BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-028684
Article Type:	Research
Date Submitted by the Author:	25-Dec-2018
Complete List of Authors:	Skarpsno, Eivind; Norges Teknisk Naturvitenskapelige Universitet Institutt for Samfunnsmedisin, Department of Public Health and Nursing; Department of Neurology and Clinical Neurophysiology, St. Olavs Hospital, Trondheim, Norway Nilsen, Tom; Norwegian University of Science and Technology, Department of Public Health and Nursing Sand, Trond; St. Olav Hospital, Department of Neurology and Clinical Neurophysiology, St. Olavs Hospital, Trondheim, Norway; Norwegian University of Science and Technology, Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology (NTNU), Trondheim, Norway Hagen, Knut; St. Olav Hospital, Department of Neurology and Clinical Neurophysiology; Norwegian University of Science and Technology , Department of Neuromedicine and Movement Science Mork, Paul Jarle; Norwegian University of Science and Technology, Department of Public Health and Nursing
Keywords:	Insomnia, PUBLIC HEALTH, Fibromyalgia, Physical activity, Body mass index, Exercise

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]

[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 University Hospital, Trondheim, Norway, [4]Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology (NTNU), Trondheim, Norway, [5]Norwegian National Headache Centre, St. Olavs Hospital, Trondheim, Norway

Corresponding author:

Eivind Schjelderup Skarpsno

Department of Public Health and Nursing, Norwegian University of Science and Technology (NTNU), 7491 Trondheim, Norway.

E-mail: eivind.s.skarpsno@ntnu.no

ORDCID ID: https://orcid.org/0000-0002-4135-0408

Telephone: +4797521297

Word count: 2975

Number of tables: 4

The authors declare no conflicts of interest.

ABSTRACT

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

Design: Prospective cohort study.

Setting: We used longitudinal data from the Norwegian HUNT Study collected in HUNT2 (1995-1997) and HUNT3 (2006-2008).

Participants: A total of 14,172 women who reported to be free from fibromyalgia at baseline in 1995-1997.

Primary and secondary outcome measures: We estimated adjusted risk ratios (RRs) for self-reported fibromyalgia at follow-up in 2006-2008 with 95% confidence interval (CI). Insomnia symptoms, leisure time physical activity and BMI served as exposures at baseline.

Results: Compared to women without insomnia symptoms, women who reported one, two or three symptoms had RRs of fibromyalgia of 1.39 (95% CI 1.08-1.80), 1.86 (95% CI 1.33-2.59) and 2.66 (95% CI 1.75-4.06), respectively. Compared to highly physically active women without insomnia symptoms, women with one or more insomnia symptoms had a RR of fibromyalgia of 1.90 (95% CI 1.30-2.79) if they reported low physical activity and a RR of 1.55 (95% CI 1.12-2.13) 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 1.73-3.21) and 2.18 (95% CI 1.42-3.35) compared to normal weight women without insomnia symptoms.

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.

Key word Insomnia, fibromyalgia, physical activity, body mass index, exercise, overweight

Strengths and limitations of this study

- The strengths of the current study include the prospective design, the large study sample of women, and the ability to adjust for several potential confounding factors.
- A limitation is that fibromyalgia was assessed by self-reports at both HUNT2 and HUNT3.
- Another limitation is that the questions on sleep in HUNT2 only refer to symptoms the last month and the question on impaired daytime function is only related to work ability. The questions 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, 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.

INTRODUCTION

Fibromyalgia is a musculoskeletal pain syndrome with chronic widespread pain as the main symptom [1, 2]. The etiology 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 based on data from the first (1984-86) and second (1995-97) wave of the Norwegian HUNT study, we showed that sleep problems were strongly and positively associated with risk of fibromyalgia [8]. However, this study had several methodological limitations, e.g., 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 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 utilizes longitudinal data on women participating in 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. More detailed information about the HUNT Study can be found at http://www.ntnu.edu/hunt.

In the current study, we used data from 20,415 women who participated in both HUNT2 and HUNT3. Of these, we excluded 1,159 women who reported fibromyalgia at baseline at HUNT2. Further, we excluded women with incomplete baseline information on fibromyalgia (n=1,472), insomnia symptoms (n=3,017) and leisure time physical activity (n=595). Thus, the prospective analyses were based on 14,172 women who answered the question about fibromyalgia at follow-up in HUNT3.

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.

Fibromyalgia

At the HUNT2 baseline survey, 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 the HUNT3 follow-up survey, incident fibromyalgia was identified by the question “Have you had, or do you have fibromyalgia?”, with response options “Yes” or “No”.

Insomnia symptoms

In HUNT2, 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?". Question 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

Standardized measurements of body height (to the nearest centimeter) 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 according to cut-offs suggested by the World Health Organization [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

In HUNT2, 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 activity. Based on this information, we constructed a new variable with three categories combining information on light and hard activity: low activity (<1 h light and no hard activity), moderate activity (≥1 h light and no hard activity) and high activity (any hard activity).

Other variables

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 dichotomized 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 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, ankles/feet (i.e., a maximum of nine chronic pain sites). We then constructed a new variable using number of chronic musculoskeletal pain sites to categorize participants into four strata: No chronic pain, 1-2 chronic pain sites, 3-4 chronic pain sites, and ≥5 chronic pain sites.

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% confidence intervals (CIs) using robust variance estimation. Women with insomnia symptoms were compared with the reference group of women with no insomnia symptoms. All associations were adjusted for potential confounding by age (20-29, 30-39, 40-49, 50-59 years), BMI (18.5-24.9 kg/m^2, 25.0-29.9 kg/m^2, ≥30 kg/m^2), leisure time physical activity (high activity, moderate activity, low activity), education (primary school, high school, college ≤4 years, college >4 years, unknown), HADS (no anxiety or depression, anxiety and/or depression, unknown), and smoking (never, former smoker, current smoker, unknown).

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. Further, 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: $RERI = RR_{\text{low activity and insomnia symptoms}} - RR_{\text{high activity and insomnia symptoms}} - RR_{\text{low activity and no insomnia symptoms}} + 1$ [16], i.e., 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 use of hypnotics and/or sedatives as a covariate in the multiadjusted models. Likewise, we included number of chronic pain sites (no pain, 1-2 chronic pain sites, 3-4 chronic pain sites, ≥5 chronic pain sites) as a covariate in the multiadjusted models. Finally, in

the analyses of joint effect, we excluded women with <1 h physical activity per week from the group of low physical activity.

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

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 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). At follow-up (HUNT3), 3.3% (466) women reported fibromyalgia.

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

	Insomnia symptoms[a]	
	No	Yes
Participants, no.	11,775	2,397
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
Low leisure time physical activity, % (no.)[b]	15.5 (1,820)	20.4 (490)
Education ≥ 13 years, % (no.)	26.0 (3,059)	23.3 (559)
Depression and/or anxiety (HADS score ≥8), % (no.)	11.8 (1,385)	34.1 (817)
Current smoker, % (no.)	15.7 (1,852)	18.7 (447)

Abbreviation: HADS, Hospital Anxiety and Depression Scale; SD, standard deviation
[a] Participants were classified with insomnia symptoms if they answered "Often/always" on at least one the questions about "Problems falling asleep" and "Waking up too early" or "Yes" on the question about "Impaired work ability due to sleep problems".
[b] Defined as <1 h light activity per week.

Table 2 shows the association between insomnia symptoms and risk of fibromyalgia. The risk of fibromyalgia increased with number of insomnia symptoms, i.e., compared to women without insomnia symptoms, women who reported one, two or three symptoms had RRs of 1.39 (95% CI 1.08-1.80), 1.86 (95% CI 1.33-2.59) and 2.66 (95% CI 1.75-4.06), respectively. When all symptoms of insomnia were collapsed into one group, women who reported one or more insomnia symptoms had a RR of 1.64 (95% CI 1.34-2.02), compared to women with no insomnia symptoms.

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[a]	Multi-adjusted, RR[b] (95% CI)
No. of symptoms[c]				
0	11,775	334	1.00	1.00 (reference)
1	1,566	71	1.60	1.39 (1.08-1.80)
2	612	40	2.36	1.86 (1.33-2.59)
3	219	21	3.53	2.66 (1.75-4.06)
Insomnia symptoms[d]				
No	11,775	334	1.00	1.00 (reference)
Yes	2,397	132	1.96	1.64 (1.34-2.02)

Abbreviations: BMI, body mass index; CI, confidence interval; RR, risk ratio

[a] Adjusted for age (20-29 years, 30-39 years, 40-49 years, 50-59 years, 60-69 years, ≥70 years).

[b] Adjusted for age (20-29 years, 30-39 years, 40-49 years, 50-59 years, 60-69 years, ≥70 years), body mass index (18.5-24.9 kg/m^2, 25.0-29.9 kg/m^2, ≥30 kg/m^2), leisure time physical activity (high activity, moderate activity, low activity), education (primary school, high school, college ≤4 years, college ≥4 years, unknown), The Hospital Anxiety and Depression Scale (no depression and no anxiety, depression and/or anxiety, unknown), smoking (never, former, current smoker, unknown).

[c] 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".

[d] Participants were classified with insomnia symptoms if they answered "Often/always" on at least one the questions about "Problems falling asleep" and "Waking up too early" or "Yes" on the question about "Impaired work ability due to sleep problems".

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

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[a]		
Physical activity	No. of persons	No. of cases	Multi-adjusted[b] RR (95% CI)	No. of persons	No. of cases	Multi-adjusted[b] RR (95% CI)
High[c]	5,770	156	1.00 (reference)	990	49	1.55 (1.12-2.13)
Moderate[d]	4,185	125	1.05 (0.82-1.34)	917	49	1.63 (1.18-2.25)
Low[e]	1,820	53	0.95 (0.69-1.29)	490	34	1.90 (1.30-2.79)

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

[a] 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".

[b] Adjusted for age (20-29 years, 30-39 years, 40-49 years, 50-59 years, 60-69 years, ≥70 years), body mass index (18.5-24.9 kg/m^2, 25.0-29.9 kg/m^2, ≥30 kg/m^2), education (primary school, high school, college ≤4 years, college ≥4 years, unknown), The Hospital Anxiety and Depression Scale (no depression and no anxiety, depression and/or anxiety, unknown), smoking (never, former, current smoker, unknown).

[c] Any hard activity per week

[d] ≥1h light and no hard activity per week

[e] <1 h light activity per week

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

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

	No insomnia symptoms			Insomnia symptoms[a]		
Body mass index (BMI, kg/m^2)	No. of persons	No. of cases	Multi-adjusted[b] RR (95% CI)	No. of persons	No. of cases	Multi-adjusted[b] RR (95% CI)
Normal weight (18.5-24.9 kg/m^2)	5,818	136	1.00 (reference)	1,125	52	1.64 (1.20-2.25)
Overweight (25.0-29.9 kg/m^2)	4,336	138	1.35 (1.07-1.70)	889	56	2.35 (1.73-3.21)
Obese (≥30 kg/m^2)	1,621	60	1.55 (1.14-2.10)	383	24	2.18 (1.42-3.35)

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

[a] 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".

[b] Adjusted for age (20-29 years, 30-39 years, 40-49 years, 50-59 years, 60-69 years, ≥70 years), leisure time physical activity (high activity, moderate activity, low activity), education (primary school, high school, college ≤4 years, college ≥4 years, unknown), The Hospital Anxiety and Depression Scale (no depression and no anxiety, depression and/or anxiety, unknown), smoking (never, former, current smoker, unknown).

Supplementary analyses

The supplementary analysis, including hypnotics and/or sedatives as a covariate in the multiadjusted models had negligible effect on the estimated associations. The association between number of insomnia symptoms and risk of fibromyalgia became somewhat attenuated when adjusting for number of chronic pain sites, i.e., women who reported one, two or three symptoms had RRs of 1.04 (95% CI 0.81-1.35), 1.30 (95% CI 0.94-1.80) and 1.67 (95% CI 1.10-2.53), respectively. Comparing highly active vs. inactive (no light and no hard activity) strengthened the association, i.e., compared to women with high physical activity and no insomnia symptoms, women with insomnia symptoms who also reported to be inactive had a RR of 2.04 (1.10-3.80).

DISCUSSION

The results from this large longitudinal study indicate a strong and independent association between insomnia symptoms and increased 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 to 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 to normal weight women with no insomnia symptoms.

Prospective studies have shown that sleep problems increase the risk of localized [11] and generalized 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 risk of fibromyalgia in women at 10-11 years follow up [19]. However, the study had several methodological limitations, e.g., 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 DSM-IV criteria for insomnia was associated with increased risk of fibromyalgia [9] and chronic widespread pain [17]. The current study extends on these findings by showing the contribution of number of insomnia symptoms in the development of fibromyalgia. Taken together, these findings suggest that reducing mild and severe sleep problems may be an important target to reduce the incidence of fibromyalgia. The underlying mechanisms that explain why women with insomnia symptoms are more susceptible to develop fibromyalgia is uncertain but can be related to the

possible relation between sleep and central sensitization of the nervous system [20]. For instance, sleep restriction and poor sleep quality may impair endogenous nociceptive-inhibitory function and increase pain [21], as well as induce generalized hyperalgesia in otherwise healthy people [22]. Further, there may exist a link between poor sleep and low-graded inflammation [23], which is supported by experimental studies showing that pro-inflammatory cytokines can be involved in the development of hyperalgesia [24-26].

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 suggest 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. Further, it is likely that pain in low back and neck/shoulder represent a condition in nature from fibromyalgia, and that insomnia symptoms and physical activity influence these pain conditions differently. Interestingly, the beneficial effect of moderate and high physical activity was present only among women with symptoms of insomnia. The explanation for this finding remains undetermined, but it is possible that the anti-inflammatory effect of physical activity [27, 28] reduces inflammation induced by disturbed sleep and short sleep duration [29, 30]. Further, some evidence has demonstrated exercise induced hypoalgesia and improvements in symptoms of fibromyalgia after a single low-intensity bout of physical exercise [31], indicating that exercise may reduce pain perception [32] and increase pain tolerance [33]. Thus, our findings underscore the importance of recreational physical activity to 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 modified the effect of insomnia symptoms on fibromyalgia risk. 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 of women, and the ability to adjust for several potential confounding factors. Further, the large sample size allowed us analyze 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 HUNT2 and HUNT3. These questions have not been validated and some of the women may not have met the American College of Rheumatology 1990 classification criteria for a diagnosis of fibromyalgia [34]. It should also be noted that HUNT2 and HUNT3 were carried out before the classification criteria for fibromyalgia was revised in 2010 [35]. Second, our classification of insomnia is somewhat different from the International Classification of Sleep Disorders (ICSD-3) criteria for insomnia diagnosis [36]. 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. Further, 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. Further, the assessment of leisure time physical activity was based on self-report. Finally, it should 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.

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 targets to reduce the incidence of fibromyalgia.

ACKNOWLEDGEMENT

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). 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.

AUTHOR CONTRIBUTIONS

Study concept and design: All authors. Drafting of the manuscript: ESS. Critical revision of the manuscript: All authors. Statistical analysis: ESS. Interpretation of data: All authors. Critical revision: All authors. Final approval: All authors.

Conflict of interest: Authors declare no conflicts of interest.

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BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-028684.R1
Article Type:	Research
Date Submitted by the Author:	26-Jun-2019
Complete List of Authors:	Skarpsno, Eivind; Norges Teknisk Naturvitenskapelige Universitet Institutt for Samfunnsmedisin, Department of Public Health and Nursing; Department of Neurology and Clinical Neurophysiology, St. Olavs Hospital, Trondheim, Norway Nilsen, Tom; Norwegian University of Science and Technology, Department of Public Health and Nursing Sand, Trond; St. Olav Hospital, Department of Neurology and Clinical Neurophysiology, St. Olavs Hospital, Trondheim, Norway; Norwegian University of Science and Technology, Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology (NTNU), Trondheim, Norway Hagen, Knut; St. Olav Hospital, Department of Neurology and Clinical Neurophysiology; Norwegian University of Science and Technology , Department of Neuromedicine and Movement Science Mork, Paul Jarle; Norwegian University of Science and Technology, Department of Public Health and Nursing
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Public health, Epidemiology, Rheumatology
Keywords:	Insomnia, PUBLIC HEALTH, Fibromyalgia, Physical activity, Body mass index, Exercise

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]

[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 University Hospital, Trondheim, Norway, [4]Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology (NTNU), Trondheim, Norway, [5]Norwegian National Headache Centre, St. Olavs Hospital, Trondheim, Norway

Corresponding author:

Eivind Schjelderup Skarpsno

Department of Public Health and Nursing, Norwegian University of Science and Technology (NTNU), 7491 Trondheim, Norway.

E-mail: eivind.s.skarpsno@ntnu.no

ORDCID ID: https://orcid.org/0000-0002-4135-0408

Telephone: +4797521297

Word count: 2975

Number of tables: 4

The authors declare no conflicts of interest.

ABSTRACT

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

Design: Prospective cohort study.

Setting: We used longitudinal data from the Norwegian HUNT 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% confidence interval (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 ~11 years follow-up period, corresponding to a crude absolute risk (AR) of 3.3%. Compared to 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 1.08-1.80), 1.86 (95% CI 1.33-2.59) and 2.66 (95% CI 1.75-4.06), respectively. Compared to 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 1.30-2.79) if they reported low physical activity and a RR of 1.55 (95% CI 1.12-2.13) 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 1.73-3.21) and 2.18 (95% CI 1.42-3.35) compared to 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.

Key word Insomnia, fibromyalgia, physical activity, body mass index, exercise, overweight

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 BMI during the follow-up.

INTRODUCTION

Fibromyalgia is a musculoskeletal pain syndrome with chronic widespread pain as the main symptom [1, 2]. The etiology 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, we have in a longitudinal study showed that sleep problems were strongly and positively associated with risk of fibromyalgia [8]. However, this study had several methodological limitations, e.g., 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 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 utilizes 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 survey, 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 1,159 women who reported fibromyalgia at baseline at HUNT2. Further, we excluded women with incomplete baseline information on insomnia symptoms (n=3,541) and leisure time physical activity (n=761). Moreover, 161 women defined as underweight (BMI<18.5kg/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).

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.

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?". Question 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

Standardized measurements of body height (to the nearest centimeter) 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 World Health Organization [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 activity. Based on this information, we constructed a new variable with three categories combining information on light and hard activity: low activity (<1 h light and no hard activity), moderate activity (≥1 h 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 categorized into "20-29 years", "30-39 years", "40-49 years", "50-59 years", "60-69 years", "≥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 dichotomized 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 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, ankles/feet (i.e., a maximum of nine chronic pain sites). We then constructed a new variable using number of chronic musculoskeletal pain sites to categorize 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 were 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% confidence intervals (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, 50-59 years), BMI (18.5-24.9 kg/m^2, 25.0-29.9 kg/m^2, ≥30 kg/m^2), leisure time physical activity (high activity, moderate activity, low activity), education (primary school, high school, college ≤4 years, college >4 years, unknown), and smoking (never, former smoker, current smoker, unknown). Further, since anxiety and/or depression are associated with both fibromyalgia and insomnia symptoms, we included HADS (no anxiety or depression, anxiety and/or depression, 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. Further, 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: $RERI = RR_{\text{low activity and insomnia symptoms}} - RR_{\text{high activity and insomnia symptoms}} - RR_{\text{low activity and no insomnia symptoms}} + 1$ [16], i.e., 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 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, ≥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, i.e., we excluded 1,686 women who reported to be physically active <1 h per week from the group of low physical activity.

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

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 ~11 years follow-up period (crude AR = 3.3%).

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

	Insomnia symptoms[a]	
	No	Yes
Participants, no.	11,775	2,397
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 (1,621)	16.0 (383)
Leisure time physical activity, % (no.)		
Low[b]	15.5 (1,820)	20.4 (490)
Moderate[c]	35.5 (4,185)	38.3 (917)
High[d]	49.0 (5,770)	41.3 (990)
Education ≥ 13 years, % (no.)	26.0 (3,059)	23.3 (559)
Unknown	1.0 (120)	1.5 (35)
Depression and/or anxiety (HADS score ≥8), % (no.)	11.8 (1,385)	34.1 (817)
Unknown	10.7 (1,265)	15.0 (359)
Current smoker, % (no.)	15.7 (1,852)	18.7 (447)
Unknown	20.4 (2,407)	23.1 (554)

Abbreviation: HADS, Hospital Anxiety and Depression Scale; SD, standard deviation

[a] 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".

[b] Defined as <1 h light activity per week.

[c] Defined as ≥1 h light and no hard activity.

[d] Defined as any hard activity.

Table 2 shows the association between insomnia symptoms and risk of fibromyalgia. The risk of fibromyalgia increased with number of insomnia symptoms, i.e., compared to women without insomnia symptoms (AR = 2.8%), women who reported one, two or three symptoms had RRs of 1.39 (95% CI 1.08-1.80), 1.86 (95% CI 1.33-2.59) and 2.66 (95% CI 1.75-4.06), 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 1.34-2.02), compared to women with no insomnia symptoms (Table 2).

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[a]	Multi-adjusted, RR[b] (95% CI)
No. of symptoms[c]				
0	11,775	334	1.00	1.00 (reference)
1	1,566	71	1.60	1.39 (1.08-1.80)
2	612	40	2.36	1.86 (1.33-2.59)
3	219	21	3.53	2.66 (1.75-4.06)
Insomnia symptoms[d]				
No	11,775	334	1.00	1.00 (reference)
Yes	2,397	132	1.96	1.64 (1.34-2.02)

Abbreviations: CI, confidence interval; RR, risk ratio

[a] Adjusted for age (20-29 years, 30-39 years, 40-49 years, 50-59 years, 60-69 years, ≥70 years).

[b] Adjusted for age (20-29 years, 30-39 years, 40-49 years, 50-59 years, 60-69 years, ≥70 years), body mass index (18.5-24.9 kg/m^2, 25.0-29.9 kg/m^2, ≥30 kg/m^2), leisure time physical activity (high activity, moderate activity, low activity), education (primary school, high school, college ≤4 years, college ≥4 years, unknown), The Hospital Anxiety and Depression Scale (no depression and no anxiety, depression and/or anxiety, unknown), smoking (never, former, current smoker, unknown).

[c] 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".

[d] 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".

Table 3 shows the joint association between insomnia symptoms and leisure time physical activity on risk of fibromyalgia. Compared to 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 1.30-2.79) if they reported low activity and 1.55 (95% CI 1.12-2.13) if they reported to be highly physically active (Table 3). Further, women without insomnia symptoms who reported low physical activity had a RR of 0.95 (95% CI 0.69-1.29).

The RERI estimate between insomnia symptoms and leisure time physical activity on risk of fibromyalgia was 0.40 (95% CI -0.37-1.19).

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[a]		
Physical activity	No. of persons	No. of cases	Multi-adjusted[b] RR (95% CI)	No. of persons	No. of cases	Multi-adjusted[b] RR (95% CI)
High[c]	5,770	156	1.00 (reference)	990	49	1.55 (1.12-2.13)
Moderate[d]	4,185	125	1.05 (0.82-1.34)	917	49	1.63 (1.18-2.25)
Low[e]	1,820	53	0.95 (0.69-1.29)	490	34	1.90 (1.30-2.79)

Abbreviations: CI, confidence interval; RR, risk ratio.
[a] 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".
[b] Adjusted for age (20-29 years, 30-39 years, 40-49 years, 50-59 years, 60-69 years, ≥70 years), body mass index (18.5-24.9 kg/m^2, 25.0-29.9 kg/m^2, ≥30 kg/m^2), education (primary school, high school, college ≤4 years, college ≥4 years, unknown), The Hospital Anxiety and Depression Scale (no depression and no anxiety, depression and/or anxiety, unknown), smoking (never, former, current smoker, unknown).
[c] Any hard activity per week
[d] ≥1h light and no hard activity per week
[e] <1 h light activity per week

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

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

	No insomnia symptoms			Insomnia symptoms[a]		
Body mass index	No. of persons	No. of cases	Multi-adjusted[b] RR (95% CI)	No. of persons	No. of cases	Multi-adjusted[b] RR (95% CI)
Normal weight (18.5-24.9 kg/m^2)	5,818	136	1.00 (reference)	1,125	52	1.64 (1.20-2.25)
Overweight (25.0-29.9 kg/m^2)	4,336	138	1.35 (1.07-1.70)	889	56	2.35 (1.73-3.21)
Obese (≥30 kg/m^2)	1,621	60	1.55 (1.14-2.10)	383	24	2.18 (1.42-3.35)

Abbreviations: CI, confidence interval; RR, risk ratio.
[a] 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".

[b] Adjusted for age (20-29 years, 30-39 years, 40-49 years, 50-59 years, 60-69 years, ≥70 years), leisure time physical activity (high activity, moderate activity, low activity), education (primary school, high school, college ≤4 years, college ≥4 years, unknown), The Hospital Anxiety and Depression Scale (no depression and no anxiety, depression and/or anxiety, unknown), smoking (never, former, current smoker, unknown).

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 adjusting for number of chronic pain sites (no chronic pain, 1-2 chronic pain sites, 3-4 chronic pain sites, ≥5 chronic pain sites), i.e., women who reported one, two or three insomnia symptoms had RRs of 1.04 (95% CI 0.81-1.35), 1.30 (95% CI 0.94-1.80) and 1.67 (95% CI 1.10-2.53), respectively. Comparing inactive (no light and no hard activity) women to highly active women strengthened the association, i.e., inactive women with insomnia symptoms had a RR of 2.04 (1.10-3.80) compared to 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 to 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 to normal weight women with no insomnia symptoms.

Prospective studies have shown that sleep problems increase the risk of localized [11] and generalized 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 risk of fibromyalgia in women at 10-11 years follow up [19]. However, the study had several methodological limitations, e.g., 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 DSM-IV criteria for insomnia was 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 sensitization of the nervous system

[20]. For instance, sleep restriction and poor sleep quality may impair endogenous nociceptive-inhibitory function and increase pain [21], as well as induce generalized hyperalgesia in otherwise healthy people [22]. Further, there may exist a link between poor sleep and low-graded inflammation [23], which is supported by experimental studies showing that pro-inflammatory cytokines can be involved in the development of hyperalgesia [24-26].

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. Further, 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 [27, 28] reduces inflammation induced by disturbed sleep and short sleep duration [29, 30]. This notion is supported by studies showing that a single bout of low-intensity physical exercise can induce hypoalgesia and improve fibromyalgia symptoms [31], indicating that physical exercise reduces pain perception [32] and increases pain tolerance [33]. 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. Further, the large sample size allowed us 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 American College of Rheumatology 1990 classification criteria for a diagnosis of fibromyalgia [34]. It should also be noted that the data collection was carried out before the classification criteria for fibromyalgia was revised in 2010 [35]. Further, 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 (ICSD-3) criteria for insomnia diagnosis [36]. 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. Further, 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. Further, 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 heterogenous 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.

ACKNOWLEDGEMENT

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.

AUTHOR CONTRIBUTIONS

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

Conflict of interest: Authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data used for this study were derived from The Nord-Trøndelag Health Study (HUNT), https://www.ntnu.edu/hunt. Any research group with a Principal Investigator affiliated with a Norwegian research institute can apply for access to analyse HUNT data. This means that research groups from non-Norwegian countries must find a collaboration partner in Norway to be able to use HUNT material. Each project needs to be approved by the HUNT Data Access Committee (DAC), regional Medical Ethical Committee, in some cases also the Data Inspectorate. Due to participant confidentiality, participant data is not publicly available.

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-9
Bias	9	Describe any efforts to address potential sources of bias	9-10
Study size	10	Explain how the study size was arrived at	6-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9-10
		(*b*) Describe any methods used to examine subgroups and interactions	10
		(*c*) Explain how missing data were addressed	9-10
		(*d*) If applicable, explain how loss to follow-up was addressed	6-7
		(*e*) Describe any sensitivity analyses	10
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8-9
		(b) Give reasons for non-participation at each stage	6-7
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11
		(b) Indicate number of participants with missing data for each variable of interest	12
		(c) Summarise follow-up time (eg, average and total amount)	2; 12
Outcome data	15*	Report numbers of outcome events or summary measures over time	11-14
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-14
		(*b*) Report category boundaries when continuous variables were categorized	8-9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	2; 12-13
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-18
Generalisability	21	Discuss the generalisability (external validity) of the study results	18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.