no), and pain-related disability (yes, no) at follow-up in 2017–19. The precision of the RRs was assessed by 95% confidence interval (CI) using robust variance estimation to obtain valid standard error, and thus CIs. Participants with chronic insomnia were compared with the reference group without insomnia. Participants reporting chronic insomnia with one, two, or three nighttime symptoms were compared with the reference group without insomnia. The selection of confounders was based on a priori knowledge about factors that potentially could be related to both the exposure and outcomes under study. After careful considerations, all associations were adjusted for age (continuous), gender (women, men), BMI (continuous), leisure time physical activity (inactive, low, moderate-to-high), shift work (no, yes), alcohol consumption (no alcohol abuse, possible alcohol abuse) and smoking (never, former, current smoker). Since physical activity (1%), smoking (2%), body mass index (0.1%), shift work (22%), and alcohol consumption (12%) had missing data, we imputed missing data (20 imputations). The predictors in the imputation model for missing data were all the variables used in the main analysis, along with other comorbid conditions and other sleep disorders.

We conducted two supplementary analyses to assess the robustness of the results. First, since there is a considerable overlap between insomnia, mental health disorders and medical conditions,<sup>23–25</sup> we repeated the main analysis adjusting for depression and/or anxiety and other comorbid conditions (diabetes, heart disease, lung disease, and rheumatic diseases). Second, since obstructive sleep apnea

syndrome and restless leg syndrome represent distinct sleep disorders that are associated with chronic pain,<sup>26,27</sup> we repeated the main analysis excluding people who self-reported frequent breathing pauses during the night and/or symptoms of discomfort, tingling or prickling in the legs.

All statistical analyses were performed using Stata for Windows, version 16.0 (StataCorp LP, College Station, Texas).

## Results

The baseline characteristics of the 10,847 participants stratified by insomnia and number of insomnia symptoms are reported in Table 1. The proportion of participants categorized with insomnia according to the ICSD-3 criteria was 3.6%. Overall, 4063 (37.5%) participants reported any chronic musculoskeletal pain, 571 (5.3%) reported CWP, and 1640 (15.1%) reported pain-related disability at follow-up.

Table 2 shows the association between insomnia and the number of insomnia symptoms at baseline and the risk of any chronic musculoskeletal pain at follow-up. Compared with the reference group of people without insomnia, people with insomnia had a RR for any chronic musculoskeletal pain of 1.39 (95% CI 1.25–1.53). When people with insomnia were categorized based on the number of nighttime symptoms, those who reported one, two or three nighttime symptoms had RRs of 1.37 (95% CI 1.20–1.57), 1.29 (95% CI 1.07–1.57) and 1.60 (95% CI 1.30–1.85), respectively.

Table 3 shows the association between insomnia and the number of insomnia symptoms at baseline and the risk of CWP. Compared to those without insomnia, people with insomnia had a RR for CWP of 1.64 (95% CI 1.26–2.14). The number of nighttime symptoms was strongly associated with the risk of CWP, ie, people who reported one nighttime symptom had a RR for CWP of 1.19 (95% CI 0.80–1.78), increasing to 3.08 (95% CI 1.93–4.92) in those who reported three nighttime symptoms.

The RRs for pain-related disability were 1.63 (95% CI 1.37–1.94) for those with insomnia, compared to those without insomnia (Table 4). Among those with insomnia, those who reported one nighttime symptom had a RR of 1.49 (95% CI 1.17–1.89) for pain-related disability, increasing to 2.46 (95% CI 1.76–3.42) in those who reported all three nighttime symptoms.

Figure 1 shows the association between the number of insomnia symptoms at baseline and the risk of CWP and pain-related disability among people with insomnia.

**Table 1** Characteristics of the Study Population at Baseline in 2006–2008 Stratified by Insomnia Symptom Status

Variables	No Insomnia Symptoms	Insomnia (ICSD-3)	Insomnia (ICSD-3) Stratified by Number of Nighttime Symptoms		
			One Symptom <sup>a</sup>	Two Symptoms <sup>b</sup>	Three Symptoms <sup>c</sup>
Participants, no.	10,459	388	213	111	64
Age, mean (SD), years	50.3 (13.7)	46.0 (14.3)	44.5 (14.5)	48.4 (13.5)	46.4 (14.5)
Females, % (no.)	53.4 (5591)	62.6 (243)	62.4 (133)	64.9 (72)	59.4 (38)
Body mass index, mean (SD), kg/m <sup>2</sup>	26.6 (4.0)	27.1 (4.7)	27.1 (4.8)	27.7 (4.9)	25.8 (4.1)
Low physical activity or inactive, % (no.) <sup>d</sup>	20.9 (2191)	27.1 (105)	23.0 (49)	32.4 (36)	31.2 (20)
Anxiety and/or depression, % (no.) <sup>e</sup>	7.3 (763)	33.8 (131)	29.6 (63)	36.0 (40)	43.8 (28)
Shift work, % (no.)	21.1 (2323)	25.0 (97)	23.5 (50)	28.8 (32)	23.4 (15)
Current smoker, % (no.)	18.3 (1911)	22.7 (88)	24.9 (53)	21.6 (24)	17.2 (11)
Possible alcohol abuse, % (no.) <sup>f</sup>	7.2 (750)	16.0 (62)	15.0 (32)	17.1 (19)	17.2 (11)
Comorbid conditions, % (no.)	21.0 (2136)	27.5 (107)	31.2 (64)	21.3 (23)	32.8 (20)
Other symptoms of self-reported sleep disorders, % (no.) <sup>g</sup>	4.0 (414)	18.0 (70)	18.9 (40)	17.1 (19)	17.5 (11)

**Notes:** <sup>a</sup>One nighttime symptom ("difficulty falling asleep", "difficulty maintaining sleep", or "waking up too early") accompanied by daytime sleepiness. <sup>b</sup>Two nighttime symptoms ("difficulty falling asleep", "difficulty maintaining sleep", and/or "waking up too early") accompanied by daytime sleepiness. <sup>c</sup>Three nighttime symptoms ("difficulty falling asleep", "difficulty maintaining sleep", and "waking up too early") accompanied by daytime sleepiness. <sup>d</sup>Defined as <2 h light and no hard activity per week. <sup>e</sup>Defined by a score ≥8 on the Hospital Anxiety and Depression Scale (HADS). <sup>f</sup>Defined by a score ≥2 on the CAGE questionnaire. <sup>g</sup>Self-report of frequent breathing pauses during the night and/or symptoms of discomfort, tingling or prickling in the legs.

**Abbreviations:** SD, standard deviation; ICSD-3, International Classification of Sleep Disorders (third edition).

**Table 2** Risk of Any Chronic Musculoskeletal Pain at Follow-Up in 2017–2019 Associated with Insomnia at Baseline in 2006–2008

	No. of Persons	No. of Cases	Age-Adjusted, RR <sup>a</sup>	Multi-Adjusted, RR <sup>b</sup> (95% CI)
Insomnia (ICSD-3)				
No <sup>c</sup>	10,459	3859	1.00	1.00 (reference)
Yes <sup>d</sup>	388	204	1.45	1.39 (1.25–1.53)
Number of nighttime symptoms				
One symptom	213	111	1.44	1.37 (1.20–1.57)
Two symptoms	111	56	1.38	1.29 (1.07–1.57)
Three symptoms	64	37	1.59	1.60 (1.30–1.85)

**Notes:** <sup>a</sup>Adjusted for age (continuous). <sup>b</sup>Multi-adjusted for age (continuous), gender (women, men), body mass index (continuous), leisure time physical activity (inactive, low activity, moderate activity, high activity), shift work (no, yes), alcohol consumption (no alcohol abuse, possible alcohol abuse), and smoking (never, former, current). <sup>c</sup>Reference category for all comparisons in the table. <sup>d</sup>At least one nighttime symptom several times a week ("difficulty falling asleep", "difficulty maintaining sleep", or "waking up too early") accompanied by daytime sleepiness.

**Abbreviations:** CI, confidence interval; RR, risk ratio; ICSD-3, International Classification of Sleep Disorders (third edition).

Taking people with one nighttime insomnia symptoms as the reference group, people with three nighttime symptoms had RRs of 2.29 (95% CI 1.24–4.23) and 1.55 (95% CI 1.04–2.32) for CWP and pain-related disability, respectively.

## Supplementary Analyses

Two supplementary analyses were conducted to assess the robustness of the results. First additional adjustments for depression and/or anxiety and other comorbid conditions (diabetes, heart disease, lung disease, and rheumatic

diseases) had negligible influence on the estimates showing ~5–15% reduction in risk compared to the main analysis. For instance, additional adjustments for poor mental health and medical conditions gave RRs for CWP of 0.99 (95% CI 0.60–1.64) for those who reported one nighttime symptoms, increasing to 2.62 (95% CI 1.46–4.70) in those who reported three nighttime symptoms. Second, the estimates in the main analysis remained unchanged after excluding people who reported frequent breathing pauses during the night and/or symptoms of discomfort, tingling or prickling in the legs.



**Table 3** Risk of Chronic Widespread Pain at Follow-Up in 2017–2019 Associated with Insomnia at Baseline in 2006–2008

	No. of Persons	No. of Cases	Age-Adjusted, RR <sup>a</sup>	Multi-Adjusted, RR <sup>b</sup> (95% CI)
Insomnia (ICSD-3)				
No <sup>c</sup>	10,459	742	1.00	1.00 (reference)
Yes <sup>d</sup>	388	54	1.88	1.64 (1.26–2.14)
Number of nighttime symptoms				
One symptom	213	22	1.37	1.19 (0.80–1.78)
Two symptoms	111	17	2.11	1.78 (1.13–2.80)
Three symptoms	64	15	3.17	3.08 (1.93–4.92)

**Notes:** <sup>a</sup>Adjusted for age (continuous). <sup>b</sup>Multi-adjusted for age (continuous), gender (women, men), body mass index (continuous), leisure time physical activity (inactive, low activity, moderate activity, high activity), shift work (no, yes), alcohol consumption (no alcohol abuse, possible alcohol abuse), and smoking (never, former, current). <sup>c</sup>Reference category for all comparisons in the table. <sup>d</sup>At least one nighttime symptom several times a week (“difficulty falling asleep”, “difficulty maintaining sleep”, or “waking up too early”) accompanied by daytime sleepiness.

**Abbreviations:** CI, confidence interval; RR, risk ratio; ICSD-3, International Classification of Sleep Disorders (third edition).

**Table 4** Risk of Pain-Related Disability at Follow-Up in 2017–2019 Associated with Insomnia at Baseline in 2006–2008

	No. of Persons	No. of Cases	Age-Adjusted, RR <sup>a</sup>	Multi-Adjusted, RR <sup>b</sup> (95% CI)
Insomnia (ICSD-3)				
No <sup>c</sup>	10,459	1536	1.00	1.00 (reference)
Yes <sup>d</sup>	388	104	1.75	1.63 (1.37–1.94)
Number of nighttime symptoms				
One symptom	213	53	1.60	1.49 (1.17–1.89)
Two symptoms	111	27	1.63	1.46 (1.04–2.05)
Three symptoms	64	24	2.46	2.46 (1.76–3.42)

**Notes:** <sup>a</sup>Adjusted for age (continuous). <sup>b</sup>Multi-adjusted for age (continuous), gender (women, men), body mass index (continuous), leisure time physical activity (inactive, low activity, moderate activity, high activity), shift work (no, yes), alcohol consumption (no alcohol abuse, possible alcohol abuse), and smoking (never, former, current). <sup>c</sup>Reference category for all comparisons in the table. <sup>d</sup>At least one nighttime symptom several times a week (“difficulty falling asleep”, “difficulty maintaining sleep”, or “waking up too early”) accompanied by daytime sleepiness.

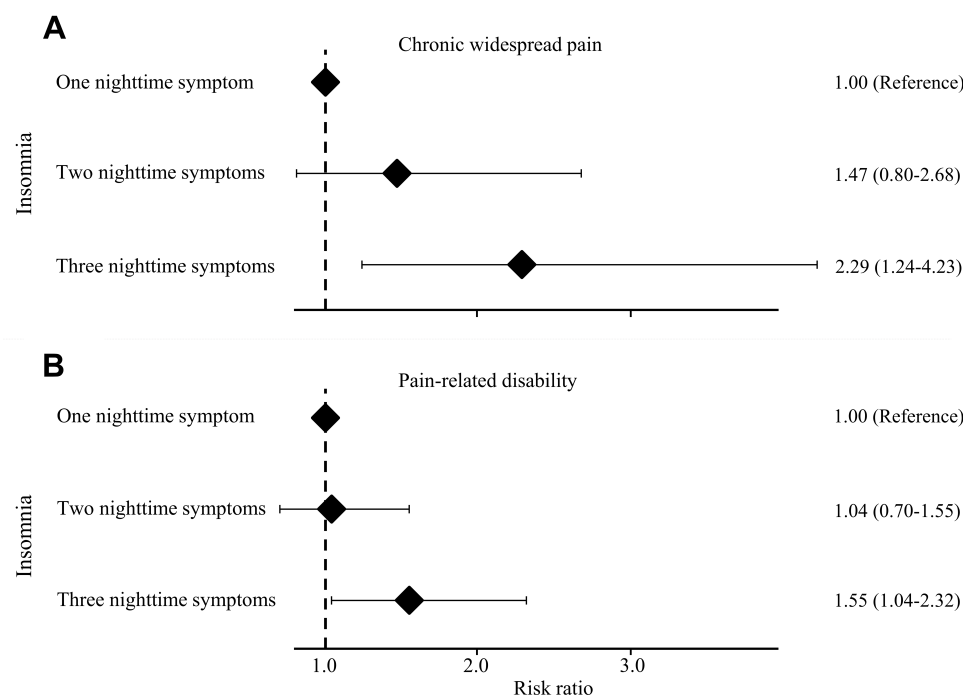
**Abbreviations:** CI, confidence interval; RR, risk ratio; ICSD-3, International Classification of Sleep Disorders (third edition).

## Discussion

Our study shows that the risk of chronic musculoskeletal pain increases with the number of nighttime insomnia symptoms. People with insomnia characterized by symptoms in all phases of the sleep period, ie, difficulty initiating sleep, trouble maintaining sleep, and early morning awakenings, have a substantially greater risk of any chronic musculoskeletal pain, CWP and pain-related disability, compared to people without insomnia or people with insomnia but fewer nighttime symptoms. These findings suggest that insomnia is a heterogeneous condition and that the number of nighttime insomnia symptoms is an important factor influencing the association between insomnia and the risk of chronic musculoskeletal pain.

No previous study has explored whether the number of nighttime symptoms in people with insomnia is differentially associated with the risk of chronic musculoskeletal pain. It has been shown that insomnia, the number of insomnia symptoms and the frequency of sleep problems

are associated with an increased risk for any chronic musculoskeletal pain,<sup>10,14</sup> localized pain<sup>10,28</sup> and widespread pain,<sup>10,13,14,29</sup> although the criteria used to categorize people with insomnia were highly variable and not based on the current classification system.<sup>3</sup> A large prospective study based on a previous survey of the HUNT Study found that the number of insomnia symptoms was strongly associated with the risk of fibromyalgia in women.<sup>13</sup> However, since questions fulfilling the insomnia diagnosis were unavailable, participants were not classified with insomnia according to the current classification system. The current study adds to the literature by showing a cumulative effect of nighttime insomnia symptoms on the risk of CWP in people with a self-reported insomnia diagnosis. Although the precision of the estimates should be considered when interpreting our findings, it should be noted that people with one nighttime symptom did not have an increased risk of CWP compared to people without insomnia, whereas the risk was more than threefold



**Figure 1** Risk of chronic widespread pain (**A**) and pain-related disability (**B**) associated with number of nighttime insomnia symptoms. People classified with chronic insomnia according to the current classification system were grouped into three categories based on the number of reported nighttime symptoms (ie, difficulty initiating sleep, trouble maintaining sleep and early morning awakenings). People with one nighttime symptom serve as the reference category.

among those who experienced three nighttime symptoms. This is in line with the view that symptoms in all phases of the sleep period (i.e., difficulty initiating sleep, trouble maintaining sleep, and early morning awakenings) are the most severe insomnia subtype,<sup>30</sup> influencing daily functioning such as energy and mood.<sup>9,30</sup> Our finding has important clinical implications, suggesting that reducing the severity of insomnia symptoms in people with chronic insomnia could be an important strategy towards the prevention of chronic pain and pain-related disability. However, further investigations are needed to establish whether it is the number of nighttime symptoms per se that impose an increased risk or if these associations are modified by certain combinations of nighttime symptoms.

There is a lack of studies investigating the association between the number of nighttime insomnia symptoms and the risk of pain-related disability. It has been shown that disturbed sleep may predict pain-related disability in patients with chronic pain, but the cross-sectional design precludes any conclusion about temporality.<sup>31,32</sup> Our findings are consistent with prospective studies that have revealed a pathway between insomnia symptoms and reduced functional ability<sup>33</sup> or work disability due to a chronic pain diagnosis.<sup>34,35</sup> However, a direct comparison with our study is difficult since previous studies used

different methods to assess pain-related disability, included participants with pain at baseline, and did not classify insomnia according to diagnostic criteria. Notably, our finding that those who reported three nighttime symptoms had more than 50% increased risk of developing disabling pain compared to those with one nighttime symptom is important because it indicates that the number of nighttime symptoms is a strong contributor to the development of chronic pain that impairs work ability and functioning in daily life.

The explanation for the strong association between the number of nighttime symptoms and risk of CWP and pain-related disability is unclear, but it is conceivable that people with sleeplessness in all phases of sleep have the greatest amount of total sleep loss or that specific nighttime symptoms are more strongly related to the development of chronic pain. Although speculative, it is possible that poor sleep maintenance is the most troublesome symptom when it comes to pain,<sup>15,16,36</sup> and that problems with initiating sleep and/or early awakening are related to other characteristics such as age, gender and comorbid conditions (eg, mental health, use of hypnotics).<sup>9</sup> However, further investigations are required to disentangle whether the development of chronic and disabling pain depends on the specific type and duration of the nighttime

symptoms. So far, the processes linking insomnia and chronic musculoskeletal pain may be conceptualized through a framework of interconnected processes including immune responses, neurobiological changes, and altered cognitive and emotional pain processing.<sup>37–41</sup> Prolonged sleep loss can induce an increased pro-inflammatory response by interfering with the hypothalamic-pituitary-adrenal axis and sympathetic nervous system.<sup>38</sup> Prolonged dysregulation of pro-inflammatory markers can induce changes in peripheral and central pain processing,<sup>42</sup> which have been implicated in the development of chronic pain states.<sup>43</sup> Sleep loss may also exaggerate the sensation of pain by moderating the protective effect of positive affect on pain,<sup>40</sup> weaken the ability to disengage from painful stimuli,<sup>41</sup> or causing significant mood disruption (eg, anxiety and/or depression).<sup>39</sup>

The strengths of the current study include the large population with detailed information about insomnia symptoms, enabling long-term prospective analyses of the association between insomnia classified according to the third version of the ICSD and risk of chronic musculoskeletal pain. Other strengths include the detailed information on several possible confounders and that we were able to classify pain-free people based on the number of nighttime symptoms. However, due to the limited number of cases of CWP and pain-related disability at follow-up we could not classify participants into insomnia subtypes based on specific combinations of nighttime insomnia symptoms as suggested in a recent study.<sup>9</sup> Unfortunately, we had no information on objectively measured sleep duration or sleep quality, nor did we have any information about pain intensity. Moreover, we could not stratify our analyses by gender, age, or other potential effect modifiers. Other limitations include the lack of information about the progression of insomnia symptoms and pain during the follow-up or if new risk factors appeared. However, such risk factors need to be differential between the insomnia categories to influence our results. Moreover, pain-related disability was assessed by two questions related to work-disability and leisure activity rather than a validated scale. Changes in insomnia, chronic pain and other important confounders occurring between these two measurement points, or before our baseline could not be considered, and we cannot exclude the possibility of reverse causation. Poor sleep may be an early symptom of an undiagnosed or subclinical disease, and it should be noted that the analytical sample comprised individuals who were available for follow-up approximately a decade after initial recruitment.

Thus, we might have had a healthy cohort that underestimates the association between insomnia and chronic pain. Finally, residual confounding by unmeasured or poorly measured factors cannot be ruled out.

## Conclusions

In conclusion, this prospective study shows that people with chronic insomnia characterized by difficulty initiating sleep, trouble maintaining sleep and early morning awakenings have a substantially greater risk of any chronic musculoskeletal pain, CWP and pain-related disability, compared to people without insomnia or people with insomnia but fewer nighttime symptoms. These findings suggest that insomnia is a heterogeneous condition and that the number of nighttime symptoms is an important factor that influences the association between insomnia and the risk of chronic musculoskeletal pain.

## Data Sharing Statement

This study used data from the HUNT Study (<https://www.ntnu.edu/hunt>). Any research group with a Principal Investigator affiliated with a Norwegian research institute can apply for access to use data from the HUNT Study. This means that researchers from non-Norwegian countries must have a collaboration partner in Norway to be able to use data from the HUNT Study. Each project needs to be approved by the HUNT Data Access Committee, Regional Medical Ethical Committee, in some cases also the Data Inspectorate. Due to participant confidentiality, participant data are not publicly available.

## Ethical Approval

The study was approved by the Regional Committee for Ethics in Medical Research (project no. 2014/612 REK Mid-Norway). The study was carried out according to the Declaration of Helsinki.

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Norwegian University of Science and Technology (NTNU).

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest for this work.

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