Clinical pain research

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The association between insomnia, c-reactive protein, and chronic low back pain: cross-sectional analysis of the HUNT study, Norway

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Abstract

Background and aims: Chronic low back pain (chronic LBP) is the number one cause for years lived with disability among 301 diseases and injuries analyzed by The Global Burden of Disease study 2013. Insomnia is highly prevalent among people with chronic LBP. To explain the sleep-pain relationship, theoretical models propose that insomnia symptoms may be associated with increased basal inflammation, operationalized as c-reactive protein (CRP) and lead to further pain and disrupted sleep. We aimed to determine the associations between insomnia, chronic LBP, and inflammation (operationalized as CRP), whilst controlling for age, body mass index, smoking, physical activity, depression, anxiety and osteoarthritis.

Methods: A cross-sectional analysis of the third Nord-Trøndelag Health Study (2006–2008), a rural population survey of 50,666 participants in Norway aged 20–96 years. Insomnia (dichotomous) was defined according to the Diagnostic and Statistical Manual of Mental Disorders 5th Edition, and chronic LBP (dichotomous) as low back pain or stiffness lasting at least 3 months. Data for CRP were obtained from non-fasting serum samples and assessed via latex immunoassay methodology. We excluded participants with the following self-reported chronic somatic diseases: chronic heart failure, chronic obstructive pulmonary disease, rheumatoid arthritis, fibromyalgia or ankylosing spondylosis. Possible associations between presence of insomnia and presence of chronic LBP (dependent), and the level of CRP and presence of chronic LBP (dependent), were assessed using logistic regression models. The possible association between insomnia and CRP (dependent) was assessed using linear regression. Multivariable analyses were conducted adjusting for confounders stated in our aim that achieved $p \leq 0.2$ in univariate regressions. We performed stratified analyses for participants with "Normal" (<3 mg/L) "Elevated" (3–10 mg/L) and "Very High" (>10 mg/L) levels of CRP.

Results: In our total included sample ($n = 30,669$, median age 52.6, 54% female), 6.1% had insomnia ($n = 1,871$), 21.4% had chronic LBP ($n = 6,559$), and 2.4% had both ($n = 719$). Twenty four thousand two hundred eighty-eight (79%) participants had "Normal" CRP, 5,275 (17%) had "Elevated" CRP, and 1,136 (4%) had "Very High" CRP. For participants with "Normal" levels of CRP, insomnia was associated with higher levels of CRP (adjusted B = 0.04, 95%CI [0.00–0.08], $p = 0.046$), but not for people with "Elevated" or "Very High" levels of CRP. There was an

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association between CRP and presence of chronic LBP in the total sample (adjusted OR = 1.01, [1.00–1.01], $p = 0.013$) and for people with "Normal" CRP (1.05, [1.00–1.10, $p = 0.034$]. Insomnia was associated with the presence of chronic LBP in the total sample (adjusted OR = 1.99, 95%CI [1.79–2.21], <0.001) and for people with "Normal", "Elevated" and "Very High".

Conclusions: Individuals with insomnia have twice the odds of reporting chronic LBP. Insomnia, CRP and chronic LBP appear to be linked but the role of CRP appears to be limited. Longitudinal studies may help further explore the causal inference between insomnia chronic LBP, and inflammation.

Implications: Given the strong relationship between insomnia and chronic LBP, screening and management of comorbid insomnia and chronic LBP should be considered in clinical practice. Further longitudinal studies are required to explore whether the presence of insomnia and increased inflammation affects the development of chronic LBP.

Keywords: chronic low back pain; insomnia; c-reactive protein; inflammation; epidemiology.

1 Introduction

Chronic low back pain (chronic LBP) is the most frequent musculoskeletal complaint worldwide with a lifetime prevalence of 60–80% [1], and 1-month prevalence of 20% [2]. Chronic LBP is the top cause for years lived with disability in The Global Burden of Disease study 2013 [3]. Insomnia symptoms are highly prevalent in individuals with chronic LBP, with 55–59% of sufferers [4–6] reporting insomnia symptoms, such as poor sleep quality, non-restorative sleep, waking up too early, and difficulty initiating and maintaining sleep [7, 8].

For people with chronic LBP, insomnia symptoms are associated with increased pain intensity (r = 0.38–0.58) [6, 9, 10] and decreased physical function (r = 0.57) [11]. People with insomnia have 1.36 times the odds of developing chronic LBP 17 months later, compared to those without insomnia [12]. To explain the sleep-pain relationship, theoretical models propose that insomnia may lead to increased basal inflammation, which could contribute to increased pain, and further disrupt sleep [13–15]. Inflammation can be measured by proxy via inflammatory markers such as tumor necrosis factor (TNF), interleukin 6 (IL-6), and c-reactive protein (CRP). CRP is of special interest as it has been commonly assessed in large population studies for cardiovascular disease risk [16].

The relationship between insomnia and CRP, and the relationship between CRP and presence of chronic LBP are not clear. This is partly due to differing definitions of insomnia ranging from symptoms (e.g. wake after sleep onset and sleep duration), validated questionnaire threshold scores, and diagnostic criteria). A systematic review has shown that CRP was associated with some but not all measures of insomnia [17], and no studies defined insomnia by diagnostic criteria [17]. Furthermore, a systematic review of the association between chronic LBP and CRP was unable to perform a meta-analysis due to high heterogeneity from varying diagnostic criteria for chronic LBP [18]. Both reviews discuss that aside from the lack of consistent insomnia and chronic LBP diagnostic criteria, other comorbidities or associated factors may not have been adequately controlled for [17, 18]. These include obesity [19], physical activity [20], depression [21–23], anxiety [23, 24] and presence of osteoarthritis [25, 26]. Moreover, several of the reviewed studies included people with highly inflammatory conditions, such as end stage cancer, which may not be comparable for people with chronic LBP. Finally, no study has modelled the associations of insomnia, CRP and chronic LBP within the same sample, requiring the need to infer the associations across different cohorts.

This study aims to investigate associations between insomnia, chronic LBP, and inflammation (operationalized as CRP) whilst controlling for confounders such as age, body mass index (BMI), smoking, physical activity, depression, anxiety and osteoarthritis, in a large population-based study of Norwegian adults. The specific research questions are as follows:

A) Is presence of insomnia associated with higher levels of CRP?
B) Is higher level of CRP associated with higher prevalence of chronic LBP?
C) Is presence of insomnia associated with higher prevalence of chronic LBP?

Results pertaining to these research questions may inform the design of longitudinal studies exploring the casual inference between insomnia, chronic LBP and inflammation.

2 Methods

2.1 Study design

This was a cross-sectional study of a large Norwegian community-based Nord-Trøndelag Health Study

(HUNT - **H**else**u**ndersøkelsen i **N**ord-**T**røndelag). The HUNT has been collected in three surveys; HUNT1 (1984–1986), HUNT2 (1995–1997), and HUNT3 (2006–2008). This study analyzed data from the HUNT3 survey. All residents of the Nord-Trøndelag County in rural mid-Norway aged 20 years and older were invited to participate ($n = 93,860$) and data were collected from 50,666 participants. A wide range of health-related data, including musculoskeletal health and insomnia, were collected through questionnaires, interviews, biological samples, and clinical examinations between October 2006 and June 2008. A comprehensive description of the cohort and methods of data collection employed can be found elsewhere [27]. Questionnaires were self-reported and answered via hardcopy at home. Clinical measurements such as BMI were collected via a basic health examination at designated health clinics. Blood samples were also collected during these health examinations and transported daily by courier to the biobank, following a strict quality protocol. Interviews were also conducted at health examinations regarding employment and women's health. Further information about the HUNT Study can be found at http://www.ntnu.edu/hunt.

The current study was approved by the Regional Committees for Medical Research Ethics in south east Norway (REK Sør-Øst) (Project No: 2016/1997) and was conducted in accordance with the Helsinki Declaration. All data were treated according to the guidelines of the Data Inspectorate. The study data were securely stored in the Oslo University Hospital (OUS) and performed according to rules that apply for research studies at OUS.

2.2 Eligibility criteria

From 50,666 Nord-Trøndelag County participants from whom data were collected, we excluded participants ($n = 5,919$) with the self-reported chronic somatic diseases of chronic heart failure, chronic obstructive pulmonary disease, rheumatoid arthritis, fibromyalgia or ankylosing spondylosis. These were chronic somatic diseases which have been reported to have a strong association with insomnia or chronic LBP. To confirm their suitability for exclusion, we considered in our data (1) the association of the presence of these conditions and the presence of insomnia and chronic LBP, (2) the median CRP of people with these conditions compared to people with either insomnia or chronic LBP, (3) the number of people with the condition. We then excluded 14,048 participants who had incomplete data for our study variables, resulting in a total sample size of 30,669 (Fig. 1).

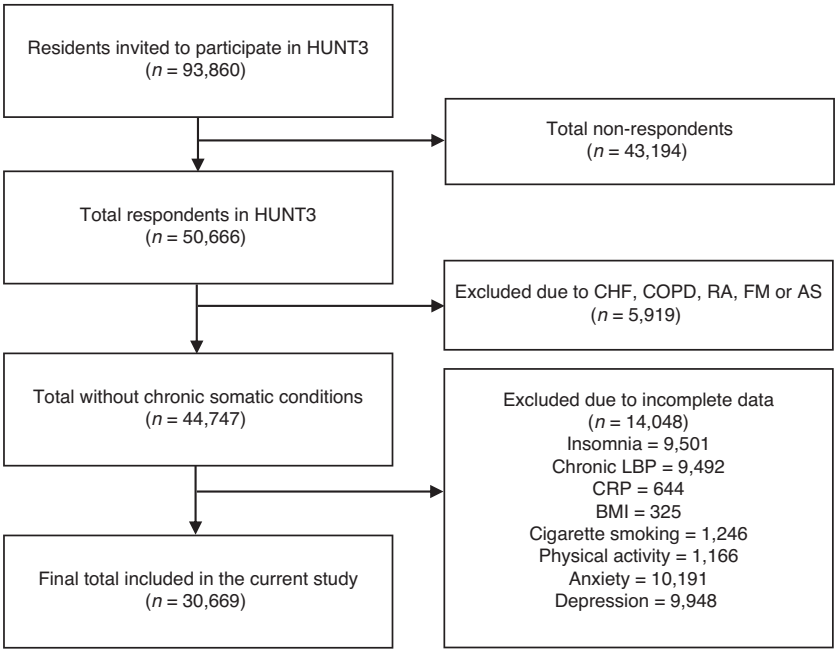

Fig. 1: Flowchart of participants. AS = ankylosing spondylosis; BMI = body mass index; CHF = chronic heart failure; Chronic LBP = chronic low back pain; COPD = chronic obstructive pulmonary disease; FM = fibromyalgia; CRP = c-reactive protein; HUNT3 = Helseundersøkelsen i Nord-Trøndelag, third survey; RA = rheumatoid arthritis.

2.3 Variables

The main outcome variables for this study were presence of chronic LBP, presence of insomnia, and level of CRP. The classification of chronic LBP, diagnosis of insomnia, and definition of possible confounding variables were determined by data from HUNT3 survey questions, while CRP was measured from blood serum samples.

2.3.1 Presence of chronic LBP

Chronic LBP was reported as low back pain or stiffness lasting for a minimum of 3 consecutive months in the past year. Using the Standardized Nordic Questionnaire for Musculoskeletal Symptoms [28], participants were asked "In the last year, have you had pain or stiffness in muscles or joints that has lasted at least 3 consecutive months?" If they answered yes, the following question was asked "Where have you had this pain or stiffness?" with the lower back as one of the nine possible regions. Participants were classified as having chronic LBP if they checked this option. This chronic LBP definition is consistent with the criteria of previous HUNT3 studies evaluating chronic LBP [20, 29] and international recommendations for observational studies in chronic LBP [30–32].

2.3.2 Presence of insomnia

Presence of insomnia was defined using modified insomnia criteria from the Diagnostic and statistical manual of mental disorders 5th Edition (DSM-5) [33]. Insomnia classification was based on four questionnaire answers. Participants were asked "How often during the last 3 months have you": (1) Had difficulty falling asleep at night? (2) Woken up repeatedly during the night? (3) Woken too early and could not get back to sleep? (4) Felt sleepy during the day? The response options for each of these questions were "Never/seldom", "Sometimes", or "Several times a week". Participants were classified as having insomnia if they answered "Several times a week" to question 4 and to at least one of questions 1–3. The first three insomnia questions in questionnaire form have good reliability in comparison to interview form (kappa value, 0.51; 95% CI, 0.40–0.63) [34].

2.3.3 c-Reactive protein

Data for high sensitive CRP were obtained from non-fasting serum samples were extracted from participants at the time of the questionnaires, with reagent kit; 6K2640 CRP Vario (Abbot, Clinical Chemistry, USA). Samples were analyzed by Levanger Hospital, Norway, following latex immunoassay methodology. The measurement range was from 0.1 to 160 mg/L, with total assay coefficient of variation being 1.5% in the low range (5.8 mg/L) and 1.7% in the high range (12.8 mg/L). CRP data were also checked for outliers.

We also planned to perform stratified analyses based on levels of CRP. This was to determine if the strength of association between insomnia and chronic LBP, and between insomnia and CRP differed for people within "Normal", "Elevated" and "Very High" CRP levels, as this had been shown for the association between CRP and chronic LBP [19]. According to the American Heart Association, the cardiac risk thresholds in relation to levels of CRP are "Low" (<1.0 mg/L), "Average" (1.0–3.0 mg/L), "High" (>3.0 mg/L), and "Acute Inflammation" (>10 mg/L) [16]. While the World Health Organization recommends to use a serum CRP threshold of <5 mg/L to define normal values for a rapid test, and <3–10 mg/L when using immunoassays [35, 36]. Given that the method of CRP analysis in HUNT3 was by immunoassay technology, we defined levels of CRP as "Normal" (<3 mg/L), "Elevated" (3–10 mg/L) and "Very High" (>10 mg/L) for the stratified analyses.

2.4 Possible confounders

Due to the potential associations with insomnia symptoms, CRP and pain, we considered the following variables as possible confounders: age, BMI, sex, cigarette smoking, physical activity, depression, anxiety and presence of osteoarthritis. Age in years was treated as a continuous variable. BMI was categorized as normal (<25 kg/m^2), overweight (25–29.9 kg/m^2), and obese (>30 kg/m^2). Sex was categorized as female or male. Cigarette smoking was categorized as "Never", "Former", or "Current" smoker. Physical activity was classified using the total duration of leisure time physical exercise per week [37]. Participants were asked "How often do you exercise?" (per week) with the following possible responses "Never", "Less than once a week", "Once a week", "2–3 times a week", "Nearly every day". If the participants answered at least "Once a week" they were also asked "How long do you exercise each time?" with the following possible responses "Less than 15 min", "15–29 min", "30 min–1 h", "More than 1 h". Following a previous HUNT study [20], we calculated the total duration of physical activity per week as: Inactive (0–59 min/week), Moderately Active (60–120 min/week),

and Active (≥120 min/week). Depression and Anxiety were assessed by the Hospital Anxiety and Depression Score [38] and were classified accordingly to the validated thresholds: Normal (0–7), Borderline (8–10), and Abnormal (11–21). Data on osteoarthritis were dichotomized, with participants regarded as cases if they answered yes to the question "Have you ever had osteoarthritis?"

2.5 Statistical analyses

Descriptive statistics were used to describe the characteristics of the sample with regards to demographics, and variables of interest. Question A (Is presence of insomnia associated with higher levels of CRP?) was assessed using multiple linear regression adjusted for possible

Table 1: Characteristics of participants in the included sample.

Characteristic	Total *n* = 30,669	Normal CRP (<3 mg/L) *n* = 24,288	Elevated CRP (3–10 mg/L) *n* = 5,275	Very High CRP (>10 mg/L) *n* = 1,136
Age				
Mean (SD)	52.2 (15.2)	51.8 (14.8)	53.8 (15.9)	53.7 (17.6)
Range	19.1–95.9	19.1–95.9	19.5–95.8	19.6–90.8
Aged 20–49 years, *n* (%)	13,461 (44%)	10,972 (45%)	2,026 (38%)	463 (41%)
Aged ≥50 years, *n* (%)	17,238 (56%)	13,316 (55%)	3,249 (62%)	673 (59%)
Sex (female)	16,663 (54%)	12,849 (53%)	3,142 (60%)	672 (59%)
Insomnia (median CRP = 1.2 mg/L)				
Yes	1,871 (6%)	1,403 (6%)	387 (7%)	81 (7%)
No	28,828 (94%)	22,885 (94%)	4,888 (93%)	1,055 (93%)
Chronic low back pain (median CRP = 1.4 mg/L)				
Yes	6,559 (21%)	4,964 (20%)	1,302 (25%)	293 (26%)
No	24,140 (79%)	19,324 (80%)	3,973 (75%)	843 (74%)
Insomnia and chronic low back pain (both)	719 (2%)	514 (2%)	168 (3%)	37 (3%)
hsCRP (mg/L)				
Mean (SD)	2.5 (5.3)	1.1 (0.7)	5.2 (1.8)	21.0 (17.9)
Median	1.1	0.9	4.7	15.0
Range	0–160.1	0–2.9	3–10	10.1–160.1
0–2.9	24,288 (79%)	24,288 (100%)	–	–
3–10	5,275 (17%)	–	5,275 (100%)	–
>10	1,136 (4%)	–	-	1,136 (100%)
BMI (kg/m^2)				
<25	10,227 (33%)	8,908 (37%)	1,022 (19%)	297 (26%)
25–29.9	13,869 (45%)	11,222 (46%)	2,220 (42%)	427 (38%)
≥30	6,603 (22%)	4,158 (17%)	2,033 (39%)	412 (36%)
Cigarette smoking				
Never	13,745 (45%)	11,231 (46%)	2,052 (39%)	462 (41%)
Former	10,026 (33%)	7,909 (33%)	1,743 (33%)	374 (33%)
Current	6,928 (23%)	5,148 (21%)	1,480 (28%)	300 (26%)
Physical activity				
Inactive (0–59 min/week)	11,777 (38%)	8,841 (36%)	2,417 (46%)	519 (46%)
Moderately actively (60–119 min/week)	10,564 (34%)	8,536 (35%)	1,653 (31%)	375 (33%)
Active (120 + min/week)	8,358 (27%)	6,911 (29%)	1,205 (23%)	242 (21%)
Depression (HADS)				
Normal (0–7)	28,175 (92%)	22,389 (92%)	4,756 (90%)	1,030 (91%)
Borderline (8–10)	1,968 (6%)	1,484 (6%)	407 (8%)	77 (7%)
Abnormal (11–21)	556 (2%)	415 (2%)	112 (2%)	29 (3%)
Anxiety (HADS)				
Normal (0–7)	26,792 (87%)	21,260 (88%)	4,546 (86%)	986 (87%)
Borderline (8–10)	2,642 (9%)	2,049 (8%)	491 (9%)	102 (9%)
Abnormal (11–21)	1,265 (4%)	979 (4%)	238 (5%)	48 (4%)
Osteoarthritis				
Yes	3,838 (13%)	2,825 (12%)	833 (16%)	180 (16%)
No	26,861 (88%)	21,463 (88%)	4,442 (84%)	956 (84%)

BMI = body mass index; CRP = c-reactive protein; HADS = hospital anxiety and depression scale; SD = standard deviation.

confounders (age, BMI, sex, cigarette smoking, physical activity, depression, and anxiety). Question B (Is higher level of CRP associated with higher prevalence of chronic LBP?) was assessed using multiple logistic regression adjusted for possible confounders. Question C (Is the presence of insomnia associated with higher prevalence of chronic LBP?) was assessed using multiple logistic regression adjusted for CRP and possible confounders. Possible confounders that achieved $p \leq 0.2$ in univariate regressions were entered into their respective multivariable regression models. Results from logistic regression models were presented as odd ratios (OR) with 95% confidence intervals (95% CI), while those from linear regressions were presented as unstandardized betas (B) with 95% CI. Stratified analyses were also performed for participants within "Normal", "Elevated" and "Very High" levels of CRP for the associations between insomnia and chronic LBP, and between insomnia and CRP. *p*-Values of ≤0.05 were considered statistically significant and all tests were two-sided. Analyses were performed using IBM SPSS 24 (Statistical Package for the Social Sciences).

3 Results

3.1 Participants

In our total included sample ($n = 30{,}669$), 6.1% had insomnia ($n = 1{,}871$), 21.4% had chronic LBP ($n = 6{,}559$), and 2.4% had both ($n = 719$). Age ranged from 19 to 96 years (median age = 52.6) and 54.3% of the sample were female ($n = 16{,}663$) (Table 1). In reference to our stratified analyses, 24,288 (79%) participants had "Normal" levels of CRP while 5,275 (17%) had "Elevated" levels and 1,136 (4%) had "Very High" levels. The proportion of participants with insomnia and/or chronic LBP was similar between all CRP subgroups.

3.2 Question A) is presence of insomnia associated with higher levels of CRP?

Unadjusted analyses of the total sample revealed all possible confounders except anxiety were independently associated with CRP (Appendix 1). For the total sample, in the multivariable adjusted analysis, insomnia was not associated with higher levels of CRP (B = 0.13, [−0.12 to 0.38], $p = 0.304$) (Table 2). However, there were differences between people with "Normal", "Elevated" and "Very High" levels of CRP concerning this relationship. Among people within "Normal" levels of CRP, the

Table 2: Multiple linear regression between insomnia and c-reactive protein.

Variable	Categories	Total sample[b] ($n = 30{,}669$, adjusted $R^2 = 0.019$)			Normal CRP (<3 mg/L)[b] ($n = 24{,}288$, adjusted $R^2 = 0.108$)			Elevated CRP (3–10 mg/L)[b] ($n = 5{,}275$, adjusted $R^2 = 0.007$)			Very High CRP (>10 mg/L)[b] ($n = 11{,}361$, adjusted $R^2 = 0.008$)		
Dependent (CRP)		**B**	**95% CI**	***p*-Value**	**B**	**95% CI**	***p*-Value**	**B**	**95% CI**	***p*-Value**	**B**	**95% CI**	***p*-Value**
Insomnia	Yes (No[a])	0.13	−0.12 to 0.38	0.304	0.04	0.00–0.08	0.046[c]	−0.00	−0.20 to 0.19	0.977	−0.61	−4.72 to 3.50	0.770
Age	Continuous	0.01	0.01–0.02	<0.001[c]	0.01	0.00–0.01	<0.001[c]	−0.01	−0.01 to −0.00	0.002[c]	0.43	−0.02 to 0.11	0.205
BMI	Categorical	0.82	0.73–0.90	<0.001[c]	0.29	0.28–0.31	<0.001[c]	0.12	0.05–0.19	0.001[c]	−2.46	−3.81 to −1.11	<0.001[c]
Sex	M (F[a])	−0.46	−0.58 to −0.33	<0.001[c]	−0.04	−0.06 to −0.02	<0.001[c]	−0.14	−0.24 to −0.03	0.011[c]	−0.24	−2.45 to 1.97	0.831
Smoking	Categorical	0.22	0.15–0.30	<0.001[c]	0.06	0.05–0.07	<0.001[c]	−0.04	−0.10 to 0.02	0.180	−0.41	−1.70 to 0.89	0.541
Physical activity	Categorical	−0.24	−0.31 to −0.16	<0.001[c]	−0.04	−0.05 to −0.03	<0.001[c]	−0.06	−0.12 to 0.01	0.069	0.36	−0.98 to 1.69	0.600
Depression	Categorical	0.08	−0.09 to 0.25	0.342	−0.02	−0.05 to 0.00	0.101	0.14	0.01–0.27	0.039[c]	−0.78	−3.44 to 1.88	0.566
Osteoarthritis	Yes (No[a])	0.13	−0.06 to 0.32	0.168	0.01	−0.02 to 0.04	0.362	0.02	−0.13 to 0.16	0.836	−0.50	−3.55 to 2.54	0.746

BMI = body mass index; CRP = c-reactive protein.
[a]Reference variable.
[b]The multiple linear regression model included all available confounders with a significant univariate association with CRP ($p \leq 0.2$).
[c]Denotes significance at 0.05 level.

presence of insomnia was associated with higher levels of CRP (adjusted B = 0.04, 95%CI [0.00–0.08], $p = 0.046$). To the contrary, among people with "Elevated levels" or "Very High" levels of CRP, insomnia was not associated with CRP (Table 2).

3.3 Question B) Is higher level of CRP associated with the prevalence of chronic LBP?

Unadjusted analyses of the total included sample revealed that all the possible confounders were associated with the presence of chronic LBP (Appendix 1). In the multivariable adjusted analysis, higher levels of CRP were associated with higher odds of chronic LBP (OR = 1.01, [1.00–1.01], $p = 0.013$) (Table 3).

Similar to the relationship between insomnia and CRP, there were differences between people with "Normal", "Elevated" and "Very High" levels of CRP concerning the association between CRP and chronic LBP. Among people within "Normal" levels of CRP, higher levels of CRP were associated with higher odds of chronic LBP (OR = 1.05, [1.00–1.10], $p = 0.034$). However, among people with "Elevated" levels or "Very High" levels of CRP, insomnia was not associated with CRP (Table 3).

3.4 Question C) is presence of insomnia associated with the prevalence of chronic LBP?

Unadjusted analyses of the total included sample revealed that all the possible confounders (age, BMI, sex, cigarette smoking, physical activity, depression, anxiety and osteoarthritis) were associated with the presence of chronic LBP (Appendix 1). In the multivariable analysis including these confounders, the individuals with insomnia had almost twice as high odds for chronic LBP compared to individuals who did not report insomnia (OR = 1.99, 95%CI [1.79–2.21], $p < 0.001$) (Table 4). There were no differences in the strength of the insomnia and chronic LBP association between people with "Normal", "Elevated" or "Very High" levels of CRP in our multivariable analyses.

4 Discussion

4.1 Summary

Our results revealed that among a general population of Norwegian adults, individuals with insomnia compared to those who did not report having it, have twice the odds of reporting chronic LBP. People with increased levels of inflammation had higher odds of reporting chronic LBP, where a unit increase in CRP increased the odds of chronic LBP by 1% (OR = 1.01). For people with "Normal" levels (<3 mg/L) of CRP, insomnia was associated with CRP, and CRP was associated with chronic LBP. However, this relationship did not hold for individuals with "Elevated" (3–10 mg/L) or "Very High" (>10 mg/L) levels of CRP.

4.2 Interpretation of findings and comparisons with previous literature

4.2.1 Answer A) presence of insomnia was associated with higher level of CRP

The association between insomnia and CRP aligns with a 2016 systematic review [17]. This was expected as it has been widely known that sleep deprivation is associated with increased levels of IL-6 and TNF, which both are associated with and regulate CRP [13, 15, 39, 40]. We found that in participants with "Normal" (≤3 mg/L) CRP, those with insomnia had 0.04 mg/L higher CRP than people without insomnia. This is similar to changes in CRP reported after eleven days of sleep deprivation (<4 h/night) [15]. However, for people with "Elevated" levels (>3 mg/L) of CRP, the association between insomnia and CRP was not evident. There are two possible reasons why inflammation was associated with insomnia or chronic LBP only for "Normal" CRP levels: (1) those in the "Elevated" and "Very High" CRP categories had a larger proportion of people with "Obese" BMI, "Current" smoking, "Inactive" physical activity, "Abnormal" Depression and Anxiety, which were confounders we had adjusted for. (2) The relative sample sizes of the "Elevated" and "Very High" CRP strata were smaller and may not be sufficiently powered to demonstrate a small statistically significant effect.

4.2.2 Answer B) higher level of CRP was associated with higher odds of chronic LBP

The association between CRP and chronic LBP was in agreement with a recent systematic review [18], which included four studies [19, 41–43] evaluating this specific relationship. Specifically, Briggs et al.'s [19] study ($n = 15{,}222$) found that people with "Elevated" (>3 mg/L) CRP had 1.74 times the odds of reporting chronic LBP

Table 3: Multiple logistic regression model for the association between c-reactive protein and chronic low back pain.

Variable	Categories	Total sample[b] ($n=30,669$, $R^2=0.051$)			Normal CRP (<3 mg/L)[b] ($n=24,288$, $R^2=0.046$)			Elevated CRP (3–10 mg/L)[b] ($n=5,275$, $R^2=0.061$)			Very High CRP (>10 mg/L)[b] ($n=1,136$, $R^2=0.062$)		
Dependent (chronic LBP)		**OR**	**95% CI**	***p*-Value**	**OR**	**95% CI**	***p*-Value**	**OR**	**95% CI**	***p*-Value**	**OR**	**95% CI**	***p*-Value**
CRP	Continuous	1.01	1.00–1.01	0.013[c]	1.05	1.00–1.10	0.034[c]	1.02	0.98–1.01	0.310	1.00	0.99–1.01	0.942
Age	Continuous	1.00	1.00–1.00	0.106	1.00	1.00–1.00	0.253	1.00	1.00–1.01	0.635	1.01	1.00–1.02	0.067
BMI	<25 kg/m^2 [a]	–	–	–	–	–	–	–	–	–	–	–	–
	25–29.9	1.20	1.19–1.28	<0.001[c]	1.16	1.08–1.26	<0.001[c]	1.21	1.00–1.46	0.052	1.40	0.96–2.03	0.078
	≥30	1.36	1.26–1.47	<0.001[c]	1.25	1.13–1.38	<0.001[c]	1.42	1.18–1.72	<0.001[c]	1.78	1.23–2.59	0.002[c]
Sex	M (F[a])	0.84	0.80–0.90	<0.001[c]	0.87	0.81–0.93	<0.001[c]	0.79	0.68–0.90	0.001[c]	0.80	0.59–1.08	0.147
Smoking	Never[a]	–	–	–	–	–	–	–	–	–	–	–	–
	Former	1.32	1.24–1.41	<0.001[c]	1.33	1.23–1.43	<0.001[c]	1.33	1.14–1.56	<0.001[c]	1.18	0.85–1.64	0.328
	Current	1.35	1.25–1.45	<0.001[c]	1.33	1.22–1.44	<0.001[c]	1.42	1.20–1.67	<0.001[c]	1.18	0.83–1.67	0.367
Physical activity	0–59 min[a]	–	–	–	–	–	–	–	–	–	–	–	–
	60–119	0.92	0.86–0.98	0.009[c]	0.91	0.84–0.98	0.018[c]	0.91	0.78–1.06	0.201	1.11	0.81–1.52	0.528
	120+	0.93	0.86–1.00	0.038[c]	0.91	0.84–0.99	0.031[c]	0.99	0.84–1.17	0.880	1.08	0.75–1.56	0.686
Depression	Normal[a]	–	–	–	–	–	–	–	–	–	–	–	–
	Borderline	1.21	1.08–1.35	0.001[c]	1.20	1.06–1.37	0.005[c]	1.21	0.95–1.54	0.124	1.35	0.79–2.31	0.274
	Possible	1.61	1.33–1.94	<0.001[c]	1.53	1.23–1.91	<0.001[c]	1.90	1.26–2.87	0.002[c]	1.65	0.72–3.79	0.208
Anxiety	Normal[a]	–	–	–	–	–	–	–	–	–	–	–	–
	Borderline	1.56	1.42–1.71	<0.001[c]	1.51	1.36–1.69	<0.001[c]	1.80	1.46–2.22	<0.001[c]	1.37	0.85–2.21	0.191
	Possible	2.02	1.77–2.30	<0.001[c]	2.10	1.81–2.44	<0.001[c]	1.82	1.34–2.47	<0.001[c]	1.61	0.82–3.13	0.164
Osteoarthritis	Yes (No[a])	3.04	2.81–3.28	<0.001[c]	3.08	2.82–3.37	<0.001[c]	2.94	2.48–3.49	<0.001[c]	2.75	1.91–3.96	<0.001[c]

BMI = body mass index; Chronic LBP = chronic low back pain; CRP = c-reactive protein.

[a]Reference variable.

[b]The multiple logistic regression model included all available confounders with a significant univariate association with Chronic LBP ($p \leq 0.2$).

[c]Denotes significance at 0.05 level.

Table 4: Multiple logistic regression model for the total effect of insomnia and c-reactive protein on chronic low back pain.

Variable	Categories	Total sample[b] ($n=30,669$, $R^2=0.055$)			Normal CRP (<3 mg/L)[b] ($n=24,288$, $R^2=0.050$)			Elevated CRP (3–10 mg/L)[b] ($n=5,275$, $R^2=0.068$)			Very High CRP (>10 mg/L)[b] ($n=1,136$, $R^2=0.074$)		
Dependent (chronic LBP)		**OR**	**95% CI**	***p*-Value**	**OR**	**95% CI**	***p*-Value**	**OR**	**95% CI**	***p*-Value**	**OR**	**95% CI**	***p*-Value**
Insomnia	Yes (No[a])	1.99	1.79–2.21	<0.001[c]	1.92	1.70–2.17	<0.001[c]	2.09	1.67–2.63	<0.001[c]	2.70	1.64–4.44	<0.001[c]
CRP	Continuous	1.01	1.00–1.01	0.016[c]	1.05	1.00–1.10	0.050[c]	1.02	0.98–1.06	0.314	1.00	0.99–1.01	0.903
Age	Continuous	1.00	1.00–1.01	0.009[c]	1.00	1.00–1.01	0.066	1.00	1.00–1.01	0.251	1.01	1.00–1.02	0.022[c]
BMI	<25 kg/m^2 [a]	–	–	–	–	–	–	–	–	–	–	–	–
	25–29.9	1.20	1.12–1.28	<0.001[c]	1.17	1.08–1.26	<0.001[c]	1.20	1.00–1.46	0.057	1.42	0.98–2.06	0.068
	≥30	1.33	1.24–1.46	<0.001[c]	1.25	1.13–1.38	<0.001[c]	1.40	1.16–1.69	0.001[c]	1.75	1.20–2.55	0.004[c]
Sex	M (F[a])	0.85	0.80–0.90	<0.001[c]	0.87	0.82–0.94	<0.001[c]	0.80	0.69–0.92	0.002[c]	0.82	0.61–1.11	0.200
Smoking	Never[a]	–	–	–	–	–	–	–	–	–	–	–	–
	Former	1.31	1.23–1.40	<0.001[c]	1.32	1.23–1.43	<0.001[c]	1.31	1.12–1.54	0.001[c]	1.12	0.80–1.57	0.502
	Current	1.34	1.24–1.44	<0.001[c]	1.32	1.21–1.44	<0.001[c]	1.40	1.19–1.65	<0.001[c]	1.13	0.79–1.60	0.516
Physical activity	0–59 min[a]	–	–	–	–	–	–	–	–	–	–	–	–
	60–119	0.92	0.86–0.99	0.020[c]	0.92	0.85–0.99	0.032[c]	0.92	0.79–1.07	0.263	1.12	0.81–1.54	0.489
	120+	0.94	0.87–1.01	0.083	0.92	0.85–1.00	0.058	1.00	0.85–1.19	0.967	1.11	0.76–1.60	0.592
Depression	Normal[a]	–	–	–	–	–	–	–	–	–	–	–	–
	Borderline	1.12	1.03–1.29	0.012[c]	1.15	1.01–1.31	0.037[c]	1.16	0.91–1.48	0.225	1.19	0.68–2.06	0.528
	Possible	1.48	1.22–1.80	<0.001[c]	1.42	1.13–1.77	0.002[c]	1.69	1.11–2.58	0.015[c]	1.67	0.72–3.87	0.228
Anxiety	Normal[a]	–	–	–	–	–	–	–	–	–	–	–	–
	Borderline	1.47	1.33–1.61	<0.001[c]	1.43	1.28–1.59	<0.001[c]	1.69	1.36–2.08	<0.001[c]	1.35	0.84–2.18	0.217
	Possible	1.75	1.53–2.00	<0.001[c]	1.82	1.56–2.12	<0.001[c]	1.61	1.18–2.19	0.003[c]	1.33	0.68–2.62	0.402
Osteoarthritis	Yes (No[a])	3.01	2.78–3.25	<0.001[c]	3.05	2.79–3.34	<0.001[c]	2.90	2.45–3.45	<0.001[c]	2.80	1.94–4.03	<0.001[c]

BMI = body mass index; Chronic LBP = chronic low back pain; CRP = c-reactive protein.

[a]Reference variable.

[b]The multiple logistic regression model included all available confounders with a significant univariate association with Chronic LBP ($p \leq 0.2$).

[c]Denotes significance at 0.05 level.

compared to those with "Normal" CRP (≤3 mg/L). This study found that a unit increase of CRP (in mg/L) was associated with increased odds of chronic LBP by 1% (OR = 1.01).

4.2.3 Answer C) is presence of insomnia associated with the prevalence of chronic LBP?

Our findings revealed that people with insomnia have twice the odds of reporting chronic LBP. This was consistent with similar cross-sectional studies which reported a moderate correlation between insomnia and chronic LBP pain intensity [6, 9, 11, 44] when insomnia was defined by sleep quality (B = −0.26) [8, 44] or questionnaires (r = 0.41–0.59) [6, 9, 11].

It is possible to infer that the relationship between insomnia and chronic LBP is bidirectional, based on studies between insomnia and chronic pain conditions such as osteoarthritis [13]. However to date, there has only been one longitudinal study which attempted to confirm the bidirectional relationship between insomnia and chronic LBP (n = 2,131). The study identified that people with insomnia had greater odds of developing chronic LBP over 17 months (OR = 1.40 [12]; 95%CI [1.36–1.51]) [20, 45], but people with chronic LBP did not show increased odds of developing insomnia [12].

In our sample, 11% of participants with chronic LBP had concomitant insomnia, which was lower than the 55–59% reported in other studies [4–6]. This was expected as our insomnia definition required daytime impairment as in the DSM-5 criteria for insomnia, rather than the any symptoms of insomnia. The prevalence rates for insomnia (6.1%) and chronic LBP (21.4%) were comparable to other studies at a population level for people over the age of 20 [30, 45–47].

4.3 Strengths

The key strength of this study is availability of a large population-based database and biobank of >30,000 participants. This ensured sufficient power to detect findings with great precision. The methodology of questionnaire data collection and CRP sampling is of high quality and well documented [27], giving confidence in the internal and external validity of our data. Our definition of insomnia was very similar to the DSM-5 insomnia criteria [33]. To ensure that our results were not masked by comorbid chronic somatic diseases, we excluded participants with these conditions and performed stratified analyses based on "Normal", "Elevated" and "Very High" CRP levels in accordance to the American Heart Association [16].

4.4 Limitations

There are some limitations of this study that need to be considered. Our definition of chronic LBP differed with the with international standards of chronic LBP [30–32] as the questionnaire included stiffness in the lumbar regions, and whether pain or stiffness occurred for 3 months in the past year. Thus, it was not possible to truly know if participants had stiffness only, and whether chronic LBP was current when CRP was measured. Also, we could not exclude subjects with nerve root compromises or previous spinal surgery due the survey questions available. Some variables had a considerable amount of missing values ranging from 21 to 23% for insomnia, chronic LBP, depression and anxiety. As these questions were all included in a second questionnaire covering other health questions, the majority of those with missing data on insomnia also had missing data for chronic LBP. Since the proportion of individuals with chronic LBP was similar for responders who had and did not have missing data on insomnia and CRP, we assumed that there was no information or pattern in missingness, e.g. we could assume missing at random. While a large sample size has great power and likelihood to detect statistical significance, it may potentially over-inflate the clinical relevance of such findings, i.e. data concerning CRP must be interpreted with caution since a quite large sample was needed to show a small effect as statistically significant. As a cross-sectional study, it was not possible to make causal inferences between the associated variables (e.g. does insomnia lead to increased inflammation and then chronic LBP) [48].

4.5 Clinical implications

Our results highlight the comorbidity between insomnia and chronic LBP. Studies and guidelines on the management of chronic LBP mention the consideration of psychological comorbidities as this may lead to more complex management, however the targeting of these factors such as insomnia is still not part of the recommendations [49–51]. Insomnia is amendable to treatment with cognitive behavioral therapy as the first line intervention [52], followed by the addition of short term sleep medication use if unsuccessful [52, 53].

The potential role of systematic inflammation has been increasingly recognized in chronic musculoskeletal conditions such as rheumatoid arthritis and osteoarthritis [13], and there is evidence that systematic inflammation may play role in chronic LBP based on our results and previous studies [18, 19]. It has been hypothesized that inflammation

promotes hyperalgesia and temporal summation [13]. People with "Elevated" (3–20 mg/L) levels of CRP have increased experimental pain sensitivity (cold-pressor pain tolerance) (hazard ratio = 1.22, 95%CI [1.09–1.36]) [54, 55], compared to people with "Normal" CRP (≤3 mg/L). Moreover, based on this assumption it has been hypothesized that insomnia may lead to increased basal inflammation, which could contribute to increased pain through these pain paradigms. However, treating insomnia in people with comorbid osteoarthritis and insomnia did not change their experimental pain sensitivity (conditioned pain modulation or temporal summation of mechanical pain) [56].

A recent systematic review of longitudinal studies on sleep and pain recommends more research to verify the possible specific links between sleep, inflammatory processes and pain [57]. Our study clarifies that there is an association between insomnia and CRP, CRP and chronic LBP, and between CRP and chronic LBP when participants are within "Normal" levels of CRP (<3 mg/L). Our study also suggests that CRP may only have a small role in the relationship between insomnia and chronic LBP. Though the present cross-sectional study design was not suitable to answer questions concerning causality, longitudinal studies may help further explore the association between insomnia and chronic LBP, and the role of inflammation.

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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.

Appendix 1

Table A: Univariate logistic regression for c-reactive protein.

Variable	Categories	Total sample (n = 30,669)		
Dependent (CRP)		**B**	**95% CI**	***p*-Value**
Insomnia	Yes (No[a])	0.26	0.01–0.51	0.039[b]
Chronic LBP	Yes (No[a])	0.39	0.25–0.54	<0.001[b]
Age	Continuous	0.02	0.01–0.02	<0.001[b]
BMI	Categorical	0.85	0.77–0.94	<0.001[b]
Sex	M (F[a])	−0.27	−0.39 to −0.15	<0.001[b]
Smoking	Categorical	0.25	0.18–0.33	<0.001[b]
Physical activity	Categorical	−0.33	−0.40 to −0.25	<0.001[b]
Depression	Categorical	0.23	0.07–0.40	0.006[b]
Anxiety	Categorical	0.07	−0.06–0.19	0.304
Osteoarthritis	Yes (No[a])	0.54	0.36–0.72	<0.001[b]

BMI = body mass index; Chronic LBP = chronic low back pain; CRP = c-reactive protein.
[a]Reference variable.
[b]Denotes significance at 0.05 level.

Table B: Univariate logistic regression for chronic low back pain.

Variable	Categories	Total sample (n = 30,669)		
Dependent (chronic LBP)		**OR**	**95% CI**	***p*-Value**
Insomnia	Yes (No[a])	2.46	2.23–2.71	<0.001[b]
CRP	Continuous	1.01	1.01–1.02	<0.001[b]
Age	Continuous	1.01	1.01–1.01	<0.001[b]
BMI	<25 kg/m^2 [a]	–	–	–
	25–29.9	1.24	1.16–1.32	<0.001[b]
	≥30	1.55	1.44–1.67	<0.001[b]
Sex	M (F[a])	0.80	0.76–0.85	<0.001[b]
Smoking	Never[a]	–	–	–
	Former	1.40	1.32–1.49	<0.001[b]
	Current	1.41	1.32–1.51	<0.001[b]
Physical activity	0–59 min[a]	–	–	–
	60–119	0.88	0.82–0.94	<0.001[b]
	120+	0.88	0.82–0.94	<0.001[b]
Depression	Normal[a]	–	–	–
	Borderline	1.66	1.50–1.84	<0.001[b]
	Possible	2.40	2.02–2.85	<0.001[b]
Anxiety	Normal[a]	–	–	–
	Borderline	1.73	1.58–1.89	<0.001[b]
	Possible	2.48	2.20–2.79	<0.001[b]
Osteoarthritis	Yes (No[a])	3.37	3.14–3.62	<0.001[b]

BMI = body mass index; Chronic LBP = chronic low back pain; CRP = c-reactive protein.
[a]Reference variable.
[b]Denotes significance at 0.05 level.

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