

**A bidirectional study of the association between insomnia, high-sensitivity C-reactive protein, and comorbid low back pain and lower limb pain**

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## **Abstract**

**Objective:** To examine the possible bidirectional association between insomnia and comorbid chronic low back pain (LBP) and lower limb pain and to explore whether high-sensitivity c-reactive protein (hsCRP) amplifies these associations.

**Methods:** We calculated adjusted risk ratios (RR) with 95% confidence intervals (CI) for the development of insomnia and mild-to-severe chronic LBP and lower limb pain at eleven years follow-up in participants aged  $\geq 32$  years and with hsCRP  $\leq 10$  mg/L at baseline in 2007-2008; 3,714 without chronic LBP or lower limb pain (sample 1) and 7,892 without insomnia (sample 2).

**Results:** Compared to participants without chronic pain, participants with comorbid chronic LBP and lower limb pain had a RR of insomnia of 1.37 (95% CI 1.12-1.66). Compared with participants without insomnia, participants with insomnia did not have an increased risk of comorbid chronic LBP and lower limb pain (RR: 1.06, 95% CI 0.76-1.46); however, participants with insomnia had a RR of chronic LBP of 1.20 (95% CI 1.02-1.42). There was no strong amplifying effect of elevated hsCRP (3.00-10.0mg/L) on these associations.

**Conclusions:** These findings suggest that elevated hsCRP does not amplify the associations between insomnia and mild-to-severe chronic LBP and lower limb pain. Further research using data on the temporal relation between insomnia, chronic pain, and inflammatory responses are required to fully understand the causal pathways.

**Keywords** Sleep; Insomnia; Inflammation; C-Reactive Protein; Lower Limb Pain; Low Back Pain

## 1. Introduction

Chronic low back pain (LBP) and chronic lower limb pain are common conditions, with prevalence estimates of 6-25% for people having chronic LBP(1) and 25% for chronic lower limb pain.(2) In people aged 55 years and older, osteoarthritis is supposed to be the most common reason for chronic lower limb pain.(2-4) Chronic LBP and lower limb osteoarthritis frequently occur together, with 58% of people with lower limb osteoarthritis reporting chronic LBP.(5, 6) Gaining further insight into risk factors for comorbid chronic LBP and lower limb pain, along with the consequences of these pain conditions will be useful to underpin the development and design of targeted interventions aimed at reducing the incidence of chronic pain.

There is evidence suggesting that chronic insomnia and chronic pain are bidirectional,(7-9) but there is uncertainty in the directionality of these associations specifically for comorbid chronic LBP and lower limb pain. It has been shown that insomnia is associated with the development of hip, knee and foot pain/stiffness,(10) but the reverse direction has not been explored. Moreover, some evidence has demonstrated that regional and widespread chronic musculoskeletal pain are associated with an increased risk of insomnia,(11, 12) although conflicting results have been reported.(13) However, chronic LBP and lower limb pain, including osteoarthritis, share many similarities. Both conditions include common signs of central sensitization and altered pain modulation, a symptom-based diagnosis, guideline recommended management strategies, and a high prevalence of insomnia.(14-16) Chronic LBP may also be the reason for (referred) chronic lower limb pain.(17) Research suggests that there is an overlap in neurobiological and psychological correlates of insomnia with the pain mechanisms of these musculoskeletal conditions, such as central sensitization, low grade systemic inflammation, mood and physical function.(18, 19) Conceptual models of the insomnia-pain relationship have proposed that low-grade inflammation might contribute.(19) Insomnia may induce an inflammatory response,(20, 21) which may contribute to increased pain sensitivity(22) and thereby increase the risk of chronic pain.(21) It is therefore conceivable

that there exists a complex interplay between low-grade inflammation and insomnia on the risk of chronic LBP and chronic lower limb pain and vice versa. Although this latter view is supported by a recent cross-sectional study,(23) it is not clear if low-grade systemic inflammation, measured by high-sensitivity c-reactive protein (hsCRP) contributes to the possible bidirectional association between insomnia and site-specific chronic pain.(12) Exploring the influence of hsCRP on the possible bidirectional association between insomnia and comorbid chronic LBP and lower limb pain may improve our understanding of the insomnia-pain relation, and lead to more effective management options in the future.

The aim of the current study was to examine the possible bidirectional association of insomnia and chronic LBP and/or lower limb pain, and also to explore whether elevated hsCRP influences these associations.

## **2. METHODS**

### *2.1 Study sample and data collection*

The present study is a longitudinal analysis of the Tromsø Study, a population-based study of people living in the municipality of Tromsø, Norway. This study analyzed questionnaire and blood sample data from the sixth wave (Tromsø 6, 2007-2008) and the seventh wave (Tromsø 7, 2015-2016) with 12,984 and 21,083 participants respectively. Participants were aged 30-87 years in Tromsø 6 and 40-99 years in Tromsø 7. In the present study, we included self-reported questionnaire data on insomnia and musculoskeletal health (chronic LBP and chronic lower limb pain), and hsCRP values from blood serum samples. A comprehensive description of Tromsø 6 study procedures has been published elsewhere.(24) The present study has been written in accordance with the 2007 STROBE Guidelines Version 4.(25)

Participants with valid data on the variables of interest at baseline and follow-up were included.

Participants with hsCRP >10mg/L at baseline were excluded, as this was considered the threshold of

acute inflammation(26), and this did not exclude a large portion of participants with chronic pain conditions. For each analysis, we excluded participants with the outcome (insomnia or chronic pain) studied present at baseline (e.g., participants with chronic LBP at baseline were excluded from the analysis when investigating the association between insomnia and risk of chronic LBP).

The present study was approved by the Regional Committee for Ethics in Medical Research (2016/1997/REK Sør-Øst and 2014/940/REK Nord) and the Norwegian Data Protection Authority. All participants gave informed consent, and the study was conducted in accordance with the Helsinki Declaration.

## *2.2 Insomnia*

Baseline insomnia was defined in accordance with a previous study,(27) where participants were classified as having insomnia if they reported “Pretty Much” or “Very Much” sleep problems during the last week (sufficient severity) and “more than once a week” for how often they suffered from sleeplessness during the last twelve months (sufficient frequency) (Table 1). The follow-up insomnia definition was based on the DSM-V criteria for insomnia(28) by adapting five items from Bergen Insomnia Scale(29) (Table 1).

## *2.3 Chronic low back pain*

Chronic LBP was constructed from the following available survey question “Have you during the last year suffered from pain and/or stiffness in muscles or joints in the lumbar regions lasting for at least three consecutive months?”. Participants were dichotomized as having chronic LBP if they answered either “Little Complaint” or “Severe Complaint” (Table 1). This question was identical at baseline and follow-up.

#### *2.4 Chronic lower limb pain*

The definition of chronic lower limb pain was constructed from the following available survey question “Have you during the last year suffered from pain and/or stiffness in muscles or joints in the hip, leg or feet lasting for at least three consecutive months?”. Participants were classified as having chronic lower limb pain if they answered either “Little Complaint” or “Severe Complaint” (Table 1). This question was identical at baseline and follow-up.

#### *2.5 Comorbid chronic low back and chronic lower limb pain*

Participants were classified having comorbid chronic LBP/lower limb pain if they met the definition criteria of both conditions (Table 1).

#### *2.6 High-sensitivity C-Reactive Protein (inflammatory marker)*

Non-fasting blood samples were collected, coagulated and centrifuged to serum, and stored at -20°C (Department of Laboratory Medicine, University Hospital North Norway, Tromsø; ISO-standard 17025).(24) Thawed samples were analyzed by particle-enhanced immunoturbidimetric assay (Modular P autoanalyzer, Roche Diagnostics, Mannheim, Germany).(24) This method is highly sensitive as the limit of quantification was 0.3 mg/L (analytical coefficients of variation is < 10%). hsCRP was categorized as “Low” (<1.0 mg/L) “Normal” (<3.0 mg/L) or “Elevated” (3.0-10.0 mg/L), in accordance to the American Heart Association(26) and the World Health Organization.(30)

#### *2.7 Possible confounders*

We selected possible confounders based on previously confirmed associations with the primary outcomes. These possible confounders were age, sex,(31) education, leisure time physical activity,(32) body mass index (BMI),(33, 34) shiftwork, alcohol consumption,(35) and smoking.(36) Due to uncertainties about the direction of association between insomnia, chronic pain and possible confounders, some variables

were considered for sensitivity analyses to evaluate the robustness of the findings: 1) mental health due to its association with insomnia,(37) and that one of the ten questions in this variable was about sleep; 2) other pain sites (e.g. chronic LBP was considered as a possible confounder when investigating insomnia as a risk for the development of chronic lower limb pain, and vice versa);(6) and 3) chronic somatic conditions which had been shown to be associated with inflammatory markers.(7, 13)

The questions, response options and categorization for the possible confounders are detailed in Table 1. Age in years was treated as a continuous variable. BMI was derived from height and weight measurements and categorized as “Normal” ( $<25 \text{ kg/m}^2$ ), “Overweight” ( $25\text{-}29.9 \text{ kg/m}^2$ ) and “Obese” ( $\geq 30 \text{ kg/m}^2$ ) for clinical relevance. Physical activity level was classified following The American College of Sports Medicine Guidelines (inactive, low, medium, high),(38) similar to previous populational survey studies.(39) Mental Health was assessed by the Hopkins symptom check list (HSCL-10),(40, 41) dichotomized into “yes” and “no” at the cut-off value of 1.85 for the descriptive statistics.(40) The following self-reported chronic somatic conditions were available in the data and considered: hypertension,(42) chronic obstructive pulmonary disease (COPD),(43) diabetes,(44) cardiovascular disease,(45) rheumatological conditions,(46, 47) asthma,(48) hypothyroidism,(49) and kidney disease.(50) Missing values for each of these possible confounders were classified as the “unknown” category, to preserve a large sample size which otherwise would have been reduced by complete case analysis.

## *2.8 Statistical Analyses*

A modified Poisson regression model was used to estimate risk ratios (RR) for insomnia, chronic LBP and chronic lower limb pain at follow-up. The precision of the RRs was assessed by 95% confidence intervals (CI) using robust variance estimation.(51) When investigating the association of insomnia and hsCRP at baseline on risk of developing chronic LBP ( $n = 4,801$ ) and lower limb pain ( $n = 4,827$ ) at



follow-up, only participants without the respective chronic pain conditions at baseline were included in the analyses. Participants with insomnia were compared with the reference group without insomnia. Participants with hsCRP 1.00-2.99 mg/L and 3.0-10.0 mg/L were compared with the reference group of people with hsCRP <1.0 for each chronic pain condition analyzed. All associations were adjusted for age (continuous), sex (women, men), education (primary/secondary school, high school, university), leisure time physical activity (inactive, low activity, medium-to-high activity, unknown), BMI (normal weight, overweight, obese, unknown), shift work (no, yes, unknown), alcohol consumption (never/rarely, sometimes, often, unknown), smoking (never, former, current smoker, unknown), and the chronic pain condition which was not the outcome (e.g. for the association between insomnia and risk of chronic LBP, the multi-adjusted analyses included the adjustment for chronic lower limb pain).

When investigating the association between chronic LBP or chronic lower limb pain at baseline on risk of insomnia at follow-up, only participants without insomnia at baseline were included in the analyses (n=7,892). Participants with chronic LBP, chronic lower limb pain, or comorbid chronic LBP and lower limb pain were compared with the reference group of individuals without chronic LBP and chronic lower limb pain. In these analyses, participants with hsCRP 1.00-2.99 mg/L and 3.0-10.0 mg/L were also compared with the reference group with hsCRP <1.0 mg/L. All associations were adjusted for the covariates specified above. Crude absolute risk ratios were also calculated by dividing the “No. of cases” (participants who developed the dependent variable condition) by “No. of persons” (participants who had the independent variable condition at baseline).

Potential effect modification between the variables at baseline was assessed as departure from additive effects calculating the relative excess risk due to interaction (RERI). RERI estimates with 95% CIs were calculated from the following equation:  $RERI = RR_{\text{insomnia(yes) and hsCRP(elevated)}} - RR_{\text{insomnia(yes) and hsCRP(normal)}} - RR_{\text{insomnia(no) and hsCRP(elevated)}} + 1$ , where a RERI>0 indicates a synergistic effect beyond an additive

effect.(52) Similar equation was used for the potential synergistic effects between chronic LBP or chronic lower limb pain with hsCRP, e.g.,  $RERI = RR_{\text{chronic LBP(yes) and hsCRP(elevated)}} - RR_{\text{chronic LBP(yes) and hsCRP(normal)}} - RR_{\text{chronic LBP(no) and hsCRP(elevated)}} + 1$ . For these analyses, hsCRP could only be categorized as <3.0 mg/l and 3.0-10.0 mg/L due to sample size limitations.

We conducted three sensitivity analyses to evaluate the robustness of the results. These were separately performed by repeating the main analysis. First, while poor mental health has been shown to be associated with insomnia, our mental health variable (HSCL-10) was not appropriate for the main analyses as it included a question on sleep “Have you had sleeping problems”.(37) Therefore we repeated the analyses adjusting for mental health as a continuous variable. Second, since several chronic somatic conditions have been shown to be associated with inflammatory markers,(7, 13) we adjusted for hypertension, bronchitis/COPD, diabetes, cardiovascular disease, asthma, kidney disease, and arthritis. Third, since it is conceivable that other pain sites distort the association between insomnia, hsCRP and risk of chronic pain, we adjusted for comorbid LBP or lower limb pain when examining the association between insomnia and risk of chronic LBP or lower limb pain.

All analyses were performed with STATA statistical software, version 15.1. (StataCorp LP, College Station, Texas).

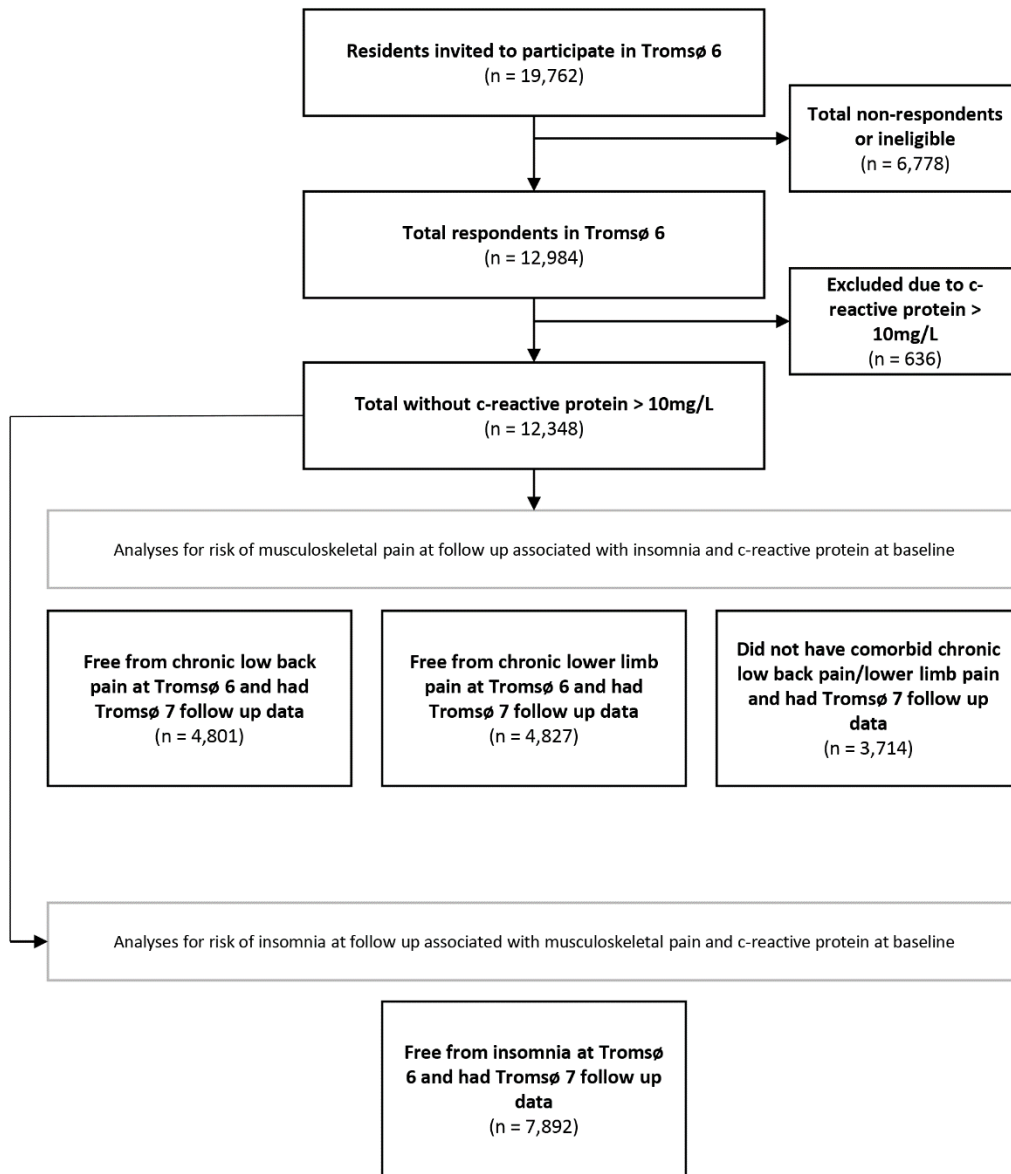
### **3. RESULTS**

#### *3.1 Sample characteristics*

Baseline characteristics of the main subsamples are detailed in Table 2. Due to exclusion of participants with the studied outcome present at baseline, the population sample varied from 4,801 to 7,892 (Figure 1).



**Figure 1.** Flowchart of Participants



Compared to participants without insomnia, participants with insomnia had an increased risk of developing chronic LBP (RR=1.20, 95% CI [1.02-1.42]) at eight years follow-up, but not chronic lower limb pain (0.97, [0.80-1.16]) or comorbid chronic LBP and lower limb pain (1.06, [0.76-1.46]) (Table 3). Normal (1.00-2.99 mg/L) and elevated (3.0-10.0 mg/L) hsCRP were not associated with an increased risk of developing chronic LBP, chronic lower limb pain or both, compared to participants with hsCRP <1.0 mg/L. The RERI estimates in the joint effect analyses were -0.01 (95% CI 0.85-1.12) and 0.21 (95% CI -0.41-0.82), indicating no significant synergistic effect of insomnia and hsCRP 3.0-10.0 mg/L at baseline on the risk of developing chronic LBP or chronic lower limb pain (Table 4).

Compared to participants without chronic LBP and lower limb pain, those with both these pain conditions had a RR for insomnia of 1.37 (95% CI 1.12–1.66) (Table 5). Normal hsCRP (1.00-2.99 mg/L) and elevated hsCRP (3.0-10.0 mg/L) were not clearly associated with an increased risk of insomnia, compared to participants with low hsCRP <1.0 mg/L, but participants with elevated hsCRP had a RR of 1.23 (0.97-1.56). We found no synergistic effect of comorbid chronic LBP and lower limb pain and hsCRP 3.0-10.0 mg/L at baseline on the risk of developing insomnia (RERI= -0.25 95% CI -0.95-0.45). However, compared to participants without chronic musculoskeletal pain and with normal hsCRP (1.00-2.99 mg/L), participants with no chronic pain and elevated hsCRP had a RR of 1.43 (95% CI 1.04–1.96).

### *3.2 Sensitivity Analyses*

The sensitivity analyses demonstrated that our results were robust. However, when adjusting for mental health on the association between insomnia and risk of chronic LBP, the RR became somewhat attenuated (1.23, 95% CI 0.97-1.38).

## TABLES

**Table 1.** Survey Questions and Study Variables Categorization

Measure	Questions	Answer Options	Categorization
<b>Poor Sleep</b>			
Insomnia (Baseline) Sivertsen et al 2015	<p>“How often have you suffered from sleeplessness during the last 12 months?”</p> <p>“Have you had sleep problems during the last week?”</p>	<p><b>Question A:</b></p> <p>1) “Never, or just a few times a year” 2) “1-3 times a month” 3) “approximately once a week” 4) “more than once a week”</p> <p><b>Question B:</b></p> <p>1) “No complaint” 2) “Little Complaint” 3) “Pretty Much” 4) “Very Much”</p>	<p><b>Insomnia (Yes)</b></p> <ul style="list-style-type: none"> <li>Option 4 for question A and either option 3 or 4 for question B.</li> </ul> <p><b>Insomnia (No)</b></p> <ul style="list-style-type: none"> <li>All other non-missing responses.</li> </ul>
Insomnia (Follow-Up)	<p>How many nights per week do you usually:</p> <p>A) use more than 30 minutes to fall asleep? B) wake up for more than 30 minutes in the middle of the night? C) wake up 30 minutes earlier than you wished, without being able to sleep again? D) “felt so tired that it has affected your work, school or private life?” E) “been dissatisfied with your sleep?”</p> <p>F) “If sleep-problems – how long time?”</p>	<p><b>Questions A-E:</b></p> <p>0) “No days” 1) “1 day” 2) “2 days” 3) “3 days” 4) “4 days” 5) “5 days” 6) “6 days” 7) “7 days”</p> <p><b>Question F:</b></p> <p>0) “Do not have sleeping problems” 1) “Less than one week” 2) “1-3 weeks” 3) “1 month” 4) “2 months” 5) “3 months” 6) “4-6 months” 7) “7 -12 months” 8) “1-5 years” 9) “6-10 years” 10) “More than 10 years”</p>	<p><b>Insomnia (Yes)</b></p> <ul style="list-style-type: none"> <li>At least 3 days/nights to at least one of questions A-C, and both questions D and E,</li> <li>At least 3 months for question F.</li> </ul> <p><b>Insomnia (No)</b></p> <ul style="list-style-type: none"> <li>All other non-missing responses.</li> </ul>
<b>Musculoskeletal Pain</b>			
Chronic Low Back Pain	<p>“Have you during the last year suffered from pain and/or stiffness in muscles or joints in the lumbar regions lasting for at least three consecutive months?”</p>	<p>0) “No complaint” 1) “Little Complaint” 2) “Severe Complaint”</p>	<p><b>Chronic Low Back Pain (Yes)</b></p> <ul style="list-style-type: none"> <li>Either Option 1 or 2.</li> </ul> <p><b>Chronic Low Back Pain (No)</b></p> <ul style="list-style-type: none"> <li>All other non-missing responses.</li> </ul>
Chronic Lower Limb Pain	<p>“Have you during the last year suffered from pain and/or stiffness in muscles or joints in the hip, leg or feet lasting for at least three consecutive months?”</p>	<p>0) “No complaint” 1) “Little Complaint” 2) “Severe Complaint”</p>	<p><b>Chronic Lower Limb Pain (Yes)</b></p> <ul style="list-style-type: none"> <li>Either Option 1 or 2.</li> </ul> <p><b>Chronic Lower Limb Pain (No)</b></p> <ul style="list-style-type: none"> <li>All other non-missing responses.</li> </ul>
Combined Chronic Low Back Pain and Chronic Lower Limb Pain	N/A	N/A	<b>Combined Chronic Low Back Pain and Chronic Lower Limb Pain (Yes)</b>

			<ul style="list-style-type: none"> <li>Those categorized to have Chronic Low Back Pain (Yes) AND Chronic Lower Limb Pain (Yes)</li> </ul> <p><b>Combined Chronic Low Back Pain and Chronic Lower Limb Pain (None/Either)</b></p> <ul style="list-style-type: none"> <li>All other non-missing responses.</li> </ul>
<b>Possible Confounders</b>			
Education	“What is the highest levels of education you have completed?”	1) “Primary/secondary school, modern secondary school” 2) “Technical school, vocation school, 1-2 years senior high school” 3) “High school diploma” 4) “College/university less than 4 years” 5) “College/university 4 years or more”	<b>“Primary/secondary school”</b> Option 1 <b>“Technical/vocational/high school”</b> Option 2 or 3 <b>“College &lt;4 years”</b> Option 4 <b>“College ≥4 years”</b> Option 5
Cigarette Smoking	“Do you/did you smoke daily?”	1) “Yes, now” 2) “Yes, previously” 3) “Never”	<b>“Never”</b> Option 1 <b>“Former”</b> Option 2 <b>“Current”</b> Option 3
Alcohol Consumption	“How often do you usually drink alcohol?”	1) “Never” 2) “Monthly or less frequently” 3) “2-4 times a month” 4) “2-3 times a week” 5) “4 or more times a week”	<b>“Never/Rarely”</b> Option 1 or 2 <b>“Sometimes”</b> Option 3 <b>“Often”</b> Option 4 or 5
Physical Activity	A) “How often do you exercise? (i.e. walking, skiing, swimming or training/sports)”  B) “If you exercise, how hard do you exercise?”  C) “For how long time do you exercise (give an average)”	[Scoring shown in <i>italics</i> ] 1) “Never” [=0] 2) “Less than once a week” [=0] 3) “Once a week” [=1] 4) “2-3 times a week” [=2.5] 5) “Approximately every day” [=5]  1) “Easy – you do not become shortwinded or sweaty” 2) “You become shortwinded and sweaty” 3) “Hard – you become exhausted”  1) Less than 15 minutes [=10min] 2) 15-29 minutes [=25min] 3) 30-60 minutes [=45min] 4) More than one hour [=75min]	<u>Duration of exercise</u> was calculated via multiplication of the responses to question A and C <u>Intensity of exercise</u> was calculated from question B <ul style="list-style-type: none"> <li><u>Moderate</u>: Options 1 or 2</li> <li><u>Vigorous</u>: Option 3</li> </ul> <b>“Inactive”</b> <ul style="list-style-type: none"> <li>Duration of Exercise = 0 minutes</li> </ul> <b>“Low” activity</b> <ul style="list-style-type: none"> <li>&lt; 150 minutes of moderate activity, or</li> <li>&lt; 75 minutes of vigorous activity.</li> </ul> <b>“Medium”</b> <ul style="list-style-type: none"> <li>150-300 minutes of moderate activity, or</li> <li>75-150 minutes of vigorous activity.</li> </ul>

			<p><b>“High”</b></p> <ul style="list-style-type: none"> <li>• &gt;300 minutes of moderate activity, or</li> <li>• &gt;150 minutes of vigorous activity.</li> </ul>
Mental Health	<p>During the last week:</p> <ol style="list-style-type: none"> <li>1) “Have you experienced sudden fear without apparent reason?”</li> <li>2) “Have you felt afraid or anxious?”</li> <li>3) “Have you experienced faintness or dizziness?”</li> <li>4) “Have you felt tense or upset?”</li> <li>5) “Have you easily blamed yourself?”</li> <li>6) “Have you had sleeping problems?”</li> <li>7) “Have you felt depressed or sad?”</li> <li>8) “Have you felt useless, worthless?”</li> <li>9) “Have you felt that everything is a struggle?”</li> <li>10) “Have you felt hopelessness with regard to the future?”</li> </ol>	<p>[Scoring shown in <i>italics</i>]</p> <ol style="list-style-type: none"> <li>1) “No complaint” [=1]</li> <li>2) “Little complaint” [=2]</li> <li>3) “Pretty much” [=3]</li> <li>4) “Very much” [=4]</li> </ol>	<p><b>Poor Mental Health (Yes)</b></p> <ul style="list-style-type: none"> <li>• Score average ≥ 1.85</li> </ul> <p><b>Poor Mental Health (No)</b></p> <ul style="list-style-type: none"> <li>• Score average &lt; 1.85</li> </ul>
Shiftwork	<p>“Have you worked in a shift work schedule during the past three months?”</p>	<ol style="list-style-type: none"> <li>0) “No”</li> <li>1) “Yes”</li> </ol>	<p><b>Shiftwork (Yes)</b></p> <ul style="list-style-type: none"> <li>• Option 1</li> </ul> <p><b>Shiftwork (No)</b></p> <ul style="list-style-type: none"> <li>• Option 0</li> </ul>
Chronic Somatic Diseases	<p>Have you ever had, or do you have:</p> <ol style="list-style-type: none"> <li>1) Hypertension?</li> <li>2) Chronic bronchitis/emphysema/COPD?</li> <li>3) Diabetes?</li> <li>4) Heart attack?</li> <li>5) Angina Pectoris (heart cramp)?</li> <li>6) Cerebral stroke/brain hemorrhage?</li> <li>7) Atrial fibrillation?</li> <li>8) Asthma?</li> <li>9) Low metabolism?</li> <li>10) Kidney disease?</li> </ol> <p>If they had any pain for more than three months:</p> <p>What do you believe is the cause of this pain:</p> <ol style="list-style-type: none"> <li>A) Rheumatoid arthritis?</li> <li>B) Bechterews syndrome?</li> </ol>	<ol style="list-style-type: none"> <li>0) “No”</li> <li>1) “Yes”</li> </ol>	<p><b>Hypertension (yes)</b></p> <ul style="list-style-type: none"> <li>• Question 1: Option 1</li> </ul> <p><b>Chronic obstructive pulmonary disease (Yes)</b></p> <ul style="list-style-type: none"> <li>• Question 2: Option 1</li> </ul> <p><b>Diabetes</b></p> <ul style="list-style-type: none"> <li>• Question 3: Option 1</li> </ul> <p><b>Cardiovascular</b></p> <ul style="list-style-type: none"> <li>• Question 4, 5, 6 or 7: Option 1</li> </ul> <p><b>Asthma</b></p> <ul style="list-style-type: none"> <li>• Question 8: Option 1</li> </ul> <p><b>Hypothyroidism</b></p> <ul style="list-style-type: none"> <li>• Question 9: Option 1</li> </ul> <p><b>Kidney diseases</b></p> <ul style="list-style-type: none"> <li>• Question 10: Option 1</li> </ul> <p><b>Rheumatological</b></p> <ul style="list-style-type: none"> <li>• Question A or B: Option 1</li> </ul>



**Table 2.** Baseline Characteristics of the study populations

Variables	Free from chronic low back pain at baseline N = 4,801		Free from chronic lower limb pain at baseline N = 4,827		Free from insomnia at baseline n = 7,892	
	Insomnia		Insomnia		LBP and lower limb pain	
	No	Yes	No	Yes	No	Yes
Participants	4,618	183	4,827	186	5,780	2,112
Age, mean (SD)	54.3 (11.9)	56.4 (11.4)	53.6 (11.7)	56.0 (12.1)	54.4 (11.9)	59.1 (11.8)
Women, no. (%)	2,201 (47.7)	117 (63.9)	2,091 (45.1)	100 (53.8)	2,686 (46.5)	1,295 (61.3)
Body mass index, mean (SD)	26.5 (4.0)	26.9 (4.0)	26.3 (3.9)	26.6 (3.9)	26.5 (4.0)	27.7 (4.3)
Obese ( $\geq 30$ kg/m <sup>2</sup> ), no. (%)	778 (16.9)	37 (20.2)	719 (15.5)	28 (15.1)	962 (16.6)	549 (26.0)
Higher education, no. (%) <sup>a</sup>	2,282 (49.4)	72 (39.3)	2,306 (49.7)	71 (38.2)	2,779 (48.1)	609 (28.8)
Current smoker, no. (%)	754 (16.3)	34 (18.6)	791 (17.0)	34 (18.3)	965 (16.7)	463 (21.9)
High physical activity, no. (%)	687 (14.9)	29 (15.9)	691 (14.9)	35 (18.8)	837 (14.5)	218 (10.3)
Elevated hsCRP ( $\geq 3$ mg/L), no. (%)	678 (14.7)	29 (15.9)	644 (13.9)	31 (16.7)	834 (14.4)	435 (20.6)
Poor mental health, no. (%)	121 (2.6)	53 (29.0)	123 (2.7)	57 (30.7)	184 (3.2)	171 (8.1)
Shift work, no. (%)	432 (9.4)	13 (7.1)	457 (9.9)	16 (8.6)	543 (9.4)	169 (8.0)
High alcohol consumption, no. (%) <sup>b</sup>	1,196 (25.9)	54 (29.5)	1,198 (25.8)	52 (28.0)	1,483 (25.7)	385 (18.2)
Hypertension, no. (%)	979 (21.2)	52 (28.4)	906 (19.5)	57 (30.7)	1,223 (21.2)	629 (29.8)
COPD, no. (%)	105 (2.3)	7 (3.8)	97 (2.1)	13 (7.0)	133 (2.3)	102 (4.8)
Diabetes, no. (%)	171 (3.7)	10 (5.5)	151 (3.3)	9 (4.8)	204 (3.5)	110 (5.2)
Cardiovascular Disease, no. (%)	187 (4.1)	13 (7.1)	191 (4.1)	12 (6.5)	258 (4.5)	157 (7.4)
Rheumatological Disease, no. (%)	39 (0.8)	3 (1.6)	15 (0.3)	2 (1.1)	49 (0.9)	141 (6.7)
Asthma, no. (%)	337 (7.3)	23 (12.6)	320 (6.9)	16 (8.6)	432 (7.5)	253 (12.0)
Hypothyroidism, no. (%)	269 (5.8)	18 (9.8)	245 (5.3)	19 (10.2)	346 (6.0)	226 (10.7)
Kidney Disease, no. (%)	137 (3.0)	10 (5.5)	123 (2.7)	9 (4.8)	169 (2.9)	99 (4.7)

Abbreviations: SD, standard deviation; hsCRP, high-sensitivity c-reactive protein; COPD, chronic obstructive pulmonary disease

<sup>a</sup> College or higher

<sup>b</sup>  $\geq 4$  times/week

**Table 3.** Risk of chronic low back pain, chronic lower limb pain and comorbid low back pain/lower limb pain at follow-up (2015-2016) associated with insomnia and high-sensitivity c-reactive protein at baseline (2007-2008)

Variables	No. of persons	No. of cases	Crude absolute risk (%)	Age-adjusted, RR <sup>a</sup>	Multi-adjusted, RR (95% CI) <sup>b</sup>
<b>Chronic low back pain</b>					
Insomnia					
No Insomnia	4,618	1,681	36.4	1.00	1.00 (reference)
Insomnia	183	82	44.8	1.22	1.20 (1.02-1.42)
C-reactive protein					
<1.00 mg/L	2,193	781	35.6	1.00	1.00 (reference)
1.00-2.99 mg/L	1,901	719	37.8	1.04	1.03 (0.94-1.12)
3.00-10.00 mg/L	707	263	37.2	1.03	0.99 (0.88-1.12)
<b>Chronic lower limb pain</b>					
Insomnia					
No Insomnia	4,641	1,831	39.5	1.00	1.00 (reference)
Insomnia	186	73	39.2	0.98	0.97 (0.80-1.16)
C-reactive protein					
<1.00 mg/L	2,264	851	37.6	1.00	1.00 (reference)
1.00-2.99 mg/L	1,888	767	40.6	1.08	1.05 (0.97-1.13)
3.00-10.00 mg/L	675	286	42.4	1.12	1.08 (0.97-1.21)
<b>Comorbid Chronic LBP/Lower Limb Pain<sup>†</sup></b>					
Insomnia					
No Insomnia	3,603	837	23.2	1.00	1.00 (reference)
Insomnia	111	28	25.2	1.06	1.06 (0.76-1.46)
C-reactive protein					
<1.00 mg/L	1,773	403	22.7	1.00	1.00 (reference)
1.00-2.99 mg/L	1,427	345	24.2	1.03	1.00 (0.87-1.14)
3.00-10.00 mg/L	514	117	22.8	0.97	0.92 (0.76-1.11)

Abbreviations: CI, confidence interval; RR, risk ratio

<sup>†</sup> Mutually for chronic low back pain or chronic lower limb pain

<sup>a</sup> Adjusted for age (continuous)

<sup>b</sup> Multi-adjusted for age (continuous), sex (women, men), education (primary/secondary school, high school, college), leisure time physical activity (inactive, low activity, medium-to-high activity, unknown), body mass index (normal weight, overweight, obese, unknown), shift work (no, yes, unknown), alcohol consumption (never/rarely, sometimes, often, unknown), smoking (never, former, current smoker, unknown)

**Table 4.** Risk of chronic low back pain and chronic lower limb pain at follow-up (2015-2016) associated with the joint effect of insomnia and high-sensitivity c-reactive protein at baseline (2007-2008)

Variables	Normal hsCRP (<3.00 mg/L)			Elevated hsCRP (3.00-10.00 mg/L)		
	No. of persons	No. of cases	Multi-adjusted, RR (95% CI) <sup>a</sup>	No. of persons	No. of cases	Multi-adjusted, RR (95% CI) <sup>a</sup>
<b>Chronic low back pain</b>						
No Insomnia	3,940	1,431	1.00 (reference)	678	250	0.98 (0.87-1.09)
Insomnia	154	69	1.20 (1.00-1.44)	29	13	1.17 (0.77-1.77)
RERI: -0.01 (95% CI 0.85-1.12)						
<b>Chronic lower limb pain</b>						
No Insomnia	3,997	1,560	1.00 (reference)	644	271	1.04 (0.94-1.15)
Insomnia	155	58	0.93 (0.75-1.15)	31	15	1.18 (0.82-1.70)
RERI: 0.21 (95% CI -0.41-0.82)						

Abbreviations: CI, confidence interval; hsCRP, high-sensitivity c-reactive protein; RERI, Relative Excess Risk due to Interaction; RR, risk ratio.

<sup>a</sup>Multi-adjusted for age (continuous), sex (women, men), education (primary/secondary school, high school, college), body mass index (normal weight, overweight, obese, unknown), shift work (no, yes, unknown), alcohol consumption (never/rarely, sometimes, often, unknown), smoking (never, former, current smoker, unknown)

**Table 5.** Risk of insomnia at follow-up (2015-2016) associated with chronic low back pain, chronic lower limb pain, and high-sensitivity c-reactive protein at baseline (2007-2008)

Variables	No. of persons	No. of cases	Crude absolute risk (%)	Age-adjusted, RR <sup>a</sup>	Multi-adjusted, RR (95% CI) <sup>b</sup>
<b>Chronic musculoskeletal pain</b>					
No pain	3,855	249	6.5	1.00	1.00 (reference)
Low back pain	948	62	6.5	1.03	1.03 (0.79-1.34)
Lower limb pain	977	76	7.8	1.28	1.26 (0.98-1.61)
Comorbid low back pain/lower limb pain	2,112	173	8.2	1.37	1.37 (1.12-1.66)
<b>C-reactive protein</b>					
<1.00 mg/L	3,439	238	6.9	1.00	1.00 (reference)
1.00-2.99 mg/L	3,184	222	7.0	1.05	1.06 (0.88-1.28)
3.00-10.00 mg/L	1,269	100	7.9	1.21	1.23 (0.97-1.56)

Abbreviations: CI, confidence interval; RR, risk ratio

† Mutually for chronic low back pain or chronic lower limb pain

<sup>a</sup> Adjusted for age (continuous)

<sup>b</sup> Multi-adjusted for age (continuous), sex (women, men), education (primary/secondary school, high school, college), body mass index (normal weight, overweight, obese, unknown), shift work (no, yes, unknown), alcohol consumption (never/rarely, sometimes, often, unknown), smoking (never, former, current smoker, unknown)

**Table 6.** Risk of insomnia at follow-up (2015-2016) associated with the joint effect of chronic low back pain, chronic lower limb pain, and high-sensitivity c-reactive protein at baseline (2007-2008)

Variables	Normal hsCRP (<3.00 mg/L)			Elevated hsCRP (3.00-10.00 mg/L)		
	No. of persons	No. of cases	Multi-adjusted, RR (95% CI) <sup>a</sup>	No. of persons	No. of cases	Multi-adjusted, RR (95% CI) <sup>a</sup>
<b>Chronic musculoskeletal pain</b>						
No pain	3,321	205	1.00 (reference)	534	44	1.43 (1.04-1.96)
Low back pain	823	55	1.11 (0.83-1.48)	125	7	0.95 (0.45-1.99)
Lower limb pain	802	64	1.35 (1.03-1.76)	175	12	1.29 (0.73-2.26)
Comorbid low back pain/lower limb pain	1,677	136	1.42 (1.15-1.76)	398	37	1.60 (1.13-2.25)

RERI: -0.25 (95% CI -0.95-0.45)

Abbreviations: CI, confidence interval; hsCRP, high-sensitivity c-reactive protein; RERI, Relative Excess Risk due to Interaction; RR, risk ratio.

<sup>†</sup> Mutually for chronic low back pain or chronic lower limb pain

<sup>a</sup> Multi-adjusted for age (continuous), sex (women, men), education (primary/secondary school, high school, college), body mass index (normal weight, overweight, obese, unknown), shift work (no, yes, unknown), alcohol consumption (never/rarely, sometimes, often, unknown), smoking (never, former, current smoker, unknown)

## 4. DISCUSSION

The results from this prospective study show no strong bidirectional association between insomnia and mild-to-severe comorbid chronic LBP and lower limb pain. However, participants with comorbid chronic LBP and lower limb pain had an increased risk of insomnia, and participants with insomnia had an increased risk of chronic LBP. There was no clear independent association between elevated hsCRP and insomnia or chronic pain, nor did elevated hsCRP amplify the association between these conditions.

### *4.1 Interpretation and comparison of the findings with previous literature*

#### *4.1.1 Is insomnia an independent risk factor for comorbid chronic LBP and chronic lower limb pain, and does hsCRP influence this association?*

We found no strong association between insomnia and risk of mild-to-severe comorbid chronic LBP and lower limb pain. However, participants with insomnia at baseline had 20% higher risk of developing chronic LBP eight years later. Despite a slightly higher relative risk, the absolute risk difference was 8.4%, indicating a substantially higher risk of LBP among those with insomnia than those without insomnia. This finding was consistent after additional adjustment for mental health and chronic somatic conditions. Our finding is in agreement with an Israeli study that examined 2,131 healthy medical center employees over four years,(13) and a Norwegian study that examined insomnia sub-types in 16,401 participants.(53) Despite differences in population characteristics and follow-up length, these findings suggest that insomnia is an independent risk factor for chronic LBP. Conversely, the lack of association between insomnia and the development of chronic lower limb pain was contrary to a five-year follow-up study examining the association between non-restorative sleep and unspecified arthritis(54).

There are some potential explanations for why insomnia was associated with chronic LBP and not chronic lower limb pain. While chronic LBP and chronic lower limb pain have shared pain mechanisms of central sensitization and altered pain modulation,(14) chronic lower limb pain potentially has a more mechanical

nature of pathogenesis as people often develop lower limb pain after mechanical injury or overload related problems.(34)

CRP and hsCRP has been found to be cross-sectionally associated with the *presence* or *intensity* of chronic LBP(55) and longitudinally associated with the pain *intensity*(56) and radiographic OA sign progression(57) of knee OA. In the current study, we did not find an association between elevated hsCRP and increased risk of *developing* chronic LBP or chronic lower limb pain. This finding is similar to previous studies that found a lack of association between baseline hsCRP levels and the *development* of chronic LBP(13) and chronic widespread pain.(12) Moreover, we found no clear synergistic effect of insomnia and elevated hsCRP on the risk of chronic LBP and chronic lower limb pain. This finding is somewhat surprising considering a recent study based on the same Tromsø surveys,(12) showing an interplay between sleeplessness and elevated hsCRP on the risk of chronic widespread pain. Although these findings indicate that elevated hsCRP could be a mechanism linking insomnia to CWP, but not LBP or lower limb pain, there are some important methodological differences between these studies. First, due to the sample size in the current study, we could not categorize hsCRP into <1.00 mg/L, 1.00-2.99 mg/L, and 3.00-10.00 mg/L in our analyses of joint effect. Second, the latter study focused on severe chronic pain and severity of sleeplessness. Thus, it is possible that low-grade systemic inflammation provides a pathway between poor sleep and chronic pain conditions, but that this pathway depends on the severity of insomnia, chronic pain, and inflammatory markers. However, a proper exploration of this inflammatory pathway requires data on the longitudinal relation between insomnia and inflammation.(7, 9, 58)

#### *4.1.2 Is comorbid chronic LBP and lower limb pain an independent risk factor for insomnia, and does hsCRP influence this association?*

Our findings showing that comorbid LBP and lower limb pain was associated with greater risk of insomnia is consistent with previous studies showing that widespread pain and the number of pain sites are strongly associated with the risk of insomnia.(12, 59) The finding that participants with chronic LBP

had no increased risk of insomnia was also consistent with Agmon et al.(13) However, since co-occurring musculoskeletal pain is common in chronic LBP,(60) it is likely that people reporting only LBP had less disabling pain, which in turn could have underestimated the association between LBP and insomnia. In the present study, participants with chronic lower limb pain at baseline had a weakly increased risk of insomnia compared to participants without chronic lower limb pain. The only previous study that has investigated this association is a two-year American study of 4,467 elderly adults which found no association between arthritis (unspecified type) and the development of trouble falling asleep.(61)

Although our data showed a weak increased risk of insomnia among those with elevated hsCRP the CI was wide, and this result should therefore be interpreted with caution. A Taiwanese six-year follow-up study(62) showed that participants with elevated hsCRP levels did not have an increased risk of developing short or long sleep duration. The latter study, together with our results question the independent contribution of elevated hsCRP on the risk of insomnia. However, it should be noted that we found that participants without chronic musculoskeletal pain and hsCRP 3.0-10.0 mg/L had a 44% increased risk of developing insomnia compared to people with no chronic musculoskeletal pain and hsCRP <3.0 mg/L. Although speculative, one possible explanation is that low-grade inflammation (from any cause) may alter central nervous system processes that regulate sleep(63) and in turn increase the risk for insomnia. Nevertheless, we found no clear synergistic effect of elevated hsCRP and either chronic musculoskeletal pain condition on the association between the chronic musculoskeletal pain and the risk of developing insomnia. It should be noted that people with comorbid low back pain and lower limb pain who also had elevated hsCRP had 60% greater risk of insomnia, indicating that people with comorbid low back pain and lower limb pain who also experience low-grade systemic inflammation are more susceptible to develop insomnia.

#### ***4.2 Strengths and Limitations***



The key strengths of this study were its longitudinal design, population-based sample, and robustness of the main analyses throughout sensitivity analyses. We only selected participants who were free of the outcome condition of interest at baseline to evaluate the risk of the respective outcome. The Tromsø Study population is also considered similar to the general Norwegian population in regards to age, gender, and level of education.(64, 65)

There are several limitations in this study that need to be addressed. Firstly, the sleep questions available in the two surveys differed. Only the follow-up definition is consistent with the DSM-V criteria for insomnia.(28) However, our baseline definition was quite strict, as participants needed to report “pretty much” or “very much” sleep problems for at least once a week during the past year. Since we excluded people with chronic pain at baseline, the insomnia prevalence rates at both time-points cannot be compared with other studies.(66, 67) Secondly, there are some caveats regarding the chronic LBP and chronic lower limb pain definitions. Since our definition of chronic low back pain and chronic lower limb pain included both pain and/or stiffness in muscles and joint, differences in the pathophysiology of stiffness and pain should be considered when interpreting the results. Though, it is likely that participants who reported stiffness in these regions experienced pain, but this categorization may include participants with only stiffness, causing an overestimate of people with chronic LBP or chronic lower limb pain. Moreover, this categorization may also have led to inclusion of fibromyalgia or other rheumatic conditions at follow-up, but additional adjustment for arthritis had only negligible influence on the estimates. In the exploration of the data, it was found that 40% of the participants who reported no chronic pain still reported “little” site-specific pain/stiffness. However, we used a case definition including both “little complaint” and “severe complaint”, as using only “severe complaint” resulted in underpowered sample sizes. Another consideration is that participants answered whether they had chronic pain in the last 12 months, rather than whether it was present at the time of blood sampling. Furthermore, the chronic lower limb pain definition may have limited generalizability to lower limb osteoarthritis as data such as *activity related* pain and *morning* stiffness were not provided to satisfy NICE OA

guidelines(2-4) and data such as radiographical findings were not available. Thus, we cannot exclude the possibility that our findings underestimate the true association between insomnia, chronic LBP and chronic lower limb pain. Thirdly, although hsCRP is a good clinical marker for acute inflammation, inflammatory processes are complex and heterogeneous, and it is uncertain whether sub-clinically elevated hsCRP is representative of the putative inflammatory mechanisms mediating the association between pain and insomnia. It is likely that other inflammatory markers (e.g., IL-6 and TNF-a) may be better candidates due to their slightly stronger associations with insomnia, chronic LBP and lower limb OA.(55, 68, 69)

## **5. Conclusions**

We found no strong bidirectional association between insomnia and mild-to-severe comorbid chronic low back pain and lower limb pain; however, participants with insomnia had an increased risk of chronic low back pain, and participants with comorbid chronic LBP and lower limb pain had an increased risk of insomnia. These associations were not amplified by elevated hsCRP.

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## ***Author Contributions***

Author contributions in reference to 1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, 2) drafting the article or revising it critically for important intellectual content, 3) final approval of the version to be submitted, are:

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Dr Eivind S SKARPSNO: 1, 2 and 3

Dr Kristian Bernhard NILSEN: 1, 2 and 3

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Informed consent: Informed consent has been obtained from all individuals included in this study.

Ethical approval: The research related to human use complies with all the relevant national regulations, institutional policies and was performed in accordance with the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

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## **Tables**

**Table 1.** Survey Questions and Study Variables Categorization

**Table 2.** Baseline Characteristics of the study populations

**Table 3.** Risk of chronic low back pain, chronic lower limb pain and comorbid low back pain/lower limb pain at follow-up (2015-2016) associated with insomnia and high-sensitivity c-reactive protein at baseline (2007-2008)

**Table 4.** Risk of chronic low back pain and chronic lower limb pain at follow-up (2015-2016) associated with the joint effect of insomnia and high-sensitivity c-reactive protein at baseline (2007-2008)

**Table 5.** Risk of insomnia at follow-up (2015-2016) associated with chronic low back pain, chronic lower limb pain, and high-sensitivity c-reactive protein at baseline (2007-2008)

**Table 6.** Risk of insomnia at follow-up (2015-2016) associated with the joint effect of chronic low back pain, chronic lower limb pain, and high-sensitivity c-reactive protein at baseline (2007-2008)