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**Influence of sleep problems and co-occurring musculoskeletal pain on long-term prognosis of chronic low back pain: the HUNT Study**

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## **ABSTRACT**

**Background:** We investigated the influence of sleeplessness and number of insomnia symptoms on the probability of recovery from chronic low back pain (LBP), and the possible interplay between sleeplessness and co-occurring musculoskeletal pain on this association.

**Methods:** The study comprised data on 3,712 women and 2,488 men in the Norwegian HUNT Study who reported chronic LBP at baseline in 1995-1997. A modified Poisson regression model was used to calculate adjusted risk ratios (RRs) for the probability of recovery from chronic LBP at follow-up in 2006-2008, associated with sleep problems and co-occurring musculoskeletal pain at baseline.

**Results:** Compared to persons without sleeplessness, persons who often/always experienced sleeplessness had a lower probability of recovery from chronic LBP (RR 0.65, 95% CI: 0.57, 0.74 in women and RR 0.81, 95% CI: 0.69, 0.95 in men). Although there was no clear evidence of statistical interaction between sleeplessness and co-occurring musculoskeletal pain, women and men who often/always experienced sleeplessness and had  $\geq 5$  additional chronic pain sites had RRs of recovery of 0.40 (95% CI: 0.33, 0.48) and 0.59 (95% CI: 0.45, 0.78), respectively, compared to persons without sleeplessness and 1-2 chronic pain sites.

**Conclusion:** These findings suggest that preventing or reducing sleep problems among people with chronic LBP may have the potential of improving the long-term prognosis of this condition, also among those with several additional pain sites.

**KEY WORDS:** Sleep, sleep deprivation, sleep disorder, pain management, recovery, population health, prospective studies

### **What is already known on this subject?**

- Previous studies have shown that sleep problems are common among people with low back pain, and that poor sleep are associated with subsequent pain intensity and persistence of pain.
- In addition to sleep problems, co-occurring musculoskeletal pain is common in chronic low back pain. Previous studies have shown that co-occurring pain may worsen the prognosis.
- However, there is a lack of studies investigating whether sleep problems influence the long-term prognosis of chronic low back pain, or if sleep problems and co-occurring pain interact on this association.

### **What this study adds?**

- Frequency of sleeplessness and number of insomnia symptoms are inversely associated with the probability of recovery from chronic low back pain during a ~10 year follow-up period.
- The probability of recovery is especially low among persons who often/always experience sleeplessness and who also suffer from co-occurring musculoskeletal pain.
- These findings add to the body of evidence regarding the influence of poor sleep on the prognosis of chronic low back pain.

## **INTRODUCTION**

Low back pain (LBP) is highly prevalent in the general population and is the leading cause of years lived with disability worldwide.[1] Gaining further insight into factors that influence the prognosis of LBP will be useful to underpin the development and design of targeted interventions aimed at reducing the disability burden caused by LBP.

Sleep problems are common among people with chronic LBP.[2-4] It has been shown that insomnia symptoms increase the risk of chronic LBP [5] and that poor sleep is associated with subsequent pain intensity [6] and persistence of pain [7] in people with LBP. Furthermore, experimental studies have revealed a possible pathway between poor sleep and pain by showing that sleep deprivation leads to elevated levels of pro-inflammatory cytokines [8] and alterations in central pain processing.[9] One observational study has shown that occasional LBP and co-existing sleep problems are associated with higher risk of troublesome LBP.[10] However, there is a lack of studies investigating the influence of sleep problems on long-term prognosis of chronic LBP.

In addition to sleep problems, co-occurring musculoskeletal pain is common in chronic LBP.[11, 12] Previous studies indicate that number of chronic pain sites are inversely and dose-dependently associated with recovery from chronic LBP,[12] and that co-occurring pain in other axial regions may worsen the prognosis.[13] Moreover, there seems to be a bidirectional relation between sleep problems and number of chronic pain sites, i.e., number of chronic pain sites are associated with risk of insomnia symptoms [14] and vice versa.[15] Thus, it is conceivable that poor sleep and co-occurring musculoskeletal pain have a synergistic effect on the prognosis of LBP.

The aim of the current study was twofold. First, to examine if sleeplessness and insomnia symptoms influence the probability of recovery from chronic LBP, and second, to explore the interplay between sleeplessness and co-occurring musculoskeletal pain on the prognosis of LBP.

## **METHODS**

### Study population

The Norwegian HUNT Study is a longitudinal population-based cohort study carried out in the Nord-Trøndelag County in Norway. All inhabitants aged  $\geq 20$  years were invited to participate in the HUNT Study, first in 1984-1986 (HUNT1), then in 1995-1997 (HUNT2) and last in 2006-2008 (HUNT3). Information on lifestyle and health related factors were collected by questionnaires and a clinical examination. More information about the HUNT study can be found at <http://www.ntnu.edu/hunt>.

We selected all 36,975 participants who participated at baseline (HUNT2, 1995-1997) and follow-up (HUNT3, 2006-2008). Of these, we excluded 27,851 persons who reported to be free from chronic LBP at baseline in 1995-1997. Further, we excluded 1,928 persons with missing information on sleeplessness and insomnia symptoms. Thirty-two persons defined as underweight (BMI  $< 18.5$  kg/m<sup>2</sup>) were also excluded to possible pre-clinical disease that could influence both sleep and pain. Of the remaining 7,164 persons, 6,200 answered relevant pain questions at follow-up in 2006-2008. Thus, the prospective analyses were based on 3,712 women and 2,488 men.

### **Chronic low back pain**

The questions on musculoskeletal pain were adopted from the Standard Nordic Questionnaire.[16] At both baseline and follow-up, all participants were asked ‘During the last year, have you had pain and/or stiffness in your muscles and joints that lasted for at least three consecutive months?’. Those who answered ‘yes’ were asked to indicate the affected body area(s): neck, shoulders/upper arms, upper back, elbows, low back, wrists/hands, hips, knees, and ankles/feet. Participants were defined to have chronic LBP if they answered ‘yes’ to the first question and reported “low back” as an affected body area. Persons who reported no chronic LBP at follow-up were defined as recovered.

### **Co-occurring musculoskeletal pain**

Total number of chronic pain sites at baseline were identified from the response to body area(s) affected by chronic pain and classified as 1-2 pain sites, 3-4 pain sites and  $\geq 5$  pain sites. Furthermore, we constructed a new variable using the affected body area(s) to categorize participants into chronic pain in upper and/or lower extremity (shoulders/upper arms, elbows, wrists/hands, hips, knees, and ankles/feet) and chronic pain in other axial regions (neck, upper back).

### **Sleeplessness**

At baseline, frequency of self-reported sleeplessness was assessed by the question: “How often do you suffer from sleeplessness?” with the response options: 1) ‘never, or just a few times a year’, 2) ‘1-2 times a month’ 3) ‘approximately once a week’, and 4) ‘more than once a week’.

These response options were categorized into ‘never/seldom’ (never, or just a few times a year, ‘sometimes’ (approximately once a week) and ‘often/always’ (more than once a week).

### **Number of insomnia symptoms**

At baseline, symptoms of insomnia were assessed by three questions: 1) ‘Have you had problems falling asleep during the last month?’, 2) ‘During the last month, did you ever wake up too early, not being able to fall asleep again?’, and 3) ‘During the last year, have you been troubled by sleeplessness to such a degree that it affected your work?’. Questions one and two had the response options ‘never’, ‘occasionally’, ‘often’ and ‘almost every night’, whereas question three had the response options ‘yes’ and ‘no’. Participants were classified to have insomnia symptoms if they answered, ‘often’ or ‘almost every night’ to questions one and two, or ‘yes’ to the third question. Number of insomnia symptoms were then defined by adding together the responses to each of the insomnia questions.

### **Possible confounding factors**

Body mass index (BMI) was calculated as weight divided by the square of height ( $\text{kg/m}^2$ ) by using the standardized measurements of height (to the nearest centimeter) and weight (to the nearest half kilogram) from the clinical examination. BMI was then classified into three groups according to the cut-offs suggested by the World Health Organization:[17] normal weight (BMI 18.5-24.9), overweight (BMI 25.0-29.9), or obese (BMI >30.0). Education was assessed by the question: ‘What is your highest level of education?’ and divided into four categories; ‘primary school’, ‘high school’, ‘college  $\leq 4$  years’, and ‘college >4 years’. 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 the question: 'How much of your leisure time have you been physically active during the last year?' where number of hours of light and/or hard activity were reported. Based on this information we defined four categories: 'inactive' (no light or hard activity), 'low activity' (<3 hours of light and no hard activity), 'moderate activity' ( $\geq 3$  hours light and/or <1 hours of hard activity) and 'high activity' (any light and  $\geq 1$  hour of hard activity). Symptoms of anxiety and depression was assessed by the validated and well-established self-rating questionnaire including seven questions on anxiety and seven questions on depression (Hospital Anxiety and Depression Scale, HADS).[18] As recommended, the cut-off score was set to  $\geq 8$  on both anxiety and depression and were dichotomized as presence or no presence of anxiety and/or depression.[18, 19] Use of hypnotics and/or sedatives was assessed by the question: 'How often have you taken sedatives or sleep medication in the last month?' with the response options 'daily', 'weekly, but not every day', 'not as often as every week', and 'never'.

### **Statistical analysis**

A modified Poisson regression model was used to estimate risk ratios (RR) of recovery from chronic LBP at follow-up (2006-2008) associated with sleeplessness and number of insomnia symptoms at baseline (1995-1997). The precision of the RRs was assessed by 95% confidence intervals (CIs) using robust variance estimation. Participants who reported sleeplessness 'sometimes' and 'often/always' were compared with the reference group of 'never/seldom' sleeplessness. Participants who reported one, two or three insomnia symptoms were compared with the reference group who reported no symptoms of insomnia. All associations were stratified by sex and adjusted for age (continuous), BMI (normal weight, overweight, obesity, unknown),

leisure time physical activity (inactive, low activity, moderate activity, high activity, unknown), education (primary school, high school, college, unknown), and smoking (never, former, current, unknown).

We estimated the joint effect of sleeplessness and number of pain sites at baseline on the probability of recovery from chronic LBP at follow-up, using participants who reported 1-2 pain sites and never/seldom sleeplessness as the reference group. The joint effect of sleeplessness and co-occurring extremity and/or axial pain was examined using participants who reported never/seldom sleeplessness along with chronic pain in upper/lower extremity as the reference group. These analyses were adjusted for all the covariates described above. Potential effect modification between the variables was assessed as departure from additive effects calculating the relative excess risk due to interaction (RERI). We calculated RERI estimates with 95% CIs from the following equation:  $RERI = RR_{\geq 5 \text{ pain sites and sleeplessness}} - RR_{\geq 5 \text{ pain sites and no sleeplessness}} - RR_{1-2 \text{ pain sites and sleeplessness}} + 1$ . [20] The same RERI calculation was performed for the joint effect of sleeplessness and site-specific co-occurring pain. Since a  $RR < 1$  indicates lower probability of recovery from chronic LBP, a  $RERI < 0$  indicates a synergistic effect beyond an additive effect.

We conducted several sensitivity analyses to test the robustness of the results. First, as chronic LBP is associated with anxiety and depression, [21] we performed a supplementary analysis excluding participants who reported a score of  $\geq 8$  on both anxiety and depression at baseline. Second, we excluded persons reporting daily use of sedatives or sleep medication at baseline. Third, because BMI (0.6%), education (1.8%), smoking (18.6%), and leisure time physical activity (5.1%) had missing data, we generated 20 imputations using ordered logistic regression for ordinal variables and logistic regression for binary variables. The predictors in the model were all variables used in the main analysis model (including the outcome variable).

Finally, we performed complete case analyses excluding participants with missing values on the covariates.

All statistical analyses were performed using Stata for Windows, version 15 (StataCorp LP, College Station, Texas).

## RESULTS

Table 1 presents the baseline characteristics stratified by sex and frequency of experiencing sleeplessness. At follow-up (2006-208), 40.6% (1,508) women and 52.1% (1,296) men had recovered from chronic LBP.

Table 1. Baseline characteristics of the study population stratified by sex and frequency of experiencing sleeplessness

	Women			Men		
	Sleeplessness			Sleeplessness		
	Never/seldom	Sometimes	Often/always	Never/seldom	Sometimes	Often/always
Persons, % (no.)	51.5 (1,911)	31.2 (1,158)	17.3 (643)	63.9 (1,590)	27.3 (680)	8.8 (218)
Age, mean (SD)	46.8 (11.2)	49.3 (10.9)	52.3 (10.5)	49.6 (10.8)	50.2 (10.6)	50.0 (10.6)
Body mass index, mean (SD)	26.6 (4.6)	26.7 (4.4)	27.0 (4.5)	26.7 (3.3)	26.7 (3.2)	27.1 (3.9)
Obese, % (no.)	19.1 (364)	19.8 (229)	20.4 (131)	14.8 (236)	14.7 (100)	20.6 (45)
Education, % (no.)						
Primary school	33.0 (631)	41.1 (476)	54.9 (353)	32.3 (514)	30.7 (209)	39.9 (87)
High school	43.9 (839)	40.5 (469)	33.3 (214)	45.9 (730)	51.5 (350)	50.5 (110)
College	21.1 (403)	16.7 (193)	10.3 (66)	20.0 (318)	15.9 (108)	8.3 (18)
Unknown	2.0 (38)	1.7 (20)	1.6 (10)	1.8 (28)	1.9 (13)	1.4 (3)
Smoking, % (no.)						
Never smoked	37.2 (710)	33.9 (392)	33.2 (214)	33.9 (539)	32.1 (218)	26.6 (58)
Former smoker	24.0 (459)	24.2 (280)	21.2 (136)	35.5 (565)	36.6 (249)	37.6 (82)
Current smoker	19.1 (364)	21.9 (253)	21.3 (137)	14.8 (235)	15.9 (108)	22.0 (48)
Unknown	19.8 (379)	20.1 (233)	24.3 (156)	15.8 (251)	15.4 (105)	13.8 (30)
Physical activity, % (no.) <sup>c</sup>						
Inactive	5.8 (110)	4.8 (55)	10.0 (64)	5.5 (88)	5.4 (37)	8.7 (19)
Low	35.6 (681)	39.9 (462)	41.4 (266)	27.6 (438)	26.3 (179)	21.1 (46)
Moderate	32.7 (625)	34.1 (395)	26.9 (173)	32.5 (517)	33.4 (227)	33.9 (74)
High	20.8 (398)	15.3 (177)	13.1 (84)	30.6 (486)	32.1 (218)	30.7 (67)
Unknown	5.1 (97)	6.0 (69)	8.7 (56)	3.8 (61)	2.8 (19)	5.5 (12)
Depression and/or anxiety, % (no.)	15.7 (300)	30.7 (355)	37.3 (240)	13.5 (215)	31.9 (217)	40.8 (89)
Unknown	14.4 (275)	16.2 (187)	20.1 (129)	10.7 (170)	10.0 (68)	8.3 (18)
Daily use of sedatives/sleep medication, % (no.)	2.3 (44)	3.9 (45)	14.9 (96)	1.2 (19)	3.8 (26)	9.2 (20)
Unknown	6.9 (131)	7.1 (82)	7.2 (46)	8.1 (129)	9.1 (62)	7.8 (17)

Abbreviations: SD, standard deviation

Table 2 shows the effect of sleeplessness and insomnia symptoms on the probability of recovery from chronic LBP at follow-up ~10 years later. Women and men who reported that they often/always experienced sleeplessness had lower probability of recovery compared to participants without sleeplessness (RR 0.65, 95% CI: 0.57, 0.74 in women and RR 0.81, 95% CI: 0.69, 0.95 in men). Further, the probability of recovery was inversely associated with number of insomnia symptoms in women, i.e., compared to women with no symptoms, women who reported one, two or three insomnia symptoms had RRs of 0.81 (95% CI: 0.72, 0.91), 0.68 (95% CI: 0.57, 0.80) and 0.60 (95% CI: 0.46, 0.77), respectively. The corresponding RRs among men were 0.99 (95% CI: 0.89, 1.10), 0.84 (95% CI: 0.71, 1.00) and 0.82 (95% CI: 0.59, 1.14).

Table 2. Relative probability of recovery from chronic low back pain at 11-year follow-up associated with baseline sleeplessness and number of insomnia symptoms stratified by sex

	Women					Men				
	No. of persons	Recovered	Age-adjusted RR <sup>a</sup>	Multi-adjusted RR <sup>b</sup>	95% CI	No. of persons	Recovered	Age-adjusted RR <sup>a</sup>	Multi-adjusted RR <sup>b</sup>	95% CI
Sleeplessness <sup>c</sup>										
Never/seldom	1,911	873	1.00	1.00	Reference	1,590	862	1.00	1.00	Reference
Sometimes	1,158	453	0.86	0.88	0.80, 0.96	680	341	0.92	0.93	0.85, 1.02
Often/always	643	182	0.63	0.65	0.57, 0.74	218	93	0.79	0.81	0.69, 0.95
No. of insomnia symptoms <sup>d</sup>										
0	2,512	1,130	1.00	1.00	Reference	1,919	1,018	1.00	1.00	Reference
1	670	237	0.80	0.81	0.72, 0.91	345	181	0.99	0.99	0.89, 1.10
2	351	106	0.67	0.68	0.57, 0.80	174	76	0.83	0.84	0.71, 1.00
3	177	45	0.58	0.60	0.46, 0.77	50	21	0.80	0.82	0.59, 1.14

Abbreviations: CI, confidence interval; RR, risk ratio

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

<sup>b</sup> Adjusted for age (continuous), leisure time physical activity (inactive, low activity, moderate activity, high activity, unknown), body mass index (18.5-24.9 kg/m<sup>2</sup>, 25.0-29.9 kg/m<sup>2</sup>, ≥30 kg/m<sup>2</sup>), education (primary school, high school, college, unknown), smoking (never, former, current, unknown)

<sup>c</sup> Sleeplessness was defined by the question: “How often do you suffer from sleeplessness?”

<sup>d</sup> No. of symptoms were defined by adding up those who responded “Often/always” on the questions about “Problems falling asleep” and “Waking up too early” and “Yes” on the question about “Impaired work ability due to sleep problems”.

We found no synergistic effect of sleeplessness and multisite pain on recovery (RERI 0.15, 95% CI: -0.14, 0.47 in women and -0.13, 95% CI: -0.62, 0.38 in men), but we observed that women with ≥5 additional pain sites had a RR of 0.40 (95% CI: 0.33, 0.48) if they reported to experience sleeplessness often/always and a RR of 0.54 (95% CI: 0.47, 0.61) if they never/seldom experienced sleeplessness (Table 3). The corresponding RRs among men were 0.59 (95% CI: 0.45, 0.78) and 0.69 (95% CI 0.60, 0.78), respectively.

Table 3. The joint effect of sleeplessness and number of chronic pain sites at baseline on the relative probability of recovery from chronic low back pain at follow-up

Variables	1-2 pain sites				3-4 pain sites				≥5 pain sites			
	No. of persons	Recovered	Multi-adjusted RR <sup>a</sup>	95% CI	No. of persons	Recovered	Multi-adjusted RR <sup>a</sup>	95% CI	No. of persons	Recovered	Multi-adjusted RR <sup>a</sup>	95% CI
Women												
Sleeplessness												
Never/seldom	487	303	1.00	Reference	645	321	0.82	0.73, 0.91	779	249	0.54	0.47, 0.61
Sometimes	194	100	0.85	0.73, 0.99	332	145	0.72	0.63, 0.83	632	208	0.55	0.48, 0.63
Often/always	61	26	0.71	0.52, 0.95	128	48	0.62	0.49, 0.78	454	108	0.40	0.33, 0.48
Men												
Sleeplessness												
Never/seldom	596	359	1.00	Reference	575	329	0.95	0.86, 1.04	419	174	0.69	0.60, 0.78
Sometimes	219	136	1.04	0.92, 1.18	238	115	0.80	0.69, 0.93	223	90	0.67	0.56, 0.80
Often/always	34	21	1.03	0.79, 1.34	87	38	0.74	0.58, 0.95	97	34	0.59	0.45, 0.78

Abbreviations: CI, confidence interval; RR, risk ratio.

<sup>a</sup> Adjusted for age (continuous), leisure time physical activity (inactive, low activity, moderate activity, high activity, unknown), body mass index (18.5-24.9 kg/m<sup>2</sup>, 25.0-29.9 kg/m<sup>2</sup>, ≥30 kg/m<sup>2</sup>), education (primary school, high school, college, unknown), smoking (never, former, current, unknown)

Table 4 shows the joint effect of sleeplessness and co-occurring extremity and/or axial pain on probability of recovery from chronic LBP. Compared to women who reported to experience sleeplessness never/seldom along with no co-occurring pain, women with co-occurring axial pain had a RR of recovery of 0.46 (95% CI: 0.38, 0.55) if they had sleeplessness often/always and a RR of 0.68 (95% CI: 0.60, 0.78) if they had sleeplessness never/seldom. The corresponding RRs among men were 0.67 (95% CI: 0.54, 0.83) and 0.81 (95% CI: 0.72, 0.91), respectively. The RERI estimates were 0.08 (95% CI: -0.71, 0.55) for women and -0.28 (95% CI: -1.04, 0.48) for men.

Table 4. The joint effect of sleeplessness and co-occurring musculoskeletal pain at baseline on the relative probability of recovery from chronic low back pain at follow-up

Variables	No co-occurring pain				Upper and/or lower extremity pain <sup>b</sup>				Axial pain <sup>c</sup>			
	No. of persons	Recovered	Multi-adjusted RR <sup>a</sup>	95% CI	No. of persons	Recovered	Multi-adjusted RR <sup>a</sup>	95% CI	No. of persons	Recovered	Multi-adjusted RR <sup>a</sup>	95% CI
Women												
Sleeplessness												
Never/seldom	190	119	1.00	Reference	520	271	0.88	0.76, 1.01	1,201	483	0.68	0.60, 0.78
Sometimes	62	32	0.85	0.65, 1.11	259	117	0.77	0.65, 0.92	837	304	0.63	0.54, 0.72
Often/always	19	8	0.71	0.42, 1.19	93	35	0.66	0.50, 0.87	531	139	0.46	0.38, 0.55
Men												
Sleeplessness												
Never/seldom	271	170	1.00	Reference	507	281	0.89	0.79, 1.00	812	411	0.81	0.72, 0.91
Sometimes	89	54	0.98	0.81, 1.18	191	113	0.96	0.82, 1.11	400	174	0.70	0.60, 0.81
Often/always	14	10	1.14	0.82, 1.58	46	19	0.67	0.47, 0.95	158	64	0.67	0.54, 0.83

Abbreviations: CI, confidence interval; RR, risk ratio.

<sup>a</sup> Adjusted for age (continuous), leisure time physical activity (inactive, low activity, moderate activity, high activity, unknown), body mass index (18.5-24.9 kg/m<sup>2</sup>, 25.0-29.9 kg/m<sup>2</sup>, ≥30 kg/m<sup>2</sup>), education (primary school, high school, college, unknown), smoking (never, former, current, unknown)

<sup>b</sup> Co-occurring pain in upper and/or lower extremity (shoulders/upper arms, elbows, wrists/hands, hips, knees, and ankles/feet)

<sup>c</sup> Co-occurring pain in other axial regions (neck, upper back).

## **Sensitivity analyses**

Exclusion of participants with anxiety and/or depression had negligible influence on the results. Likewise, exclusion of participants using sedatives or sleep medication had marginal influence on the association; however, compared to the reference group of men without insomnia symptoms, men with three insomnia symptoms had a RR of 0.75 (95% CI: 0.52, 1.08). Finally, multiple imputations and complete case analyses did not change the estimated associations.

## **DISCUSSION**

The current study shows that sleeplessness and insomnia symptoms are inversely associated with the probability of recovery from chronic LBP. These associations were somewhat stronger in women than in men. Although we found no additive interaction between sleeplessness and co-occurring musculoskeletal pain on the probability of recovery, our analyses of joint effects showed that people who experienced sleeplessness often/always along with co-occurring pain had the lowest probability of recovery. Thus, preventing or reducing sleep problems among people with chronic LBP may have the potential of improving the long-term prognosis.

Few studies have investigated the influence of sleep problems on the prognosis of chronic LBP. A recent study of LBP patients showed that co-existing sleep problems lowered the probability of recovering from LBP at six months follow-up.[7] Further, an observational study of persons with occasional LBP showed that sleep problems increased the risk of developing troublesome LBP at four years follow-up.[10] The current study expands on these findings by showing that frequency of sleeplessness and number of insomnia symptoms are inversely and dose-dependently associated with the long-term prognosis of chronic LBP. Compared to women without sleeplessness, women who experienced sleeplessness 1-2 times a month up to once a

week had 13% lower probability of recovery from chronic LBP at the 10-11 year follow-up while women who experienced sleeplessness more than once a week had 35% lower probability of recovery. This association was somewhat weaker among men with 7% and 19%, respectively. A similar dose-dependent association was observed for number of insomnia symptoms and probability of recovery from LBP, but with a somewhat weaker association in men than women. These findings suggest that sleeplessness and number of insomnia symptoms have significant influence on the long-term prognosis of chronic LBP. It is unclear why the association is stronger among women than men, but it has been suggested that there exist an interplay between insomnia and female gender on pain,[22] possibly explained by a female predisposition to both pain and insomnia.[23, 24] Further, it has been shown that sleep disruption amplifies central sensitization in women and men differently, suggesting that there exists sex-specific differences for the association between poor sleep and development of chronic pain.[9] However, we cannot exclude the possibility that these sex-differences may be due to chance.

The mechanisms underlying the adverse effect of sleeplessness and insomnia symptoms on the recovery from chronic LBP are not clear, but a possible explanation is that poor sleep fuels physiological processes that alter peripheral and central sensitization.[25, 26] Experimental studies have shown that disrupted sleep or insufficient sleep duration may lead to increased sensitivity to potentially noxious stimuli.[27, 28] A possible mechanism is that sleep restriction induces a low-level systemic inflammation, which in turn increase sensitivity and exacerbate pain [8] as well as reinforcing maintenance of pain.[29-31] This hypothesis is supported by studies showing that the serum level of pro-inflammatory cytokines is closely associated with pain intensity in chronic pain patients.[32] Further, we have in a recent study showed that there is an interplay between sleeplessness and low-grade inflammation on risk of chronic

musculoskeletal pain.[33] However, further investigation is required to disentangle the temporal association between sleep problems, inflammatory responses and prognosis of chronic pain.

Although musculoskeletal comorbidity is strongly associated with prognosis of LBP,[12, 13] we found no synergistic effect of sleeplessness and co-occurring musculoskeletal pain on the probability of recovery from chronic LBP. However, compared to persons with one to two musculoskeletal pain sites but without sleeplessness, women and men with five or more pain sites and who experienced sleeplessness more than once a week had 41-60% lower probability of recovery from chronic LBP. Almost similar associations were found for the joint effect of sleeplessness and co-occurring axial pain. Thus, these findings show that persons who experienced sleeplessness more than once a week accompanied by co-occurring musculoskeletal pain had the lowest probability of recovery from chronic LBP.

Strengths of the current study include the prospective design, the large population, and the possibility to adjust for several potential confounders. Moreover, the size of the study sample allowed us to analyze joint effects of sleeplessness and co-occurring musculoskeletal pain on the long-term prognosis of chronic LBP. Some limitations should be considered in the interpretation of the results. First, frequency of sleeplessness was assessed by a single question and do not include information about problems initiating sleep, nocturnal awakenings, early awakenings or daytime sleepiness. Thus, our assessment of sleeplessness do not fulfill the International Classification of Sleep Disorders (ICSD-3) criteria for insomnia diagnosis.[34] For instance, nighttime awakenings are common among patients with chronic pain [35] and it has been shown that disruption of sleep continuity is more strongly associated with spontaneous pain reports, compared to restricted but continuous sleep.[36] It is therefore possible that our results underestimate the influence of sleeplessness and insomnia symptoms on the prognosis of chronic

LBP. Further, we had only three insomnia items and no information about nighttime awakenings, and the question on impaired daytime function is only related to work ability. It should also be noted that information about sleeplessness, insomnia symptoms and co-occurring musculoskeletal pain were collected at the same time point and we had no information about changes that may have occurred in these symptoms during the follow-up period. Thus, we were unable to examine whether improvements or worsening in sleeplessness and insomnia symptoms influence the probability of recovery from chronic LBP. Since the questions on chronic musculoskeletal pain were based on the participants' recollection of pain the last 12 months, we cannot exclude the possibility of misclassification. Although speculative, it is possible that participants reporting higher frequency of sleeplessness at baseline had more disabling pain, which in turn could have overestimated the inverse association between sleeplessness and probability of recovery from chronic LBP. Likewise, pain intensity or pain duration could have influenced the association at follow-up. For instance, it is possible that those who had experienced an acute episode with more disabling pain the past 12 months would be more likely to report pain at follow-up, even though the duration of the pain was less than three consecutive months. Unfortunately, we had no detailed information on pain intensity or pain duration and cannot rule out the possibility of misclassification as exemplified above.

In conclusion, sleeplessness and insomnia symptoms are inversely and dose-dependently associated with the probability of recovery from chronic LBP. We found no additive interaction between sleeplessness and co-occurring musculoskeletal pain on the probability of recovery, but our analyses of joint effects showed that people who experienced sleeplessness often/always along with  $\geq 5$  additional pain sites or axial pain had the lowest probability of recovery. Thus,

preventing or reducing sleep problems among people with chronic LBP may have the potential of improving the long-term prognosis.

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#### LICENCE FOR PUBLICATION

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Substantial contributions to the design of the work; or the acquisition, analysis, or interpretation of data for the work: ESS, ALN, PJM, TILN. ESS and ALN did the statistical analysis. Drafting of the manuscript: ESS and ALN. Revising the work critically: ESS, ALN, PJM, TILN. Final approval of the version to be published: ESS, ALN, PJM, TILN. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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