Do physical activity and body mass index modify the association between chronic musculoskeletal pain and insomnia? Longitudinal data from the HUNT study, Norway

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SUMMARY

We investigated the prospective association between chronic musculoskeletal pain and risk of insomnia, and if leisure-time physical activity and body mass index modify this association. The study comprised historical data on 11 909 women and 9938 men in the Norwegian HUNT study without sleep problems at baseline in 1995–97 and followed-up for insomnia in 2006–08. Poisson regression was used to estimate adjusted risk ratios (RRs) with 95% confidence intervals (CIs). Compared to pain-free participants, any chronic pain was associated with a RR of insomnia of 2.27 (95% CI: 1.93, 2.66) in women and 1.58 (95% CI: 1.28, 1.95) in men, whereas reporting ≥5 chronic pain sites gave RRs of 3.20 (95% CI: 2.60, 3.95) and 2.40 (95% CI: 1.76, 3.27), respectively. Analysis of joint effects showed that: (i) compared to pain-free physically active people, RRs in people with ≥5 chronic pain sites were 3.77 (95% CI: 2.42–5.85) if they were inactive and 2.76 (95% CI: 2.29, 3.31) if they were active; and (ii) compared to pain-free people with normal weight, RRs in people with ≥5 chronic pain sites were 3.52 (95% CI: 2.81, 4.40) if they were obese and 2.93 (95% CI: 2.24, 3.84) if they had normal weight. In conclusion, chronic musculoskeletal pain increases the risk of insomnia, particularly among those who report several pain sites. Although there was no clear evidence of modifying effects, our results suggest that a healthy active lifestyle reduces the risk of insomnia in people with chronic musculoskeletal pain.

INTRODUCTION

Insomnia is a common sleep disorder that may have severe health consequences, such as increased risk of cardiovascular disease, type 2 diabetes, hypertension and mental disorders (Anothaisintawee *et al.*, 2015; Dew *et al.*, 2003; Sivertsen *et al.*, 2009; Sofi *et al.*, 2014; Vgontzas *et al.*, 2009). Approximately 25–30% in the adult population suffer from insomnia symptoms (Leblanc *et al.*, 2009; Roth, 2007) while 6–10% fulfil the diagnostic criteria for insomnia disorder (Buysse, 2013; Ohayon, 2002; Uhlig *et al.*, 2014). In observation studies, however, insomnia is defined usually by insomnia symptoms rather than an insomnia diagnosis. The high prevalence and the negative health consequences underscore the importance of identifying possible risk factors and mechanisms to improve prevention of insomnia.

Some evidence indicates that musculoskeletal pain may increase the risk of insomnia (Ødegård *et al.*, 2013; Tang *et al.*, 2015), although contrasting results have been reported (Leblanc *et al.*, 2009). In a longitudinal cohort study, Ødegård *et al.* (2013) found that chronic musculoskeletal pain was associated positively with risk of insomnia at 10–11 years' follow-up in adult women and men who were free from insomnia at baseline. A recent study of older adults found

that reporting of 1 day or more with musculoskeletal pain during the previous month was associated with increased risk of insomnia at 3-year follow-up (Tang *et al.*, 2015).

Although the current evidence indicates an association between chronic musculoskeletal pain and risk of insomnia, the exact nature of this association remains unclear. It is conceivable that the impact of chronic musculoskeletal pain on risk of insomnia may interact with modifiable risk factors such as physical activity and obesity. Obesity and weight gain have been associated with increased risk of insomnia (Palm *et al.*, 2015; Singareddy *et al.*, 2012), while regular physical activity is considered important for promotion of good sleep (Chennaoui *et al.*, 2015; Yang *et al.*, 2012). Although chronic pain, obesity and physical activity may be closely intertwined, little is known about their joint effect on risk of insomnia.

In a population-based prospective study, we investigated the association between chronic musculoskeletal pain and risk of insomnia defined by insomnia symptoms. We hypothesized that (i) risk of insomnia is associated positively and dose-dependently with number of chronic musculoskeletal pain sites, and (ii) that excess body mass and low leisure-time physical activity amplify the adverse effect of chronic musculoskeletal pain on risk of insomnia.

METHODS

Study population

This is a prospective study utilizing historical data from the population based HUNT study, conducted within the Nord-Trøndelag County in Norway. All inhabitants aged 20 years or older were invited to participate in three consecutive surveys; first in 1984–86 (HUNT1), then in 1995–97 (HUNT2) and lastly in 2006–08 (HUNT3). Information on lifestyle and health-related factors were collected by questionnaires and clinical examination at all three surveys. More detailed information about the HUNT study can be found at http://www.ntnu.edu/hunt.

Information about chronic pain was not included in HUNT1, and the current study is therefore based on information from HUNT2 and HUNT3. At HUNT2, 93 898 people were invited to participate and 65 232 eventually participated in the study. At HUNT3, 93 860 people were invited to participate and 50 839 attended the study. For the purpose of the current study, we selected all 36 984 who participated at both HUNT2 and HUNT3 (Fig. 1). Of these, we excluded 10 316 people with incomplete information on the insomnia questions at HUNT2 and/or HUNT3. Of the remaining 26 668 people, we excluded people at HUNT2 who reported insomnia symptoms ($n = 3275$), use of hypnotics and/or sedatives ($n = 1519$), did not answer questions about chronic pain ($n = 22$) or were underweight ($n = 5$), i.e. body mass index (BMI) < 18.5 kg/m^2. Thus, the prospective analysis of incident insomnia at HUNT3 was based on information from 21 847 people (11 909 women and 9938 men). All participants signed a written consent, and the study was approved by the Regional Committee for Ethics in Medical Research (project no. 2014/612 REK midt). The study was carried out according to the Declaration of Helsinki.

Chronic musculoskeletal pain

Presence of chronic musculoskeletal pain was assessed by the question: 'During the last year, have you had pain and/or stiffness in your muscles and limbs that has lasted for at least 3 consecutive months?'. Response options were 'yes' and 'no'. If answering 'yes', the participants were asked to indicate the affected body area(s): neck, shoulders, elbows, wrists/hands, upper back, low back, hips, knees and ankles/feet (i.e. a maximum of nine chronic pain sites). Based on these answers we constructed a new variable using number of chronic musculoskeletal pain sites to categorize participants into four strata: no chronic musculoskeletal pain, one to two chronic musculoskeletal pain sites, three to four chronic musculoskeletal pain sites and greater than or equal to five chronic musculoskeletal pain sites. A similar categorization has been used in a previous study of the association between chronic pain sites and sleep problems (Kamaleri *et al.*, 2008).

Physical activity

Leisure-time physical activity was assessed by the following question: 'How much of your leisure time have you been physically active during the last year? (Think of a weekly average for the year. Your commute to work counts as leisure time)'. The participants were then asked to specify number of hours per week of light (no sweating or heavy breathing) and/or hard (sweating and heavy breathing) physical activity with the response options: 'none', 'less than 1 hour', '1–2 hours' and '3 or more hours' for both light and hard activity. Based on this information, we constructed a new variable with four categories combining information on light and hard activity: inactive (no light or no hard activity), low activity (<3 h light and no hard activity), moderate activity (≥ 3 h light and/or <1 h hard activity) and high activity (any light and ≥ 1 h hard activity). For the purpose of the joint effect analysis, the three

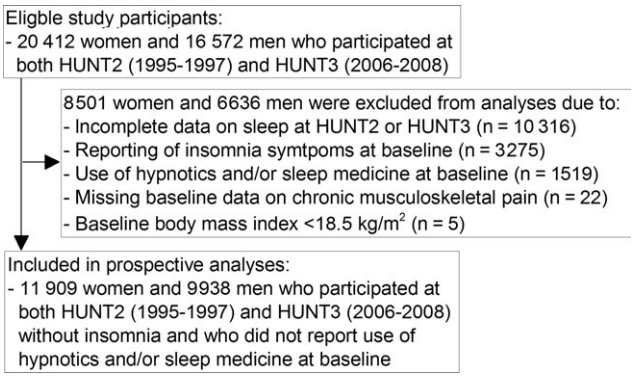

Figure 1. Selection of study participants.

latter (i.e. low, moderate and high) were collapsed into one category.

Body mass index

Standardized measurements of body height (to the nearest centimetre) and weight (to the nearest half-kilogram) obtained at the clinical examination at HUNT2 was used to calculate BMI (kg/m^2). Participants were then classified into one of three BMI groups according to the cutoff points suggested by the World Health Organization (World Health Organization, 1995): normal weight (BMI: 18.5–24.9 kg/m^2), overweight (BMI: 25.0–29.9 kg/m^2) or obese (BMI: ≥30.0 kg/m^2). For the purpose of the joint effect analysis, overweight and obese were collapsed into one category.

Insomnia symptoms

Insomnia symptoms in HUNT2 were assessed by two questions: 'Have you had problems falling asleep during the last month?' and 'During the last month, did you ever wake up too early, not being able to fall asleep again?', with four response options for each question: 'never', 'occasionally', 'often', and 'almost every night'. Participants who reported 'never' or 'occasionally' for both questions were considered unlikely to have insomnia at baseline and were included into the study. Participants who reported 'often' or 'almost every night' on one or both of the questions were excluded from the study.

In HUNT3, classification of insomnia was based on the following four questions: (i) 'How often during the last 3 months have you had difficulty falling asleep at night?', (ii) 'How often during the last 3 months have you woken up repeatedly during the night?', (iii) 'How often during the last 3 months have you woken too early and couldn't get back to sleep?' and (iv) 'How often during the last 3 months have you felt sleepy during the day', with three response options for each question: 'never/seldom', 'sometimes' and 'several times a week'. Participants were classified with insomnia if they answered 'several times a week' for at least one of questions 1–3 and 'several times a week' for question 4. The information retrieved from these four questions approximates the information necessary to diagnose insomnia according to the DSM-V criteria (American Psychiatric Association, 2013). Nevertheless, it should be noted that the classification used in the current study is a proxy of an insomnia diagnosis.

Other variables

Education was assessed by the question: 'What is your highest level of education?'. Based on this information, the participants were categorized into three groups: '<10 years', '10–12 years' and '≥13 years'. The Hospital Anxiety and Depression Scale (HADS) was used to assess symptoms of anxiety and depression. HADS is a validated and well-established self-rating questionnaire including seven questions on anxiety and seven questions on depression (Bjelland *et al.*, 2002). As recommended, the cutoff score was set to ≥8 on both anxiety and depression and were dichotomized as presence or no presence of anxiety and/or depression (Bjelland *et al.*, 2002; Lisspers *et al.*, 1997). Shift work was assessed by the question: 'Do you work shifts, at night, or on call?', with two response options: 'no' and 'yes'. Alcohol consumption was assessed by the CAGE (Cut down, Annoyed, Guilty, Eye-opener) questionnaire using a cutoff score ≥2 to indicate possible alcohol abuse (Ewing, 1984). The CAGE questionnaire has good reliability and is a valid tool for detecting severe forms of alcohol abuse (Dhalla and Kopec, 2007).

Statistical analysis

Poisson regression was used to estimate risk ratios (RRs) of insomnia associated with chronic musculoskeletal pain and number of chronic pain sites. Participants who reported any chronic musculoskeletal pain and number of chronic pain sites were compared with the reference group of participants without baseline chronic musculoskeletal pain. Precision of RRs were assessed by 95% confidence intervals (CIs), and trend tests across categories of number of pain sites were calculated by treating the categories as ordinal variables in the regression model. All associations were stratified by gender and adjusted for possible confounding by age (20–29, 30–39, 40–49, 50–59, 60–69 or ≥70 years), education (<10, 10–12, ≥13 years, unknown), smoking (never, former, current, unknown), alcohol consumption (no abuse, possible abuse, unknown), shift work (no, yes, unknown) and HADS score (0–7, 8–21). The independent associations of chronic musculoskeletal pain and number of pain sites with insomnia were also adjusted for leisure-time physical activity (inactive, low activity, moderate activity, high activity and unknown) and BMI (normal weight, overweight, obesity). In similar multi-adjusted analyses we estimated the independent association of leisure-time physical activity and BMI with risk of insomnia, using high physical activity and normal weight as reference, respectively. For these associations, we conducted a sensitivity analysis where we excluded participants reporting use of painkillers.

Moreover, we estimated the joint effect of chronic musculoskeletal pain and BMI on risk of insomnia using participants with normal weight without chronic pain as the reference group. Correspondingly, the joint effect of chronic musculoskeletal pain and leisure-time physical activity was examined using physically active participants without chronic pain as the reference group. These analyses were conducted on a pooled sample adjusting for sex (woman, man) in addition to the possible confounders described above (excluding the variable under the study). Potential effect modification between the variables was assessed both as departure from additive effects calculating the relative excess risk due to interaction (RERI) and as departure from multiplicative effects in a likelihood ratio test of a product term in the

regression model. We calculated RERI estimates with 95% CIs from the following equation: RERI = $RR_{\text{inactive and } \geq 5 \text{ pain sites}} - RR_{\text{physically active and } \geq 5 \text{ pain sites}} - RR_{\text{inactive and no pain}} + 1$ (Andersson *et al.*, 2005), i.e. RERI > 0 indicate a synergistic effect beyond an additive effect. To test the robustness of these associations, we conducted two sensitivity analyses where we excluded participants with (i) 'low' and 'moderate' physical activity from the analyses of the joint effect of chronic musculoskeletal pain and leisure-time physical activity and (ii) overweight from the analyses of the joint effect of chronic musculoskeletal pain and BMI.

All statistical analyses were performed using Stata for Windows, version 13.1 (StataCorp LP, College Station, TX, USA).

RESULTS

Table 1 presents the baseline characteristics of the study population stratified by presence of chronic musculoskeletal pain. Approximately 45% of the women and 43% of the men reported chronic musculoskeletal pain at baseline. Of 11 909 women and 9938 men who were free from insomnia symptoms at baseline (HUNT2), 662 (5.6%) women and 384 (3.8%) men reported insomnia at follow-up (HUNT3).

Table 2 shows that risk of insomnia was associated positively with any chronic musculoskeletal pain. Compared to participants without chronic musculoskeletal pain, women and men who reported any chronic musculoskeletal pain had RRs of 2.27 (95% CI: 1.93, 2.66) and 1.58 (95% CI: 1.28, 1.95), respectively. Further, number of chronic musculoskeletal pain sites was associated dose-dependently with risk of insomnia (*P*-trend <0.001 in both genders). Women and men who reported one to two chronic musculoskeletal pain sites had RRs 1.80 (95% CI: 1.47, 2.22) and 1.18 (95% CI: 0.90, 1.53), respectively, increasing to 3.20 (95% CI: 2.60, 3.95) and 2.40 (95% CI: 1.76, 3.27) among women and men who reported ≥5 chronic musculoskeletal pain sites. Leisure-time physical activity was not associated with risk of insomnia, except for inactive women who had a RR of 1.70 (95% CI: 1.24, 2.32) compared to highly active women. BMI was associated dose-dependently with risk of insomnia in both women and men (*P*-trend <0.03 in both genders). Women and men classified as obese had RRs of 1.25 (95% CI: 1.00, 1.56) and 1.48 (95% CI: 1.08, 2.01), respectively, compared to normal weight participants. Furthermore, excluding participants who reported use of painkillers did not change the results.

Table 3 shows the joint effect of number of chronic musculoskeletal pain sites and leisure-time physical activity on risk of insomnia. There was no statistical evidence of a synergistic effect of inactivity and ≥5 pain sites on risk of insomnia with RERI of 0.88 (95% CI: −0.85, 2.60). Physically active participants had a lower risk of insomnia compared to inactive participants within the strata with one to two pain sites (*P*-value from stratified analysis <0.01) and three to four pain sites (*P*-value from stratified analysis 0.03). Furthermore, no statistically significant interaction was found on a multiplicative scale ($P = 0.27$). In sensitivity analysis, the association remained unchanged when we excluded participants with low and moderate physical activity and compared risk of insomnia between highly active versus inactive participants within the different pain strata.

Table 4 shows the joint effect of number of chronic musculoskeletal pain sites and BMI on risk of insomnia. There was no evidence of a synergistic effect of overweight/obesity and ≥5 pain sites on risk of insomnia with RERI of 0.32 (95% CI: −0.52, 1.17). Furthermore, no statistical interaction was found on a multiplicative scale ($P = 0.59$). Stratified analysis comparing normal weight participants with overweight/obese participants with the same number of pain sites indicated similar risk of insomnia. In supplementary analyses, excluding those with overweight, the association with insomnia became somewhat stronger within strata of pain sites, e.g. obese participants with ≥5 pain sites had a RR of 4.19 (95% CI: 3.04, 5.78) compared to a RR of 2.95 (95% CI: 2.26, 3.86) in normal-weight participants with same

Table 1 Baseline characteristics of the study population stratified by gender and chronic musculoskeletal pain

	Women		*Men*	
	No chronic pain	*Chronic pain*	*No chronic pain*	*Chronic pain*
Participants, *n*	6605	5304	5692	4246
Age, mean ± SD, years	43.0 ± 13.1	47.6 ± 12.0	45.6 ± 12.9	50.0 ± 12.0
Body mass index, mean ± SD, kg/m^2	25.4 ± 4.0	26.3 ± 4.3	26.2 ± 3.1	26.7 ± 3.2
High leisure time physical activity, % (*n*)[a]	28.9 (1842)	20.5 (1086)	37.8 (2151)	31.9 (1356)
Education ≥13 years, % (*n*)	28.6 (1886)	21.7 (1153)	27.7 (1578)	19.1 (809)
Depression and/or anxiety, % (*n*)	9.2 (609)	15.8 (835)	8.8 (500)	15.1 (642)
Current smoker, % (*n*)	13.7 (902)	17.2 (913)	12.6 (719)	14.9 (633)
Shift work, % (*n*)	19.3 (1278)	19.6 (1037)	16.5 (939)	13.9 (588)
Possible alcohol abuse, % (*n*)[b]	1.8 (118)	1.7 (90)	10.3 (585)	11.5 (487)

SD, standard deviation.
[a]Defined as any light and ≥1 h hard activity per week.
[b]Defined by a score ≥2 on the CAGE questionnaire.

Table 2 Risk of insomnia at 11-year follow-up associated with any chronic musculoskeletal pain and number of chronic pain sites, leisure time physical activity, and body mass index stratified by gender

	Women				*Men*			
	No. of people	*No. of cases*	*Age-adjusted RR*[a]	*Multi-adjusted RR*[b] (95% CI)	*No. of people*	*No. of cases*	*Age-adjusted RR*[a]	*Multi-adjusted RR*[b] (95% CI)
Any chronic pain								
No	6605	243	1.00	1.00 (reference)	5692	174	1.00	1.00 (reference)
Yes	5304	419	2.51	2.27 (1.93–2.66)	4246	210	1.74	1.58 (1.28–1.95)
No. of chronic pain sites								
1–2	2159	134	1.91	1.80 (1.47–2.22)	2234	81	1.25	1.18 (0.90–1.53)
3–4	1710	133	2.47	2.26 (1.84–2.78)	1279	74	2.10	1.93 (1.46–2.56)
≥5	1421	152	3.75	3.20 (2.60–3.95)	727	55	2.89	2.40 (1.76–3.27)
Physical activity[c]								
High	2929	173	1.00	1.00 (reference)	3508	140	1.00	1.00 (reference)
Moderate	4155	219	0.97	0.95 (0.78–1.15)	3264	116	0.90	0.91 (0.71–1.16)
Low	3820	193	0.98	0.92 (0.75–1.13)	2291	93	1.06	1.02 (0.79–1.33)
Inactive	443	47	1.99	1.70 (1.24–2.32)	559	25	1.12	1.05 (0.69–1.59)
BMI categories[d]								
Normal weight	5675	310	1.00	1.00 (reference)	3373	116	1.00	1.00 (reference)
Overweight	4387	241	1.13	1.15 (0.97–1.35)	5285	209	1.20	1.22 (0.97–1.53)
Obese	1728	99	1.24	1.25 (1.00–1.56)	1252	59	1.46	1.48 (1.08–2.01)

CI, confidence interval; RR, risk ratio; BMI, body mass index.
[a]Adjusted for age (20–29, 30–39, 40–49, 50–59, 60–69, ≥70 years).
[b]Multi-adjusted: age (20–29, 30–39, 40–49, 50–59, 60–69, ≥70 years), leisure time physical activity (high activity, moderate activity, low activity, inactive, unknown), body mass index (18.5–24.9, 25.0–29.9, ≥30 kg/m^2), education (<10, 10–12, ≥13 years, unknown), smoking (never, former, current smoker, unknown), shift work (no, yes, unknown), alcohol consumption (no abuse, possible abuse, unknown), HADS (no depression and no anxiety, depression and/or anxiety, unknown).
[c]Multi-adjusted physical activity: all above except leisure time physical activity.
[d]Multi-adjusted BMI: all above except BMI.

Table 3 The joint effect of number of chronic pain sites and leisure time physical activity on risk of insomnia

	Physically active[a]			*Inactive*[b]			
	No. of people	*No. of cases*	*Multi-adjusted*[c] RR (95% CI)	*No. of people*	*No. of cases*	*Multi-adjusted*[c] RR (95% CI)	P-*value*[d]
No chronic pain	11 378	389	1.00 (reference)	505	17	1.00 (0.62–1.60)	0.85
1–2 pain sites	3990	189	1.46 (1.23–1.74)	215	20	2.61 (1.70–4.00)	<0.01
3–4 pain sites	2687	182	2.05 (1.72–2.44)	151	17	3.39 (2.15–5.34)	0.03
≥5 pain sites	1895	174	2.76 (2.29–3.31)	130	18	3.77 (2.42–5.85)	0.09

CI, confidence interval; RR, risk ratio.
[a]Any light and/or hard activity.
[b]No light or hard activity.
[c]Adjusted for: gender, age (20–29, 30–39, 40–49, 50–59, 60–69, ≥70 years), body mass index (18.5–24.9, 25.0–29.9, ≥30 kg/m^2), education (<10, 10–12, ≥13 years, unknown), smoking (never, former, current smoker, unknown), shift work (no, yes, unknown), alcohol consumption (no abuse, possible abuse, unknown), HADS (no depression and no anxiety, depression and/or anxiety, unknown).
[d]*P*-value from stratified analysis of leisure time physical activity by categories of number of chronic pain sites.

number of chronic pain sites (*P*-value from stratified analysis 0.06).

DISCUSSION

An important finding in the current study is the positive and dose-dependent association between number of chronic musculoskeletal pain sites and risk of insomnia symptoms. This association was somewhat stronger in women than men. In people with ≥5 chronic musculoskeletal pain sites, the risk of insomnia was approximately threefold higher than among people without chronic musculoskeletal pain. Overall, leisure-time physical activity and BMI showed weak independent associations with risk of insomnia. Although analyses of joint effects showed no clear evidence of effect modification, the results suggest that being physically active

Table 4 The joint effect of number of chronic pain sites and body mass index on risk of insomnia

	Normal weight[a]			*Overweight/obese*[b]			
	No. of people	*No. of cases*	*Multi-adjusted*[c] RR (95% CI)	*No. of people*	*No. of cases*	*Multi-adjusted*[c] RR (95% CI)	P-*value*[d]
No chronic pain	5444	181	1.00 (ref.)	6758	231	1.24 (1.02–1.50)	0.06
1–2 pain sites	1783	93	1.65 (1.30–2.11)	2589	120	1.74 (1.38–2.19)	0.39
3–4 pain sites	1092	83	2.35 (1.82–3.01)	1876	120	2.42 (1.93–3.05)	0.96
≥5 pain sites	723	69	2.93 (2.24–3.84)	1,415	137	3.52 (2.81–4.40)	0.16

CI, confidence interval; RR, risk ratio.
[a]Body mass index (BMI) 18.5–24.9 kg/m^2.
[b]Body mass index ≥25.0 kg/m^2.
[c]Adjusted for: gender, age (20–29, 30–39, 40–49, 50–59, 60–69, ≥70 years), leisure time physical activity (high activity, moderate activity, low activity, inactive, unknown), education (<10, 10–12, ≥13 years, unknown), smoking (never, former, current smoker, unknown), shift work (no, yes, unknown), alcohol consumption (no abuse, possible abuse, unknown), HADS (no depression and no anxiety, depression and/or anxiety, unknown).
[d]*P*-value from stratified analysis of BMI by categories of number of chronic pain sites.

in leisure time reduces the adverse effect of chronic musculoskeletal pain on risk of insomnia. Similarly, analysis of the joint effect of BMI and chronic musculoskeletal pain showed that obese participants had a somewhat higher risk of insomnia than normal-weight participants with the same number of pain sites. Thus, a healthy active lifestyle with maintenance of normal body weight may reduce the risk of insomnia in pain-afflicted individuals.

Few studies have investigated the association between chronic musculoskeletal pain and risk of insomnia symptoms. A recent study of adults above 50 years of age found a positive and dose-dependent association between the extent of musculoskeletal pain at baseline and risk of insomnia at 3-year follow up (Tang *et al*., 2015). A previous study based partly on the same data as that used in the current study showed that chronic musculoskeletal pain was associated with increased odds of insomnia in both women and men (Ødegård *et al*., 2013). However, they did not examine the possible modifying effect of physical activity and BMI on the relation between chronic pain and insomnia. These analyses were included in the current study and provide novel insight into the interplay between chronic pain, lifestyle factors and risk of insomnia.

Leisure-time physical activity was associated weakly with risk of insomnia symptoms, except for an increased risk among inactive women. Nevertheless, in the analyses of the joint effect of chronic musculoskeletal pain and physical activity we observed an overall increased risk among inactive pain-afflicted participants compared to active participants with the same number of chronic musculoskeletal pain sites. This finding indicates that leisure-time physical activity to some extent can reduce the adverse effect of chronic musculoskeletal pain on risk of insomnia. The sleep-promoting effect of physical activity is not understood fully, but physical activity can improve psychological health and wellbeing (Park, 2014; Teychenne *et al*., 2015) which, in turn, may reduce the risk of insomnia (Smagula *et al*., 2015). Regular physical activity is also associated with a more favourable sleep architecture and is therefore recommended as a pertinent non-pharmacological supplement to manage various sleep disorders (Chennaoui *et al*., 2015; Varrasse *et al*., 2015). It should be noted that 'being physically active' in the analyses of joint effects was defined as any light and/or hard activity, ranging from less than 1 h per week to 3 h or more per week. In a sensitivity analysis, comparing highly active and inactive participants we observed no additional reduction in risk of insomnia among the highly active participants. This result indicates that the main beneficial effect of physical activity is achieved when changing from inactivity to some activity with no further effect when adding more hours or increasing the intensity.

Our finding of a weak association between obesity and risk of insomnia symptoms is in line with previous findings in prospective studies. One prospective study found that baseline obesity was associated weakly with risk of insomnia at 7.5-year follow-up (Singareddy *et al*., 2012), while another study found no association between baseline obesity and risk of insomnia at 10- to 13-year follow-up (Palm *et al*., 2015). However, in the latter study it was observed that weight gain during the follow-up period increased the risk of insomnia. This may indicate that insomnia and obesity develop in parallel, rather than having a distinct temporal separation. In the analyses of the joint effect of BMI and chronic musculoskeletal pain, the risk of insomnia was somewhat lower among normal weight individuals compared to overweight/obese individuals with the same number of chronic pain sites. Sensitivity analysis restricted to a comparison between normal weight and obese individuals showed a slightly increased risk in obese individuals. This result suggests that individuals with chronic musculoskeletal pain may reduce their risk of insomnia by maintaining a normal body weight.

Strengths of the current study include the large and population-based study sample, the prospective design and the standardized measurements of height and weight along

with information on several potentially confounding variables. Furthermore, we had the possibility to exclude people at baseline with insomnia symptoms and people who used sedative and/or sleeping medicine. The large study sample also allowed for analysis of joint effects of lifestyle factors and chronic musculoskeletal pain on the risk of insomnia. The three questions used to assess insomnia in HUNT3 have been found to have acceptable reliability with kappa-values between 0.35 and 0.44 (Engstrøm *et al.*, 2011). The questionnaire on chronic musculoskeletal pain in HUNT2 has been adopted from the Standardized Nordic Questionnaire (SNQ), and has been shown to have acceptable reliability and validity (Hagen *et al.*, 2011; Kuorinka *et al.*, 1987; Palmer *et al.*, 1999). The physical exercise questionnaire used in HUNT2 has been validated against measured maximal oxygen uptake and objective recordings of physical activity in a random sample of men, with acceptable validity of vigorous activity, while the 'light' activity question had poor reproducibility and did not correlate well (Kurtze *et al.*, 2007). Thus, in the joint effect analysis of pain and physical activity, we tried to minimize this weakness by comparing inactive individuals (i.e. no light or hard activity) with individuals who reported any form of physical activity (i.e. any light or hard activity).

Some limitations should be mentioned. First, the classification of insomnia was based on self-reports and the questions differed between HUNT2 and HUNT3. The questions in HUNT2 did not include information about night-time awakenings or daytime sleepiness. Further, there is no information about insomnia symptoms beyond 1 month in HUNT2. Thus, the insomnia questions available in HUNT2 do not approximate the DSM-IV or the more recent DSM-V insomnia criteria. In HUNT3, information was available on frequency of difficulty initiating sleep, difficulty maintaining sleep and waking up too early during the last 3 months, which approximate the DSM-V criteria for insomnia. In individuals with insomnia, these complaints are accompanied by a report of impaired daytime function. Thus, daytime sleepiness was included as an additional subdomain to make our classification of insomnia more specific. However, it is uncertain whether the question about daytime sleepiness is a good measure of all types of daytime impairments. Furthermore, the response option 'several times a week' have been shown to include people who have sleep problems twice a week or more (Engstrøm *et al.*, 2011), while the DSM-V criteria requires the symptoms to be present three times or more per week. Moreover, we attempted to make the classification of insomnia at baseline (i.e. HUNT2) more specific by excluding participants who reported use of hypnotics or sleep medications. Nevertheless, we have no information about the progression of insomnia symptoms during the follow-up period or if new risk factors appeared during the follow-up period. Similarly, information about chronic musculoskeletal pain, leisure-time physical activity and BMI was obtained only at baseline, and changes occurring during the 11-year follow-up period could not be taken into account. Musculoskeletal pain may fluctuate over time (Lagersted-Olsen *et al.*, 2016) and may also be worsened by insomnia symptoms (Mork *et al.*, 2014). Thus, it is possible that people who developed insomnia symptoms during the follow-up also experienced an exacerbation of musculoskeletal symptoms which, in turn, worsen their sleep problems (i.e. a vicious circle). This is in line with the well-established view that a bidirectional association exist between pain and sleep problems (Smith and Haythornthwaite, 2004). Further, a reduction in physical activity during the follow-up could influence both sleep (Chennaoui *et al.*, 2015; Yang *et al.*, 2012) and BMI (Parsons *et al.*, 2006), and an increase in BMI would then be associated with an increased risk of insomnia. Thus, disentangling the complex association between musculoskeletal pain, physical activity, BMI and sleep problems require longitudinal data with repeated measurements of these factors. Finally, although previous research have confirmed a female predisposition of both chronic musculoskeletal pain (Wijnhoven *et al.*, 2006) and insomnia (Zhang and Wing, 2006), the underlying mechanisms are poorly understood. Unfortunately, in the present study we had insufficient statistical power to examine the joint effects stratified by sex. Thus, further studies are needed to evaluate if possible modifying effects of lifestyle factors are differential between women and men.

In conclusion, the current study provides evidence that chronic musculoskeletal pain is positively associated with risk of insomnia in adult women and men. The risk increases in a dose-dependent manner with increasing number of chronic pain sites. Although there was no clear evidence of modifying effects, an important finding is that leisure-time physical activity and maintenance of normal body weight can reduce the risk of insomnia in pain-afflicted individuals.

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AUTHOR CONTRIBUTIONS

Study concept and design, drafting of the manuscript and critical revision of the manuscript: all authors. Statistical analysis: ESS, TILN and PJM. Analysis and interpretation of data: ESS, TILN and PJM. Final approval: all authors.

CONFLICT OF INTEREST

None.

REFERENCES

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 5th edn. American Psychiatric Publishing, Washington, DC, 2013.

Andersson, T., Alfredsson, L., Kallberg, H., Zdravkovic, S. and Ahlbom, A. Calculating measures of biological interaction. *Eur. J. Epidemiol.*, 2005, 20: 575–579.

Anothaisintawee, T., Reutrakul, S., Van Cauter, E. and Thakkinstian, A. Sleep disturbances compared to traditional risk factors for diabetes development: systematic review and meta-analysis. *Sleep Med. Rev.*, 2015, 30: 11–24.

Bjelland, I., Dahl, A. A., Haug, T. T. and Neckelmann, D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J. Psychosom. Res.*, 2002, 52: 69–77.

Buysse, D. J. Insomnia. *JAMA*, 2013, 309: 706–716.

Chennaoui, M., Arnal, P. J., Sauvet, F. and Leger, D. Sleep and exercise: a reciprocal issue? *Sleep Med. Rev.*, 2015, 20: 59–72.

Dew, M. A., Hoch, C. C., Buysse, D. J. *et al.* Healthy older adults' sleep predicts all-cause mortality at 4 to 19 years of follow-up. *Psychosom. Med.*, 2003, 65: 63–73.

Dhalla, S. and Kopec, J. A. The CAGE questionnaire for alcohol misuse: a review of reliability and validity studies. *Clin. Invest. Med.*, 2007, 30: 33–41.

Engstrøm, M. O. S., Sand, T., Stovner, L. J., Zwart, J. A. and Hagen, K. The reliability of a new sleep screening questionnaire for large population-based studies: the third Nord-Trøndelag Health Study. *Open Sleep J.*, 2011, 4: 14–19.

Ewing, J. A. Detecting alcoholism. The CAGE questionnaire. *JAMA*, 1984, 252: 1905–1907.

Hagen, K., Linde, M., Heuch, I., Stovner, L. J. and Zwart, J. A. Increasing prevalence of chronic musculoskeletal complaints. A large 11-year follow-up in the general population (HUNT 2 and 3). *Pain Med.*, 2011, 12: 1657–1666.

Kamaleri, Y., Natvig, B., Ihlebaek, C. M., Benth, J. S. and Bruusgaard, D. Number of pain sites is associated with demographic, lifestyle, and health-related factors in the general population. *Eur. J. Pain*, 2008, 6: 742–748.

Kuorinka, I., Jonsson, B., Kilbom, Å., Vinterberg, H., Biering-Sørensen, F. and Andersson, G. Standardised Nordic questionnaires for the analysis of musculoskeletal symptoms. *Appl. Ergon.*, 1987, 18: 233–237.

Kurtze, N., Rangul, V., Hustvedt, B. E. and Flanders, W. D. Reliability and validity of self-reported physical activity in the Nord-Trondelag Health Study (HUNT 2). *Eur. J. Epidemiol.*, 2007, 22: 379–387.

Lagersted-Olsen, J., Bay, H., Jørgensen, M. B., Holtermann, A. and Søgaard, K. Low back pain patterns over one year among 842 workers in the DPhacto Study and predictors for chronicity based on repetitive measurements. *BMC Musculoskelet. Disord.*, 2016, 17: 453.

Leblanc, M., Mérette, C., Savard, J., Ivers, H., Baillargeon, L. and Morin, C. M. Incidence and risk factors of insomnia in a population-based sample. *Sleep*, 2009, 32: 1027–1037.

Lisspers, J., Nygren, A. and Söderman, E. Hospital Anxiety and Depression Scale (HAD): some psychometric data for a Swedish sample. *Acta Psychiatr. Scand.*, 1997, 96: 281–286.

Mork, P. J., Vik, K. L., Moe, B., Lier, R., Bardal, E. M. and Nilsen, T. I. L. Sleep problems, exercise and obesity and risk of chronic musculoskeletal pain: the Norwegian HUNT Study. *Eur. J. Public Health*, 2014, 24: 924–929.

Ødegård, S. S., Sand, T., Engstrøm, M., Zwart, J. A. and Hagen, K. The impact of headache and chronic musculoskeletal complaints on the risk of insomnia: longitudinal data from the Nord-Trondelag health study. *J. Headache Pain*, 2013, 14: 24.

Ohayon, M. M. Epidemiology of insomnia: what we know and what we still need to learn. *Sleep Med. Rev.*, 2002, 6: 97–11.

Palm, A., Janson, C. and Lindberg, E. The impact of obesity and weight gain on development of sleep problems in a population-based sample. *Sleep Med.*, 2015, 16: 593–597.

Palmer, K., Smith, G., Kellingray, S. and Cooper, C. Repeatability and validity of an upper limb and neck discomfort questionnaire: the utility of the standardized Nordic questionnaire. *Occup. Med. (Lond.)*, 1999, 49: 171–175.

Park, S. Associations of physical activity with sleep satisfaction, perceived stress, and problematic internet use in Korean adolescents. *BMC Public Health*, 2014, 14: 1143.

Parsons, T. J., Manor, O. and Power, C. Physical activity and change in body mass index from adolescence to mid-adulthood in the 1958 British cohort. *Int. J. Epidemiol.*, 2006, 35: 197–204.

Roth, T. Insomnia: definition, prevalence, etiology, and consequences. *J. Clin. Sleep Med.*, 2007, 3: 7–10.

Singareddy, R., Vgontzas, A. N., Fernandez-Mendoza, J. *et al.* Risk factors for incident chronic insomnia: a general population prospective study. *Sleep Med.*, 2012, 13: 346–353.

Sivertsen, B., Krokstad, S., Øverland, S. and Mykletun, A. The epidemiology of insomnia: associations with physical and mental health: the HUNT-2 study. *J. Psychosom. Res.*, 2009, 67: 109–116.

Smagula, S. F., Reynolds, C. F. III, Ancoli-Israel, S. *et al.* Sleep architecture and mental health among community-dwelling older men. *J. Gerontol. B Psychol. Sci. Soc. Sci.*, 2015, 70: 673–681.

Smith, M. T. and Haythornthwaite, J. A. How do sleep disturbance and chronic pain inter-relate? Insight from the longitudinal and cognitive–behavioral clinical trials literature. *Sleep Med. Rev.*, 2004, 8: 119–132.

Sofi, F., Cesari, F., Casini, A., Macchi, C., Abbate, R. and Gensini, G. F. Insomnia and risk of cardiovascular disease: a meta-analysis. *Eur. J. Prev. Cardiol.*, 2014, 21: 57–64.

Tang, N. K., McBeth, J., Jordan, K. P., Blagojevic-Bucknall, M., Croft, P. and Wilkie, R. Impact of musculoskeletal pain on insomnia onset: a prospective cohort study. *Rheumatology (Oxford)*, 2015, 54: 248–256.

Teychenne, M., Costigan, S. A. and Parker, K. The association between sedentary behaviour and risk of anxiety: a systematic review. *BMC Public Health*, 2015, 15: 513.

Uhlig, B. L., Sand, T., Ødegard, S. S. and Hagen, K. Prevalence and associated factors of DSM-V insomnia in Norway: the Nord-Trondelag Health Study (HUNT 3). *Sleep Med.*, 2014, 15: 708–713.

Varrasse, M., Li, J. and Gooneratne, N. Exercise and sleep in community-dwelling older adults. *Curr. Sleep Med. Rep.*, 2015, 1: 232–240.

Vgontzas, A. N., Liao, D., Bixler, E. O., Chrousos, G. P. and Vela-Bueno, A. Insomnia with objective short sleep duration is associated with a high risk for hypertension. *Sleep*, 2009, 32: 491–497.

Wijnhoven, H. A., de Vet, H. C. and Picavet, H. S. Prevalence of musculoskeletal disorders is systematically higher in women than in men. *Clin. J. Pain*, 2006, 8: 717–724.

World Health Organization. *Physical Status: The Use of and Interpretation of Anthropometry*. Report of a WHO Expert Committee. Technical Report Series no. 854. WHO, Geneva, 1995.

Yang, P. Y., Ho, K. H., Chen, H. C. and Chien, M. Y. Exercise training improves sleep quality in middle-aged and older adults with sleep problems: a systematic review. *J. Physiother.*, 2012, 58: 157–163.

Zhang, B. and Wing, Y. K. Sex differences in insomnia: a meta-analysis. *Sleep*, 2006, 1: 85–93.