BMJ Open

The joint effect of insomnia symptoms and lifestyle factors on risk of self-reported fibromyalgia in women: longitudinal data from the HUNT Study

Eivind Schjelderup Skarpsno,[1,2] Tom Ivar Lund Nilsen,[1,3] Trond Sand,[2,4] Knut Hagen,[2,4,5] Paul Jarle Mork[1]

To cite: Skarpsno ES, Nilsen TIL, Sand T, *et al*. The joint effect of insomnia symptoms and lifestyle factors on risk of self-reported fibromyalgia in women: longitudinal data from the HUNT Study. *BMJ Open* 2019;**9**:e028684. doi:10.1136/bmjopen-2018-028684

► Prepublication history for this paper is available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2018-028684).

Received 25 December 2018
Revised 26 June 2019
Accepted 11 July 2019

For numbered affiliations see end of article.

Correspondence to
Mr
Eivind Schjelderup Skarpsno;
eivind.s.skarpsno@ntnu.no

ABSTRACT

Objectives To investigate the association between insomnia symptoms and risk of self-reported fibromyalgia in women, and to explore whether leisure time physical activity and body mass index (BMI) modify this association.

Design Prospective cohort study.

Setting We used longitudinal data from the Norwegian Nord-Trøndelag Health Study collected in 1995–1997 (baseline) and 2006–2008 (follow-up).

Participants A total of 14 172 women who reported to be free from fibromyalgia at baseline.

Primary outcome measures We estimated adjusted risk ratios (RRs) with 95% CI for self-reported fibromyalgia at follow-up associated with baseline insomnia symptoms, leisure time physical activity and BMI.

Results Overall, 466 incident cases of fibromyalgia were reported during the follow-up period of approximately 11 years, corresponding to a crude absolute risk (AR) of 3.3%. Compared with women without insomnia symptoms (crude AR=2.8%), women who reported one, two or three symptoms had RRs of fibromyalgia of 1.39 (95% CI: 1.08 to 1.80), 1.86 (95% CI: 1.33 to 2.59) and 2.66 (95% CI: 1.75 to 4.06), respectively. Compared with highly physically active women without insomnia symptoms (crude AR=2.7%), women with one or more insomnia symptoms had a RR of fibromyalgia of 1.90 (95% CI: 1.30 to 2.79) if they reported low physical activity and a RR of 1.55 (95% CI: 1.12 to 2.13) if they reported high physical activity. We found no synergistic effect between insomnia symptoms and BMI on risk of fibromyalgia; however, overweight and obese women with one or more insomnia symptoms had RRs of 2.35 (95% CI: 1.73 to 3.21) and 2.18 (95% CI: 1.42 to 3.35) compared with the reference group of normal weight women without insomnia symptoms (crude AR=2.3%).

Conclusions Insomnia symptoms are strongly and positively associated with risk of fibromyalgia in adult women. Leisure time physical activity may compensate for some of the adverse effect of insomnia symptoms on risk of fibromyalgia.

Strengths and limitations of this study

- The strengths of the current study include the prospective design, the large study sample of women and the possibility to adjust for several potential confounding factors.
- Fibromyalgia was assessed by self-reports at both baseline and follow-up.
- The questions on sleep at baseline referred to symptoms the last month and the question on impaired daytime function was only related to work ability.
- The questions on sleep did not capture whether the insomnia symptoms occur despite adequate opportunity and conditions for sleep or if they were explained by another sleep disorder.
- We have no information about changes to insomnia symptoms, leisure time physical activity and body mass index during the follow-up.

INTRODUCTION

Fibromyalgia is a musculoskeletal pain syndrome with chronic widespread pain as the main symptom.[1 2] The aetiology and pathophysiology remain undetermined, but a disturbance in the central regulation of pain seems to be an important contributor to the development of fibromyalgia.[3] Depending on the diagnostic criteria used, the prevalence of fibromyalgia is between 2% and 7% in the general adult population but up to fourfold higher among women than men.[4]

Almost all women with fibromyalgia report some sleep problems,[5] and several studies applying polysomnographic recordings have documented signs of disordered sleep in fibromyalgia.[6] This is not surprising considering that chronic widespread pain has been identified as a strong and independent risk factor for insomnia.[7] Conversely, epidemiological studies indicate that insomnia symptoms increase the risk of fibromyalgia and widespread pain among an otherwise healthy population.[8–10] For instance, in a longitudinal study, we have showed that sleep problems were strongly and positively associated with risk of fibromyalgia.[8] However, this study had several methodological limitations, for

example, sleep problems were assessed by a single question and baseline information about fibromyalgia was not available. More recently, two longitudinal studies have shown that insomnia symptoms are associated with increased risk of fibromyalgia and widespread pain in a working population[9] and among elderly.[10] Although these latter studies indicate an independent association between insomnia symptoms and risk of fibromyalgia, it is not clear if number of insomnia symptoms is dose dependently associated with risk of fibromyalgia and if lifestyle factors can modify this association.

Some evidence indicates that leisure time physical activity and maintenance of normal body weight to some extent can reduce the adverse effect of sleep problems on risk of chronic pain in the low back and neck/shoulders.[11] Furthermore, excessive body weight may represent an independent risk factor of fibromyalgia,[12] whereas regular physical activity seems to reduce the risk of fibromyalgia.[12] Thus, it is conceivable that leisure time physical activity and obesity influence the association between insomnia symptoms and risk of fibromyalgia. Improved knowledge about the interplay between insomnia symptoms and lifestyle factors would be valuable for improved prevention of fibromyalgia.

The aim of the current study was to investigate the prospective association between insomnia symptoms and risk of self-reported fibromyalgia in women, and to explore if leisure time physical activity and body mass index (BMI) modify this association.

MATERIALS AND METHODS

Study population

This prospective population-based study utilises longitudinal data on women participating in the Nord-Trøndelag Health Study (the HUNT Study). All inhabitants in the Nord-Trøndelag County in Norway aged 20 years or older were invited to participate in three consecutive surveys; 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 at all three surveys. The invitation files were created from periodically updated census data from Statistics Norway. In the second and third surveys, the invitation letter was sent by mail attached along with a three-page questionnaire. This questionnaire was returned when the participants attended the clinical examination. At the clinical examination, the participants were given a second questionnaire that they were asked to complete at home and return in a pre-stamped envelope. More detailed information about the HUNT Study can be found at http://www.ntnu.edu/hunt.

Information on fibromyalgia and insomnia symptoms were not collected at HUNT1, and the current study is therefore based on data from HUNT2 and HUNT3. At the HUNT2 baseline survey, a total of 47 312 women were invited and 75.5% (n=35 280) participated. At the HUNT3 follow-up survey, 47 293 women were invited and 58.7% (n=27 758) participated. In the current study, we used data from the 20 415 women who participated in both HUNT2 and HUNT3. Of these, we excluded 1159 women who reported fibromyalgia at baseline at HUNT2. Furthermore, we excluded women with incomplete baseline information on insomnia symptoms (n=3541) and leisure time physical activity (n=761). Moreover, 161 women defined as underweight (BMI <18.5 kg/m^2) were excluded due to possible pre-clinical disease that could influence insomnia, lifestyle factors or fibromyalgia. Of the remaining 14 793 women, 14 172 answered the question about fibromyalgia at the follow-up survey (HUNT3).

Fibromyalgia

At baseline, women reported physician diagnosed fibromyalgia according to the following question: 'Has a doctor ever said that you have fibromyalgia (fibrositis/chronic pain syndrome)?', with response options 'Yes' or 'No'. At follow-up, incident fibromyalgia was identified by the question 'Have you had, or do you have fibromyalgia?', with response options 'Yes' or 'No'.

Insomnia symptoms

At baseline, classification of insomnia symptoms was based on the following three questions: (1) 'During the last month, have you had problems falling asleep?', (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 insomnia to such a degree that it influenced your work ability?' Questions 1 and 2 had the response options: 'Never', 'Occasionally', 'Often' and 'Almost every night', whereas question 3 had the response options 'No' and 'Yes'. Participants were classified to have insomnia symptoms if they answered, 'Often' or 'Almost every night' on at least one of the questions 1–2 or 'Yes' on question 3.

Body mass index

Standardised measurements of body height (to the nearest centimetre) and weight (to the nearest half kilogram) obtained at the clinical examination at baseline was used to calculate BMI (kg/m^2). Participants were then classified according to cut-offs suggested by the WHO[13] : 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). Women defined as underweight (BMI <18.5 kg/m^2) were excluded from the analyses to reduce the possibility of reverse causation due to undetected disease.

Leisure time physical activity

At baseline, leisure time physical activity was assessed by the 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', '<1 hour', '1–2 hours' and '≥3 hours' for both light and hard activities. Based on this information, we constructed a new variable with three categories combining information on light and hard activities: low activity (<1-hour light and no hard activity), moderate activity (≥1-hour light and no hard activity) and high activity (any hard activity).

Other variables

Potential confounders were assessed at baseline. Age was determined from the Norwegian national identity number and categorised into '20–29 years', '30–39 years', '40–49 years', '50–59 years', '60–69 years' and '≥70 years'. Education was assessed by the question: 'What is your highest level of education?' and divided in four categories: 'Primary school', 'High school', 'College≤4 years' and 'College>4 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.[14] As recommended, the cut-off score was set to ≥8 on both anxiety and depression and were dichotomised as presence or no presence of anxiety and/or depression.[14 15] Smoking was assessed by questions about past and present smoking and then divided into three categories: 'Never smoked', 'Former smoker' and 'Current smoker'. 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 three 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, ankles/feet (ie, a maximum of nine chronic pain sites). We then constructed a new variable using number of chronic musculoskeletal pain sites to categorise participants into four strata: no chronic pain, 1–2 chronic pain sites, 3–4 chronic pain sites and ≥5 chronic pain sites. 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 was used to estimate risk ratios (RRs) of fibromyalgia associated with insomnia symptoms and number of insomnia symptoms. The precision of the RRs was assessed by 95% CIs using robust variance estimation. Women with insomnia symptoms were compared with the reference group of women with no insomnia symptoms. Crude estimates of absolute risk (AR) were calculated for the total sample, as well as for each of the reference categories to help determine the clinical importance of the associations. All associations were adjusted for potential confounding by age (20–29, 30–39, 40–49 and 50–59 years), BMI (18.5–24.9, 25.0–29.9 and ≥30 kg/m^2), leisure time physical activity (high activity, moderate activity and low activity), education (primary school, high school, college ≤4 years, college >4 years and unknown) and smoking (never, former smoker, current smoker and unknown). Furthermore, since anxiety and/or depression are associated with both fibromyalgia and insomnia symptoms, we included HADS (no anxiety or depression, anxiety and/or depression and unknown) in the multi-adjusted model.

We estimated the joint effect of insomnia symptoms and leisure time physical activity on risk of fibromyalgia, using highly physically active women without insomnia symptoms as the reference group. Furthermore, in the analysis of the joint effect of insomnia symptoms and BMI on risk of fibromyalgia, normal weight women without insomnia symptoms formed the reference group. These analyses were adjusted for all the potential confounders described above (excluding the variable under study). 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 by the following equation: $\mathrm{RERI} = \mathrm{RR}_{\text{low activity and insomnia symptoms}} - \mathrm{RR}_{\text{low activity and no insomnia symptoms}} - \mathrm{RR}_{\text{high activity and insomnia symptoms}} + 1$,[16] that is, RERI >0 indicates a synergistic effect beyond an additive effect. The same RERI calculation was performed for the joint effect of BMI and insomnia symptoms.

Supplementary analyses were conducted to assess the robustness of the results. First, we included the use of hypnotics and/or sedatives as a covariate in the multi-adjusted models. Likewise, since some persons with multisite pain may have undiagnosed fibromyalgia, we included number of chronic pain sites (no chronic pain, 1–2 chronic pain sites, 3–4 chronic pain sites and ≥5 chronic pain sites) as a covariate in the multi-adjusted models. Finally, in the analyses of joint effect, we attempted to classify the participants into more contrasting categories of physical activity, that is, we excluded 1686 women who reported to be physically active <1 hour per week from the group of low physical activity.

All statistical analyses were performed using Stata for Windows, V.15.1 (StataCorp LP, College Station, TX, USA).

Patient and public involvement

No patients were involved in the development and design of this prospective study.

RESULTS

Table 1 presents the baseline characteristics of the 14 172 participants stratified by the presence of insomnia symptoms. The proportion of women who reported one or more insomnia symptoms at baseline (HUNT2) was 20% (2,397 women). Overall, 466 incident cases of fibromyalgia were reported during the follow-up period of approximately 11 years (crude AR=3.3%).

Table 2 shows the association between insomnia symptoms and risk of fibromyalgia. The risk of fibromyalgia

Table 1 Baseline characteristics of the study population stratified by insomnia symptoms

	Insomnia symptoms*	
	No	Yes
Participants, no.	11 775	2397
Age, mean±SD, years	43.5±12.0	47.0±11.8
Body mass index, mean±SD, kg/m^2	25.7±4.1	26.0±4.4
Obese, % (no.)	13.8 (1621)	16.0 (383)
Leisure time physical activity, % (no.)		
Low†	15.5 (1820)	20.4 (490)
Moderate‡	35.5 (4185)	38.3 (917)
High§	49.0 (5770)	41.3 (990)
Education≥13 years, % (no.)	26.0 (3059)	23.3 (559)
Unknown	1.0 (120)	1.5 (35)
Depression and/or anxiety (HADS score ≥8), % (no.)	11.8 (1385)	34.1 (817)
Unknown	10.7 (1265)	15.0 (359)
Current smoker, % (no.)	15.7 (1852)	18.7 (447)
Unknown	20.4 (2407)	23.1 (554)

*Participants were classified with insomnia symptoms if they answered 'Often/always' on at least one of the questions about 'Problems falling asleep' and 'Waking up too early' or 'Yes' on the question about 'Impaired work ability due to sleep problems'.
†Defined as <1-hour light activity per week.
‡Defined as ≥1-hour light and no hard activity.
§Defined as any hard activity.
HADS, Hospital Anxiety and Depression Scale.

increased with number of insomnia symptoms, that is, compared with women without insomnia symptoms (AR = 2.8%), women who reported one, two or three symptoms had RRs of 1.39 (95% CI: 1.08 to 1.80), 1.86 (95% CI: 1.33 to 2.59) and 2.66 (95% CI: 1.75 to 4.06), respectively (table 2). When all symptoms of insomnia were merged into one group, women who reported one or more insomnia symptoms had a RR of 1.64 (95% CI: 1.34 to 2.02), compared with women with no insomnia symptoms (table 2).

Table 3 shows the joint association between insomnia symptoms and leisure time physical activity on risk of fibromyalgia. Compared with the reference group of highly physically active women with no insomnia symptoms (AR=2.7%), women with one or more insomnia symptoms had RRs of 1.90 (95% CI: 1.30 to 2.79) if they reported low activity and 1.55 (95% CI: 1.12 to 2.13) if they reported to be highly physically active (table 3). Furthermore, women without insomnia symptoms who reported low physical activity had a RR of 0.95 (95% CI: 0.69 to 1.29). The RERI estimate between insomnia symptoms and leisure time physical activity on risk of fibromyalgia was 0.40 (95% CI: −0.37 to 1.19).

Table 4 shows the joint association between insomnia symptoms and BMI on risk of fibromyalgia. There was no evidence of interaction, that is, the RERI estimate between insomnia symptoms and BMI was −0.01 (95% CI: −0.99 to 0.97).

Supplementary analyses

The supplementary analysis, including hypnotics and/or sedatives as a covariate in the multi-adjusted models, had negligible effect on the estimated associations. The association between number of insomnia symptoms and risk of fibromyalgia became somewhat attenuated when

Table 2 Risk of fibromyalgia at 11-year follow-up associated with baseline insomnia symptoms

Insomnia symptoms	No. of persons	No. of cases	Age-adjusted RR*	Multi-adjusted RR† (95% CI)
No. of symptoms‡				
0	11 775	334	1.00	1.00 (reference)
1	1566	71	1.60	1.39 (1.08 to 1.80)
2	612	40	2.36	1.86 (1.33 to 2.59)
3	219	21	3.53	2.66 (1.75 to 4.06)
Insomnia symptoms§				
No	11 775	334	1.00	1.00 (reference)
Yes	2397	132	1.96	1.64 (1.34 to 2.02)

*Adjusted for age (20–29, 30–39, 40–49, 50–59, 60–69 and ≥70 years).
†Adjusted for age (20–29, 30–39, 40–49, 50–59, 60–69 and ≥70 years), body mass index (18.5–24.9, 25.0–29.9 and ≥30 kg/m^2), leisure time physical activity (high activity, moderate activity and low activity), education (primary school, high school, college ≤4 years, college ≥4 years and unknown), The Hospital Anxiety and Depression Scale (no depression and no anxiety, depression and/or anxiety, and unknown) and smoking (never, former, current smoker and unknown).
‡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'.
§Participants were classified with insomnia symptoms if they answered 'Often/always' on at least one of the questions about 'Problems falling asleep' and 'Waking up too early' or 'Yes' on the question about 'Impaired work ability due to sleep problems'.
RR, risk ratio.

Table 3 The joint effect of insomnia symptoms and leisure time physical activity on risk of fibromyalgia at 11-year follow-up

	No insomnia symptoms			Insomnia symptoms*		
Physical activity	No. of persons	No. of cases	Multi-adjusted† RR (95% CI)	No. of persons	No. of cases	Multi-adjusted† RR (95% CI)
High‡	5770	156	1.00 (reference)	990	49	1.55 (1.12 to 2.13)
Moderate§	4185	125	1.05 (0.82 to 1.34)	917	49	1.63 (1.18 to 2.25)
Low¶	1820	53	0.95 (0.69 to 1.29)	490	34	1.90 (1.30 to 2.79)

*Participants were classified to have insomnia symptoms if they answered 'Often/always' on one of the questions about 'Problems falling asleep' and 'Waking up too early' or 'Yes' on the question about 'Impaired work ability due to sleep problems'.
†Adjusted for age (20–29, 30–39, 40–49, 50–59, 60–69 and ≥70 years), body mass index (18.5–24.9, 25.0–29.9 and ≥30 kg/m^2), education (primary school, high school, college ≤4 years, college ≥4 years and unknown), The Hospital Anxiety and Depression Scale (no depression and no anxiety, depression and/or anxiety, and unknown) and smoking (never, former, current smoker and unknown).
‡Any hard activity per week.
§≥1-hour light and no hard activity per week.
¶<1-hour light activity per week.
RR, risk ratio.

adjusting for number of chronic pain sites (no chronic pain, 1–2 chronic pain sites, 3–4 chronic pain sites and ≥5 chronic pain sites), that is, women who reported one, two or three insomnia symptoms had RRs of 1.04 (95% CI: 0.81 to 1.35), 1.30 (95% CI: 0.94 to 1.80) and 1.67 (95% CI: 1.10 to 2.53), respectively. Comparing inactive (no light and no hard activity) women to highly active women strengthened the association, that is, inactive women with insomnia symptoms had a RR of 2.04 (95% CI: 1.10 to 3.80) compared with highly active women without insomnia symptoms.

DISCUSSION

The results from this prospective study indicate a strong and independent association between insomnia symptoms and risk of fibromyalgia. The risk increased with number of insomnia symptoms and was more than twofold higher among women who reported three or more symptoms compared with women who reported no symptoms. High level of leisure time physical activity may to some extent attenuate the adverse effect of insomnia symptoms on risk of fibromyalgia. We found no synergistic effect of insomnia symptoms and BMI, but overweight and obese women with insomnia symptoms had more than twofold increased risk of fibromyalgia compared with normal weight women with no insomnia symptoms.

Prospective studies have shown that sleep problems increase the risk of localised[11] and generalised chronic pain.[17 18] However, the different definitions of both sleep problems and pain limit the possibility to directly compare our results with previous findings. In a large longitudinal study based on a previous wave of the HUNT Study, we showed that sleep problems were strongly and positively associated with the risk of fibromyalgia in women at 10-year to 11-year follow-up.[8] However, the study had several methodological limitations, for example, sleep problems were assessed by a single question and baseline information about fibromyalgia and chronic pain was not available. More recently, two studies based on the same data as the current study showed that a proxy of the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) insomnia diagnosis was

Table 4 The joint effect of insomnia symptoms and BMI on risk of fibromyalgia at 11-year follow-up.

	No insomnia symptoms			Insomnia symptoms*		
BMI	No. of persons	No. of cases	Multi-adjusted† RR (95% CI)	No. of persons	No. of cases	Multi-adjusted† RR (95% CI)
Normal weight (18.5–24.9 kg/m^2)	5818	136	1.00 (reference)	1125	52	1.64 (1.20 to 2.25)
Overweight (25.0–29.9 kg/m^2)	4336	138	1.35 (1.07 to 1.70)	889	56	2.35 (1.73 to 3.21)
Obese (≥30 kg/m^2)	1621	60	1.55 (1.14 to 2.10)	383	24	2.18 (1.42 to 3.35)

*Participants were classified to have insomnia symptoms if they answered 'Often/always' on one of the questions about 'Problems falling asleep' and 'Waking up too early' or 'Yes' on the question about 'Impaired work ability due to sleep problems'.
†Adjusted for age (20–29, 30–39, 40–49, 50–59, 60–69 and ≥70 years), leisure time physical activity (high activity, moderate activity and low activity), education (primary school, high school, college ≤4 years, college ≥4 years and unknown), The Hospital Anxiety and Depression Scale (no depression and no anxiety, depression and/or anxiety, and unknown) and smoking (never, former, current smoker and unknown).
BMI, body mass index; RR, risk ratio.

associated with increased risk of fibromyalgia[9] and chronic widespread pain.[17] The current study extends on these findings by showing the dose-dependent association between number of insomnia symptoms and risk of fibromyalgia. Taken together, these findings suggest that reducing both mild and severe sleep problems may be an important target to reduce the incidence of fibromyalgia. The underlying mechanism for the association between insomnia symptoms and susceptibility to develop fibromyalgia is unclear but can be related to the possible relation between sleep problems and central sensitisation of the nervous system.[19] For instance, sleep restriction and poor sleep quality may impair endogenous nociceptive-inhibitory function and increase pain,[20] as well as induce generalised hyperalgesia in otherwise healthy people.[21] Furthermore, there may exist a link between poor sleep and low-graded inflammation,[22] which is supported by experimental studies showing that pro-inflammatory cytokines can be involved in the development of hyperalgesia.[23–25]

Our results show that moderate and high leisure time physical activity may modify the adverse effect of insomnia symptoms on risk of fibromyalgia. Although the precision in our analysis of additive interaction was low, the estimate suggests a synergistic effect of insomnia symptoms and leisure time physical activity on risk of fibromyalgia. This result is partly in line with a previous study showing that leisure time physical activity to some extent compensate the risk of mild sleep problems on chronic pain in low back and neck/shoulders.[11] However, sleep problems were assessed by a single question and the definition of leisure time physical activity differed from the current study. Furthermore, it is possible that pain in the low back and neck/shoulder represent a condition that differs in nature from fibromyalgia, and that insomnia symptoms and physical activity influence these pain conditions differently. Interestingly, in the current study, the beneficial effect of moderate and high physical activity was present only among women with symptoms of insomnia. A possible explanation for this finding is that the anti-inflammatory effect of physical activity[26 27] reduces inflammation induced by disturbed sleep and short sleep duration.[28 29] This notion is supported by studies showing that a single bout of low-intensity physical exercise can induce hypoalgesia and improve fibromyalgia symptoms,[30] indicating that physical exercise reduces pain perception[31] and increases pain tolerance.[32] Although the exact underlying mechanism remains undetermined, our findings suggest that regular recreational physical activity may reduce the risk of fibromyalgia in persons with symptoms of insomnia.

Although excessive body weight has been linked to increased risk of fibromyalgia,[12] we found no evidence that BMI modifies the effect of insomnia symptoms on risk of fibromyalgia. However, a high BMI was associated with an increased risk of fibromyalgia within all strata of insomnia symptoms.

Strengths of the current study include the prospective design, the large study sample and the possibility to adjust for several potential confounding factors. Furthermore, the large sample size allowed us to analyse the joint effect of insomnia symptoms and lifestyle factors. Some limitations should also be considered when interpreting the results. First, no information about the time of the fibromyalgia diagnosis was collected and fibromyalgia was assessed by self-reports at both baseline and follow-up. These questions have not been validated and some of the women may not have met the[33] classification criteria for a diagnosis of fibromyalgia.[33] It should also be noted that the data collection was carried out before the classification criteria for fibromyalgia was revised in 2010.[34] Furthermore, we cannot exclude the possibility that women reporting multisite pain have undiagnosed fibromyalgia. Second, our classification of insomnia is somewhat different from the International Classification of Sleep Disorders (3rd edition) criteria for insomnia diagnosis.[35] For instance, the questions on sleep in HUNT2 only refer to symptoms the last month and the question on impaired daytime function in HUNT2 is only related to work ability. Furthermore, the questions on sleep in HUNT2 do not capture whether the insomnia symptoms occur despite adequate opportunity and conditions for sleep or if they are explained by another sleep disorder. Furthermore, the assessment of leisure time physical activity was based on self-report. It should also be noted that insomnia symptoms, leisure time physical activity and BMI were collected only at the baseline survey, and we have no data on changes to these variables during the follow-up period. Finally, the study population consisted of a heterogeneous group of women, and future studies should investigate whether there exist subgroups where insomnia symptoms and lifestyle factors have different impact on risk of fibromyalgia.

In conclusion, insomnia symptoms are associated with increased risk of fibromyalgia in adult women. Notably, the risk increases proportionally with number of insomnia symptoms. Leisure time physical activity may modify some of the adverse effect of insomnia symptoms on risk of fibromyalgia. These findings indicate that preventing sleep problems and promoting a healthy active lifestyle are important to reduce the incidence of fibromyalgia.

Author affiliations
[1]Department of Public Health and Nursing, Norwegian University of Science and Technology (NTNU), Trondheim, Norway
[2]Department of Neurology and Clinical Neurophysiology, St. Olavs Hospital, Trondheim, Norway
[3]Clinic of Anaesthesia and Intensive Care, St. Olavs Hospital, Trondheim, Norway
[4]Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology, Trondheim, Norway
[5]Norwegian Advisory Unit on Headaches, St. Olavs Hospital, Trondheim, Norway

Contributors Study concept and design: ESS, TILN, TS, KH and PJM. Drafting of the manuscript: ESS. Critical revision of the manuscript: ESS, TILN, TS, KH and PJM. Statistical analysis: ESS. Interpretation of data: ESS, TILN, TS, KH and PJM. Final approval of the version to be published: ESS, TILN, TS, KH and PJM.

Funding This work was supported by a grant to Eivind Schjelderup Skarpsno from the Liaison Committee between the Central Norway Regional Health Authority (RHA) and the Norwegian University of Science and Technology (NTNU) (project number:

46056929). The Nord-Trøndelag Health Study (HUNT) is a collaboration between the HUNT Research Centre (Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology), the Nord-Trøndelag County Council and the Norwegian Institute of Public Health.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval 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.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

REFERENCES

1. Sarzi-Puttini P, Atzeni F, Mease PJ. Chronic widespread pain: from peripheral to central evolution. *Best Pract Res Clin Rheumatol* 2011;25:133–9.
2. Sluka KA, Clauw DJ. Neurobiology of fibromyalgia and chronic widespread pain. *Neuroscience* 2016;338:114–29.
3. Martínez-Lavín M, Hermosillo AG. Autonomic nervous system dysfunction may explain the multisystem features of fibromyalgia. *Semin Arthritis Rheum* 2000;29:197–9.
4. Gran JT. The epidemiology of chronic generalized musculoskeletal pain. *Best Pract Res Clin Rheumatol* 2003;17:547–61.
5. Bigatti SM, Hernandez AM, Cronan TA, *et al*. Sleep disturbances in fibromyalgia syndrome: relationship to pain and depression. *Arthritis Rheum* 2008;59:961–7.
6. Diaz-Piedra C, Catena A, Sánchez AI, *et al*. Sleep disturbances in fibromyalgia syndrome: the role of clinical and polysomnographic variables explaining poor sleep quality in patients. *Sleep Med* 2015;16:917–25.
7. Skarpsno ES, Nilsen TIL, Sand T, *et al*. Do physical activity and body mass index modify the association between chronic musculoskeletal pain and insomnia? longitudinal data from the HUNT study, Norway. *J Sleep Res* 2018;27:32–9.
8. Mork PJ, Nilsen TIL. Sleep problems and risk of fibromyalgia: longitudinal data on an adult female population in Norway. *Arthritis Rheum* 2012;64:281–4.
9. Sivertsen B, Lallukka T, Salo P, *et al*. Insomnia as a risk factor for ill health: results from the large population-based prospective HUNT study in Norway. *J Sleep Res* 2014;23:124–32.
10. McBeth J, Lacey RJ, Wilkie R. Predictors of new-onset widespread pain in older adults: results from a population-based prospective cohort study in the UK. *Arthritis Rheumatol* 2014;66:757–67.
11. Mork PJ, Vik KL, Moe B, *et al*. Sleep problems, exercise and obesity and risk of chronic musculoskeletal pain: the Norwegian HUNT study. *Eur J Public Health* 2014;24:924–9.
12. Mork PJ, Vasseljen O, Nilsen TIL. Association between physical exercise, body mass index, and risk of fibromyalgia: longitudinal data from the Norwegian Nord-Trøndelag health study. *Arthritis Care Res* 2010;62:611–7.
13. World Health Organization. *Physical status: the use of and interpretation of anthropometry. Report of a who expert Committee. technical report series no.854*. Geneva: WHO, 1995.
14. Bjelland I, Dahl AA, Haug TT, *et al*. The validity of the hospital anxiety and depression scale. An updated literature review. *J Psychosom Res* 2002;52:69–77.
15. Lisspers J, Nygren A, Söderman E, *et al*. Hospital anxiety and depression scale (had): some psychometric data for a Swedish sample. *Acta Psychiatr Scand* 1997;96:281–6.
16. Andersson T, Alfredsson L, Källberg H, *et al*. Calculating measures of biological interaction. *Eur J Epidemiol* 2005;20:575–9.
17. Uhlig BL, Sand T, Nilsen TI, *et al*. Insomnia and risk of chronic musculoskeletal complaints: longitudinal data from the HUNT study, Norway. *BMC Musculoskelet Disord* 2018;19:128.
18. Nitter AK, Pripp AH, Forseth Karin Ø. Are sleep problems and non-specific health complaints risk factors for chronic pain? A prospective population-based study with 17 year follow-up. *Scand J Pain* 2012;3:210–7.
19. Nijs J, Loggia ML, Polli A, *et al*. Sleep disturbances and severe stress as glial activators: key targets for treating central sensitization in chronic pain patients? *Expert Opin Ther Targets* 2017;21:817–26.
20. Smith MT, Edwards RR, McCann UD, *et al*. The effects of sleep deprivation on pain inhibition and spontaneous pain in women. *Sleep* 2007;30:494–505.
21. Schuh-Hofer S, Wodarski R, Pfau DB, *et al*. One night of total sleep deprivation promotes a state of generalized hyperalgesia: a surrogate pain model to study the relationship of insomnia and pain. *Pain* 2013;154:1613–21.
22. Haack M, Sanchez E, Mullington JM. Elevated inflammatory markers in response to prolonged sleep restriction are associated with increased pain experience in healthy volunteers. *Sleep* 2007;30:1145–52.
23. Dina OA, Green PG, Levine JD. Role of interleukin-6 in chronic muscle hyperalgesic priming. *Neuroscience* 2008;152:521–5.
24. Uçeyler N, Eberle T, Rolke R, *et al*. Differential expression patterns of cytokines in complex regional pain syndrome. *Pain* 2007;132:195–205.
25. Sommer C, Kress M. Recent findings on how proinflammatory cytokines cause pain: peripheral mechanisms in inflammatory and neuropathic hyperalgesia. *Neurosci Lett* 2004;361:184–7.
26. Hamer M, Sabia S, Batty GD, *et al*. Physical activity and inflammatory markers over 10 years: follow-up in men and women from the Whitehall II cohort study. *Circulation* 2012;126:928–33.
27. Das UN. Anti-Inflammatory nature of exercise. *Nutrition* 2004;20:323–6.
28. Okun ML, Coussons-Read M, Hall M. Disturbed sleep is associated with increased C-reactive protein in young women. *Brain Behav Immun* 2009;23:351–4.
29. Chiang J-K. Short duration of sleep is associated with elevated high-sensitivity C-reactive protein level in Taiwanese adults: a cross-sectional study. *J Clin Sleep Med* 2014;10:743–9.
30. Newcomb LW, Koltyn KF, Morgan WP, *et al*. Influence of preferred versus prescribed exercise on pain in fibromyalgia. *Med Sci Sports Exerc* 2011;43:1106–13.
31. Hoffman MD, Hoffman DR. Does aerobic exercise improve pain perception and mood? A review of the evidence related to healthy and chronic pain subjects. *Curr Pain Headache Rep* 2007;11:93–7.
32. Jones MD, Booth J, Taylor JL, *et al*. Aerobic training increases pain tolerance in healthy individuals. *Med Sci Sports Exerc* 2014;46:1640–7.
33. Wolfe F, Smythe HA, Yunus MB, *et al*. The American College of rheumatology 1990 criteria for the classification of fibromyalgia. *Arthritis & Rheumatism* 1990;33:160–72.
34. Wolfe F, Clauw DJ, Fitzcharles M-A, *et al*. The American College of rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Res* 2010;62:600–10.
35. American Academy of Sleep Medicine. *International classification of sleep disorders re*. Darien, IL: American Academy of Sleep Medicine, 2014.