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The relation between leisure time physical exercise, physical and psychosocial work demands, and risk of fibromyalgia in working women; The Nord-Trøndelag Health Study

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Abstract

Background The associations between physical exercise, physical and psychosocial work demands, and risk of musculoskeletal pain are well documented. However, studies investigating these independent associations related to the risk of fibromyalgia (FM) are limited. Further, the protective effect of physical exercise on the risk of FM among subjects with physical and psychosocial work demands has never been assessed. Hence, the purpose of the present study was to examine the independent effect of leisure time physical exercise, physical work demands, and psychosocial work demands, on the future risk of FM. A second objective was to assess the combined effect of physical exercise and respectively, physical and psychosocial work demands, on the risk of FM to investigate if physical exercise could compensate for the possible adverse effects of high work demands.

Methods A population-based health survey (HUNT 1) was conducted from 1984 to 1986 in Nord-Trøndelag County, Norway, with follow-up during 1995-97 (HUNT 2). With baseline measurements of physical exercise (frequency, duration and intensity), and physical and psychosocial work demands, the risk of FM among 16,785 women aged ≥20 years without FM or physical impairments at baseline was examined. Risk of FM was assessed by calculations of odds ratio (OR), with adjustments for possible confounders.

Results At follow-up, 366 cases of incident FM were reported. A moderate inverse dose-response association was found between physical exercise and risk of FM (P for trend, 0.02), where women who reported ≥2.0 hours of exercise per week had a 35% lower risk of FM compared to inactive women (OR 0.65, 95% CI 0.42-1.00). Furthermore, a positive dose-response association was observed between physical and psychosocial work demands and risk of FM (P for trend, <0.001 for both types of demands), with an OR of 2.08 (95% CI 1.26-3.43) and 2.25 (95% CI 1.32-3.82) among women who reported the highest level of physical and psychosocial work demands, respectively. The combined analysis showed an increased risk of FM among inactive women who reported high physical and psychosocial work demands; ORs were respectively 1.86 (95% CI 1.29-2.68) and 2.18 (95% CI 1.48-3.21).

Conclusion In this prospective longitudinal study of female workers, we found that being physical inactive during leisure time and having high physical and psychosocial work demands were associated with an increased risk of FM, whereas physical exercise seemed to reduce the risk of FM among women with high work demands. Thus, emphasizing the importance of leisure time physical exercise in relation with high physical and psychosocial work demands is important when recommending strategies for the prevention of FM.

Contents

Introduction

Fibromyalgia (FM) is a chronic pain syndrome associated with widespread musculoskeletal pain in all four body quadrants [1]. It represents the extreme end of the spectrum of musculoskeletal pain [2], and is defined by reduced pain threshold and tenderness in at least 11 out of 18 tender point sites, with a duration for >3 months [1]. Recently, additional non-tender point criteria for diagnosing FM were developed. These include a widespread pain index (WPI) and a symptom severity (SS) scale, representing a new case definition of FM: (WPI >7 and SS >5) or (WPI 3–6 and SS >9) [3]. The prevalence of FM in the general population in European countries varies from 1.4-2.9%. The prevalence is higher among women than men, and it increases with age [4,5]. Fibromyalgia is frequently accompanied by rapid fatigue, reduced muscle strength, concentration difficulties, headache, sleep disturbance, anxiety and depression [6,7]. These associated features affect FM patients' aspects of life and have a vital influence on the ability to work [7]. The etiology of FM is not adequately understood. However, abnormal functions of the neuroendocrine and autonomic nervous system involving deficits in the hypothalamic-pituitary-adrenal axis (HPA axis) and sympathetic nervous system are thought to contribute to alterations in pain perception and pain inhibition [2,8,9].

Musculoskeletal pain and disorders are considered as the main reason for sick leave [10,11], accounting for 35% of all sick leave pays in Norway [10]. Fibromyalgia constitutes 1.9% of these expenditures [10]. Further, chronic musculoskeletal pain is associated with increased healthcare-seeking and reduced occupational activity [12]. Recommending physical activity is therefore important for the promotion of public health. Nevertheless, the health-promoting physical activity, according to these public guidelines, does not make any difference between physical activity during leisure time or at the workplace [13].

Documentation regarding the health-beneficial and preventive effect of physical exercise on several chronic diseases, like hypertension [14], type 2 diabetes mellitus [15], and cardiovascular diseases [16], is comprehensive. However, when taking physical work demands into account, the evidence is less consistent. Nevertheless, a recently performed study found that medium and high levels of physical activity during leisure time reduced the risk of ischemic heart disease mortality among men with medium and high physical activity at work [17]. Physical fitness and an active lifestyle are also found to protect against development of cardiovascular diseases among men with high physical work demands [18].

The influence of psychosocial work demands, and the preventive effect of physical exercise on the risk of cardiovascular diseases, is more inconsistent [19,20].

Regarding localized chronic musculoskeletal pain, it is documented that physical exercise during leisure time reduced the risk of incident and persistent of severe shoulder pain in workers with physically strenuous work and overload at work [21]. Physically strenuous work has further been related to more lower-extremity symptoms and sick leave among workers with low leisure time exercise [22]. Considering workers in the Royal Norwegian Navy, a physically active lifestyle during both work and leisure was found to be associated with fewer musculoskeletal disorders [23]. As inactivity may represent a risk factor for chronic musculoskeletal pain [24], individual work-related psychosocial factors may also be linked to an increased risk of musculoskeletal disorders and problems [25-30]. Conversely, whether physical exercise during leisure time can reduce the risk for chronic musculoskeletal pain related to high psychosocial work demands remains unknown according to these studies.

Studies investigating the primary protective effect of leisure time physical exercise on the risk of FM are limited. However, a weak inverse dose-response association was found between level of leisure time physical activity and future risk of FM in a recently longitudinal study [31]. Physical exercise is further found to have a protective effect on future development of FM on men suffering from post-traumatic stress disorder [32]. Conversely, no association was found between physical activity, summarized by activity during leisure time and work, and risk of FM in a study of women with 25-year follow-up [33]. Regarding physical and psychosocial work demands, a prospective study discovered that work stress (i.e., low decision latitude and high workload) was related to a higher risk for developing FM [34]. Work place mechanical and posture exposures have both been weak and higher associated with an elevated risk of FM [35,36]. However, whether physical exercise during leisure time can protect against development of FM resulting from high physical and psychosocial work demands is at present unknown.

The main purpose of the present study was to examine the independent effect of leisure time physical exercise, physical work demands, and psychosocial work demands on the future risk of FM in a large unselected population of adult women. A second objective was to assess the combined effect of physical exercise and physical work demands, and of physical exercise and psychosocial work demands, on the risk of FM to examine if physical exercise could compensate for the possible adverse effects of high work demands.

Materials and methods

Study population

During three separate waves, in 1984-86, 1995-97 and 2006-08, all inhabitants aged ≥20 years in Nord-Trøndelag County in Norway were invited to participate in the Nord-Trøndelag Health Study (the HUNT Study). The HUNT Study is one of the largest health surveys ever performed, and it is a cooperation between The Norwegian Institute of Public Health, the HUNT Research Centre (Faculty of Medicine, Norwegian University of Science and Technology), and the Nord-Trøndelag County Council. The population of Nord-Trøndelag is considered as stable and fairly representative, as the gender and age distributions are similar to the total Norwegian population [37,38].

The present study is a prospective longitudinal study, based on data from subjects who participated in the first HUNT Study (HUNT 1) performed during 1984-86, and who also participated in HUNT 2 (1995-97).

A total of 42,568 women were invited to participate in HUNT 1, and 38,274 women (89.9%) accepted the invitation, filled in a questionnaire that was included in the invitation, and attended a clinical examination. At the examination, the women received a second questionnaire to complete and return from home. The collected information concerned a variety of health- and lifestyle related factors, like diseases, physical activity, smoking, education and work situation. The clinical examination incorporated measurements of body weight and height, heart rate, blood pressure, and blood glucose.

At the follow-up study performed during 1995-97 (HUNT 2), 46,709 eligible women were invited. Among these, 34,518 women (73.9%) accepted the invitation. Although the procedures regarding the questionnaires and clinical examination were similar to those explained for HUNT 1, they were more comprehensive and informative at HUNT 2.

For the longitudinal perspective and purpose of the present study, all 24,357 women who participated in both HUNT 1 and HUNT 2 were selected. The questionnaire at HUNT 1 did not include any specific question on FM, and to ensure that no women had FM at baseline, we excluded 986 women who reported at HUNT 2 that their musculoskeletal pain had lasted for ≥10 years, and also 1620 women who reported to be physically impaired at HUNT 1 were excluded. Additionally, 798 women reported that they did not work, and 4158 women had missing data on this variable, and were thereby excluded, as were 10 women without information on body mass index. As a result, the present study is based on data from 16,785 women with adequate information on relevant variables at both HUNT 1 and HUNT 2.

The study was approved by the Regional Committee for Ethics in Medical Research, and each subject gave written informed consent prior to participation.

Outcome measure

FM, representing this study's primary outcome variable, was measured and diagnosed in the questionnaire at HUNT 2 (Appendix I). The respondents were asked to answer "yes" or "no" to the question "Has a doctor ever said that you have fibromyalgia (fibrositis/chronic pain syndrome)?". Information regarding the time of diagnosis was on the other hand not collected. Therefore, to ensure that only cases with FM diagnosed after HUNT 1 (i.e., incident FM) were included in the study, participants who reported musculoskeletal pain that had lasted for ≥10 years at HUNT 2, were excluded. The subjects gave information about this duration by answering the following question: "During the last year, have you had pain and/or stiffness in your muscles or limbs that has lasted for at least 3 consecutive months?". If the participants answered yes, they stated the number of months if the symptoms had lasted for <1 year, and the number of years if the symptoms had lasted for >1 year.

Study variables

The level of physical exercise during leisure time was measured at baseline (HUNT 1), and the participants were asked to answer questions concerning frequency, duration and intensity of different activities (i.e., walking, skiing, swimming, or other sports without further specification) (Appendix II). The frequency question consisted of five categories (0, <1, 1, 2-3, and ≥4 times per week; coded 1-5). Respondents who reported to exercise at least once a week were also asked to fill in the average level of duration per session (<15, 15-30, 31-60, and >60 minutes; coded 1-4), and the average intensity per session (light, moderate, and vigorous; coded 1-3). The questionnaire has been validated against measurement of maximal oxygen consumption (VO_{2max}), and is found to provide a useful measure of leisure time physical exercise [37]. However, the validation was only done on young adult men.

Based on the reported frequency, duration and intensity, a physical exercise index was constructed for women exercising once a week or more. Each participant's responses were summarized by giving each measure equal weight in accordance with the following equation:

frequency/5 + intensity/3 + duration/4. This equation gave each subject a maximum score of 1.0 per constituent of the summary index, and it resulted in four categories (inactive, low, medium, and high; coded 1-4). In order to classify the women, the inactive subjects did not exercise, and those in the low category exercised <1 times per week. Those in the medium category had a median value <1.8833, and those in the high category had a median value >1.8833 on the physical exercise index, representing the cutoff values.

Additionally, a new variable was constructed, estimating the average hours of exercise per week based on reported frequency and duration. Regarding the frequency question, 2-3 times per week was considered as 2.5 times, and ≥4 times per week were counted as 5 times. Concerning the duration question, <15 minutes was counted as 10 minutes, 15-30 minutes was counted as 25 minutes, 31-60 minutes was counted as 45 minutes, and >60 minutes was counted as 75 minutes. Summarizing, the new variable consisted of four categories (0, <1, 1.0-1.9, and ≥2.0 hours of exercise per week; coded 0-3).

At baseline, the participants were asked to report their physical and psychosocial work demands (Appendix III). For working women, including subjects who were full time house workers, physical work demands was assessed by asking the following question; "Does your job require physical work leaving your body exhausted after working hours?". The question consisted of four categories (never or almost never, fairly seldom, fairly often, yes, nearly always; coded 1-4). Psychosocial work demands, consisting of the same categories as with physical work demands, was measured by the question "Does your work request excessive concentration and attention leading to exhaustion after working hours?".

Statistical analyses

The baseline characteristics of the study population were analyzed in a descriptive analysis. They were categorized by hours of exercise per week, and presented as frequencies, percentages and means with standard deviations (SD).

A binary logistic regression analysis was conducted to estimate odds ratio (OR) of FM, comparing different levels of physical exercise with the reference groups consisting of inactive women, i.e. those who reported no exercise or <1 exercise session per week. The OR for FM between categories of physical and psychosocial work demands was estimated in analogous analysis. Here, the reference categories consisted of women who never or almost never reported physical or psychosocial work demands. A 95% confidence interval (95% CI) was assessed to estimate the precision of ORs. Furthermore, trend tests across categories of physical exercise and physical and psychosocial work demands were conducted in the regression model by treating the categories as ordinal variables.

The basic logistic regression analysis was adjusted for age reported at baseline. In the multivariate analysis, adjusted differences were calculated to examine if age at baseline, smoking status (never, former, current, and unknown), education (<10 years, 10-12 years, and >12 years) and body mass index (BMI) could have a potential confounding effect on the relations.

In an additional analysis, to investigate if physical exercise during leisure time could reduce the risk of having high work demands, we estimated the combined effect of physical exercise and respectively, physical and psychosocial work demands, on the OR of FM. Two new variables were computed; one combining hours of exercise per week and physical work demands, and another combining hours of exercise per week and psychosocial work demands. Hours of physical exercise per week was classified into two categories; physical inactive (inactive + <1.0 hours per week) and physical active (1.0-1.9 hours per week + ≥2.0 hours per week). Physical and psychosocial work demands were dichotomized into low physical/ psychosocial work demands (never or almost never + fairly seldom) and high physical/ psychosocial work demands (fairly often + yes, almost always). Thus, the reference categories consisted of being physical active and having low physical or psychosocial work demands. The analysis was adjusted for age at baseline, smoking status (never, former, current, and unknown), education (<10 years, 10-12 years, and >12 years) and BMI. To test for potential statistical interaction between physical exercise and physical and psychosocial work demands, a product term of physical exercise and physical work demands, and physical exercise and psychosocial work demands was entered in the regression model.

All statistical tests were two-sided, and all statistical analyses were conducted using PASW Statistics 18.0 (SPSS Statistics).

Results

Baseline characteristics

The baseline characteristics of the study population are presented in Table 1. Among the 16,785 women who participated in the present study, 366 cases of incident FM were registered during the period between HUNT 1 (1984-86) and HUNT 2 (1995-97). Age reported at baseline was somewhat higher for those who reported ≥2.0 hours of exercise per week, compared to the remaining exercise categories (Table 1). Measurements of BMI were fairly similar across all exercise categories. Among inactive women, 40.0% were current smokers, compared to 25.9% and 27.1% of the women reporting 1.0-1.9 hours and ≥2.0 hours of exercise per week, respectively (Table 1). Among those who exercised 1.0-1.9 hours per week, 14.0% had an education of >12 years, whereas only 8.0% of the inactive women had higher education (Table 1).

Table 1. Baseline characteristics of the study population categorized by hours of exercise per week*

Characteristic	**Inactive‡**	**<1hours**	**1.0-1.9 hours**	**≥2.0 hours**
Women, no.	5,988	4,405	3,553	1,735
Age†, mean ± SD years	42.0 ± 12.9	42.2 ± 13.0	43.4 ± 13.3	47.3 ± 14.9
BMI, mean ± SD kg/m^2	24.5 ± 4.3	24.2 ± 3.8	24.2 ± 3.6	24.4 ± 3.8
Current smoker	40.0	31.8	25.9	27.1
Higher education¶	8.0	12.0	14.0	10.8

* Values are percentage unless otherwise are indicated. BMI = body mass index (kg/m^2). SD = standard deviations.

‡ Subjects who reported no exercise or <1 exercise session per week.

† Age at baseline.

¶ Subjects who reported an education of >12 years.

Leisure time physical exercise and risk of FM

Table 2 illustrates the age-adjusted and multi-adjusted associations for measurements of physical exercise and physical and psychosocial work demands with the risk of FM. The adjusted analysis of hours of exercise per week showed an inverse and moderate dose-response effect related to the risk of FM (P for trend, 0.02), with the strongest association for those who exercised ≥2.0 hours per week (adjusted OR 0.65, 95% CI 0.42-1.00).

Although marginally non-significant, women who reported to exercise 1.0-1.9 hours per week also had a lower risk of FM compared with inactive women (adjusted OR 0.75, 95% CI 0.55-1.02). Those who reported to exercise <1.0 hours per week had no different OR than the reference group of inactive women (adjusted OR 1.00, 95% CI 0.77-1.29).

Table 2. OR of FM associated with leisure time physical exercise, physical work demands and psychosocial work demands*

	Women, no	**Cases, no**	**Age-adjusted OR‡**	**Multi-adjusted OR (95% CI)†**	***P* for trend**
Exercise per week, hours					
Inactive¶	5,988	155	1.00	1.00 (reference)	
<1.0	4,405	103	0.91	1.00 (0.77-1.29)	
1.0 – 1.9	3,553	58	0.64	0.75 (0.55-1.02)	
≥2.0	1,735	24	0.58	0.65 (0.42-1.00)	0.02
PA index §					
Inactive	1,339	31	1.00	1.00 (reference)	
Low	4,649	124	1.05	1.12 (0.75-1.67)	
Medium	4,311	96	0.95	1.07 (0.71-1.62)	
High	5,259	87	0.66	0.81 (0.53-1.23)	0.07
Physical work demands					
Never or almost never	1,863	26	1.00	1.00 (reference)	
Fairly seldom	6,202	118	1.36	1.22 (0.79-1.87)	
Fairly often	5,803	146	1.80	1.57 (1.03-2.40)	
Yes, almost always	1,253	41	2.44	2.08 (1.26-3.43)	< 0.001
Psychosocial work demands					
Never or almost never	1,920	28	1.00	1.00 (reference)	
Fairly seldom	6,011	124	1.34	1.48 (0.97-2.24)	
Fairly often	6,000	153	1.62	1.95 (1.30-2.95)	
Yes, almost always	991	29	1.87	2.25 (1.32-3.82)	< 0.001

* OR = odds ratio; FM = fibromyalgia; 95% CI = 95% confidence interval.

‡ Age at baseline.

† Adjusted for age at baseline, smoking status (never, former, current, unknown), education (<10 years, 10-12 years, and >12 years) and body mass index.

¶ Subjects who reported no exercise or <1 exercise session per week.

§ Physical activity index; combining information on frequency, duration and intensity of activity.

The analysis of the physical activity index, where information on frequency, duration and intensity of the exercise was combined, showed less clear associations (P for trend, 0.07) (Table 2). Low and medium activity levels was not associated with a reduced risk of FM, whereas women with the highest activity level had a non-significant 19% lower risk of FM (adjusted OR 0.81, 95% CI 0.53-1.23) compared with the reference group.

Physical and psychosocial work demands and risk of FM

Concerning physical and psychosocial work demands, an overall and significant positive dose-response association was found across increasing levels of work demands and risk of FM (P for trend, <0.001 for both types of work demands) (Table 2). The adjusted analysis showed that women who reported that they fairly seldom, fairly often, or almost always had physical work demands had higher risk of FM than the reference group; adjusted ORs were 1.22 (95% CI 0.79-1.87), 1.57 (95% CI 1.03-2.40), and 2.08 (95% CI 1.26-3.43), respectively. Regarding psychosocial work demands, women who fairly seldom had these demands, had an OR of 1.48 (95% CI 0.97-2.24). Further, those who reported to fairly often having psychosocial work demands had a slightly higher risk of FM, with an OR of 1.95 (95% CI 1.30-2.95). Finally, women with the highest level of psychosocial work demands, had more than twofold higher risk of FM (adjusted OR 2.25, 95% CI 1.32-3.82) compared with the reference group.

Combined effect of physical exercise and work demands on the risk of FM

Table 3 illustrates the combined effect of physical exercise and physical and psychosocial work demands on the risk of FM. There was no statistical evidence for interaction between physical exercise, i.e. hours of physical exercise per week, and physical work demands (P-value, 0.99) and psychosocial work demands (P-value, 0.98). However, the analysis showed that women who had low physical work demands and were physical inactive had a higher risk of FM (OR 1.34, 05% CI 0.92-1.95) compared with the reference group, i.e. those who had low physical work demands and were physical active. Investigating women with high physical work demands, a somewhat similar risk of FM was found among physical active women, with an OR of 1.39 (95% CI 0.89-2.18). Conversely, those who were inactive and had high physical work demands had the highest risk of FM (OR 1.86, 95% CI 1.29-2.68).

Table 3. Combined effect of leisure time physical exercise and physical work demands, and leisure time physical exercise and psychosocial work demands on the risk of FM*

Physical exercise and work demands categories‡	**Women, no**	**Cases, no**	**Multi-adjusted OR (95% CI)†**
Low physical work demands			
Physical active (1)	2,851	38	1.00 (reference)
Physical inactive (3) (2)	5,002	103	1.34 (0.92-1.95)
High physical work demands			
Physical active (2) (1)	2,037	40	1.39 (0.89-2.18)
Physical inactive (4) (3)	4,813	142	1.86 (1.29-2.68)
Low psychosocial work demands			
Physical active (1)	2,613	33	1.00 (reference)
Physical inactive (3) (2)	5,087	115	1.56 (1.06-2.31)
High psychosocial work demands			
Physical active (2) (1)	2,224	44	1.70 (1.08-2.69)
Physical inactive (4) (3)	4,605	133	2.18 (1.48-3.21)

* OR = odds ratio; FM = fibromyalgia; 95% CI = 95% confidence interval.

‡ Low physical work demands = never or almost never and fairly seldom; high physical work demands = fairly often and yes, almost always; low psychosocial work demands = never or almost never and fairly seldom; high psychosocial work demands = fairly often and yes, almost always; physical active = 1.0-1.9 and ≥2.0 hours of exercise per week; physical inactive = 0 and <1 hours of exercise per week.

† Adjusted for age at baseline, smoking status (never, former, current, unknown), education (<10 years, 10-12 years, and >12 years), and body mass index.

In the analysis of psychosocial work demands, an OR of 1.56 (95% CI 1.06-2.31) was found among inactive women with low psychosocial work demands (Table 3). When high psychosocial work demands were examined, the association between level of exercise and risk of FM was stronger. Physical active women with high psychosocial work demands had a higher risk of FM (OR 1.70, 95% CI 1.08-2.69) than those at the similar activity level but with low psychosocial work demands. Additionally, women who were inactive had more than twofold higher risk of FM (OR 2.18, 95% CI 1.48-3.21) compared with the reference group.

Discussion

In this large and prospective longitudinal study of adult women, the main objective was to examine the associations of leisure time physical exercise, physical work demands, and psychosocial work demands, with the risk of FM during 11-year follow-up. The second purpose was to investigate the combined effect of physical exercise and respectively, physical and psychosocial work demands on the risk of FM. Overall, an inverse dose-response association was found between hours of physical exercise per week and incidence of FM during the follow-up. A positive dose-response association was additionally found between physical and psychosocial work demands and risk of FM. Regarding the combined effect, the results indicated that being physical active reduced the risk of FM among women with both high physical and psychosocial work demands. To the best of the author's knowledge, this is the first study to document the possible protective effect of physical exercise on the risk of FM among women with high physical and psychosocial work demands.

Leisure time physical exercise and risk of FM

The findings in the current study are in accordance with previous studies which have documented an individual association between physical exercise and future risk of FM [31,32]. Existing literature on the association between physical exercise and chronic musculoskeletal pain [21], and musculoskeletal symptoms [22] and disorders [23], also supports the results found in the present study. In a prospective study, based on HUNT 1 and HUNT 2 with a study population similar as in the present study, Mork and colleagues [31] found a weak inverse dose-response association between level of leisure time physical exercise and risk of FM, with a 23% lower risk of FM among women who exercised 2 hours or more per week. Further, high BMI (i.e., BMI ≥ 25 kg/m^2) was pointed out as an independent risk factor, which is considered as a potential confounder in the current study. However, the risk estimates in the present study were only slightly affected when adjusted for potential confounders. Arnson and colleagues [32] found that physical exercise protected against future development of FM among men suffering from post-traumatic stress disorder. However, as their study population consisted of men, it is uncertain whether their results also apply for women. Nevertheless, physical activity was measured by a frequency question (i.e., if the subjects exercised often, occasionally, or not at all) [32], and this can be linked to the results in the present study, where the strongest association between physical exercise and risk of FM was showed through the analysis of hours of exercise per week. On the contrary, when we analyzed the relation between the physical activity index and risk of FM, the results showed less clear association. This may suggest that the amount of physical exercise (i.e., hours of physical exercise per week) may be of greater influence than the intensity component in the physical activity index, when investigating the protective effect of physical exercise. However, Mork and colleagues [31] found a somewhat similar association with FM for a summary score of exercise and hours of exercise per week. As a result, this emphasizes the need for further research regarding the intensity component of the activity related to the prevention of future development of FM.

As described earlier, the etiology of FM is not adequately understood. However, abnormal functions of the neuroendocrine and autonomic nervous system, involving deficits in the HPA axis and sympathetic nervous system, are thought to contribute to alterations in pain perception and pain inhibition [2,8,9]. Lowered pain threshold (allodynia) and increased sensitivity to painful stimuli (hyperalgesia) is considered as features in the modification of the pain processing [31]. Conservation or improvement of the endogenous pain inhibitory capacity has been proposed as mechanisms related to the protective effect of physical exercise on the development of FM [31]. Analgesia after exercise (i.e., often termed as exercise-induced analgesia), is a phenomena consisting of increased pain threshold and pain tolerance following aerobic exercise [39]. Although the exact mechanisms underlying exercise-induced analgesia are not completely understood, it is proposed to include activation of the endogenous opioid system and temporary pain relief after exercise. Through evidence from a study conducted on pregnant women and the effect of physical exercise related to perception of labor pain [40], it can be suggested that exercise-induced analgesia can accumulate and convert into a more constant buffer against the effects of stress, and furthermore, the development of pain. Elevated plasma levels of beta-endorphin were found among women who performed aerobic exercise during pregnancy, compared with pregnant women who did not exercise [40]. The difference of plasma beta-endorphin was maintained through labor, and resulted in reduced labor pain among women who exercised. Additionally, in a study performed on rats, it was found that rats with high aerobic capacity had higher pain threshold before and after exercise, together with shorter periods of hyperalgesia following exercise, compared with rats with low aerobic capacity [41]. These findings indicate that the reduction in pain perception may be a result of regular exercise and a high level of physical fitness, probably caused by a raised activation of the endogenous opioid system.

The protective effect of physical exercise on the development of FM and pain perception has further been indicated through studies investigating sleep deprivation. Among healthy subjects, exposed to both selective stage 4 (slow wave sleep) interruptions and total sleep deprivation, it was observed similar symptoms (i.e., decrease mechanical pain thresholds and increased muscle tenderness) as associated with patients with FM [42-44]. Conversely, among a small sample of physically fit subjects who regular performed aerobic exercise, the selective stage 4 interruptions did not lead to developing of pain symptoms [42]. Improvement of the endogenous pain inhibitory capacity may therefore be a consequence from high aerobic fitness and regular exercise. These studies, together with the abovementioned findings, shows that durability of musculoskeletal symptoms which potentially can lead to the development of FM, may be prevented by regular physical exercise and being physically fit. The examined association between exercise and the risk of FM in the current study, which pointed out an inverse dose-response between physical exercise and future development of FM, can therefore be supported by these findings.

Physical work demands and risk of FM, and combined effect of physical exercise and physical work demands on the risk of FM

The positive dose-response association between physical work demands and risk of FM that was found in the present study, find limited and inconsistent support in the existing literature. Only a weak association was detected between FM and mechanical work place factors in a population-based prospective survey [35]. However, it was suggested that the results may had been influenced by the "healthy worker effect", leading to a possible underestimating of the true effect of work-related risk factors as some workers may had left the work as a result of their pain. Conversely, in another prospective study [36], several work place posture and mechanical exposures predicted the onset of FM among male and female newly employed workers. Nevertheless, when investigating the risk of FM in relation to physical work demands, it may be of importance to take into consideration the musculoskeletal symptoms that potentially may lead to the development of FM. Physical load at work and physical strenuous work has been associated with an increased risk of back pain [26], incidence and persistent of severe shoulder pain [21], and an increased number of anatomical pain sites [27]. Other studies have conversely showed more inconsistent findings on risk factors for work-related musculoskeletal disorders [25]. Although these studies often were prospective, some of them had short follow-up periods. In addition, the measurements of physical work demands were frequently compassed by a compilation of forces (i.e., lift postures, excessive repetition, and awkward postures), compared to the more global variable measuring physical work demands in the current study. However, the HUNT 1 questionnaire did not include specified questions similar to the abovementioned studies on musculoskeletal pain, which can make comparisons more difficult. Further research on the development of FM associated with a compilation of work-related forces could therefore be of interest.

The pathology behind the elevated risk of FM as a result of high work demands is, to the best of the author's knowledge, not known. However, mechanisms behind the development of localized musculoskeletal pain have been investigated. It has been hypothesized that low back pain can be caused by excessive loads and repetitive loading on the spinal structures [28]. In occupations requiring prolonged periods of being seated in one posture, musculoskeletal disorders can be developed by muscle fatigue and muscle imbalance as muscles adapt by lengthening and shortening [45]. Such factors can result in muscle ischemia, trigger points and muscle substitution, which further can cause pain and muscle contractions that protects the affected pain area. This can predispose subjects to stiffness of joints and nerve compression, which consequently can result in chronic musculoskeletal pain. Therefore, it can be suggested that permanence of high physical demands may increase the risk for chronic musculoskeletal pain and symptoms, which further can trigger the development of FM.

A link between physical and psychosocial work demands, when considering the mechanisms underlying musculoskeletal pain, has also been suggested. Work-related psychosocial factors may be important in the development and worsening of musculoskeletal disorders, as these can directly affect physical load [46]. Time pressure may increase the occurrence of inadequate postures and acceleration of movements, and psychosocial demands may enhance tension in the muscles and worsening the biomechanical request of work tasks. Sensitivity to pain and attention to symptoms can further be influenced by psychosocial work demands. However, no statistical analysis was performed to investigate the interaction between physical and psychosocial work demands in the current study. It is therefore unknown whether women with high psychosocial demands also reported high physical demands, or opposite. Nevertheless, as the observed dose-response associations between both types of work demands and risk of FM showed somewhat similar values, it may be important to consider this possible interaction in the interpretation of the results.

The possible protective effect of physical exercise in subjects with high physical work demands on the risk of FM, as found in the present study, can be supported by a study performed by Miranda and colleagues [21]. Here, physically strenuous work and overload at work increased the risk for incidence and severe shoulder pain, whereas exercise tended to be more preventive than impairing on the shoulders. Jogging and cross-country skiing was identified as preventive and advantageous activities, as the movements not exposed tendons or joints in the shoulder to static tension or heavy external loads. However, exercise was not measured separately by different activities in the current study. Thus, it is unknown what types of activities which can be favorable when preventing the development of FM. Contrary to the findings in the current study, it has been found that subjects without musculoskeletal symptoms did not participate in more leisure time physical activities than subjects who developed severe symptoms [47]. However, high muscular strength was found to be important for sustaining a good musculoskeletal health after years with physically heavy work. In other words, it seemed that physical strength increased the tolerance for physically strenuous work before developing musculoskeletal symptoms. Although information about different types of exercise was not collected in the present study, it may be possible that subjects who were active during leisure time enhanced their tolerance for physically heavy work. This can further be a possible explanation behind the somewhat similar risk estimates found among active women with high physical work demands and inactive women with low physical work demands in the present study. In addition, the protective effect of exercise can be linked to the conservation and improvement of the endogenous pain inhibitory capacity [31]. As accumulation of exercise-induced analgesia can convert into a more constant buffer against the development of pain [40], and elevated pain threshold has been associated with high aerobic fitness [41], this may be an explanation concerning the reduced risk of FM among physical active women although they had high physical work demands.

Psychosocial work demands and risk of FM, and combined effect of physical exercise and psychosocial work demands on the risk of FM

The examined association between psychosocial work demands and future development of FM find some support in previously performed studies. Work load, including aspects of time pressure, was related to incidence of newly diagnosed FM in a prospective cohort study [34]. Here, a twofold higher risk of FM was found among subjects who reported high workload compared with those who reported low workload. Nevertheless, the measure of work load was different than the question measuring psychosocial work demands in the current study (i.e., excessive concentration and attention leading to exhaustion after working hours), but it may be possible that subjects who reported high psychosocial work demands experienced time pressure although this was not assessed. Two other studies have additionally examined the risk of FM among workers with psychosocial work demands, reporting both a weak association [36] and no association [35] between stressful work conditions and new onset of FM. However, as described earlier, the study by McBeth and colleagues [35] may have been influenced by the "healthy worker effect". The two abovementioned studies were additionally characterized by short follow-up periods, and it may be possible that they would have found a stronger association between psychosocial work conditions and incidence of FM by using longer follow-up periods.

Numerous studies have investigated the association between musculoskeletal pain and psychosocial work demands, and found that psychosocial factors may be related to an increased risk for musculoskeletal symptoms and pain [21,25-30]. As with physical work demands, the measurements of psychosocial work demands in these studies were frequently segmented by a variety of factors, leading to some difficulties when comparing these results to the findings in the current study. Nevertheless, in a review conducted by Davis and Heaney [28], it was found that concentration demands were positively associated with low back pain. Difficulty at work has additionally been related to the persistence of severe shoulder pain [21], and suggested to be a sign of psychologically too demanding work. These results can be linked to the psychosocial measurement in the current study, and support the increased risk of FM among women with high levels of such demands. Further, we found that the risk of FM related to different levels of psychosocial work demands were slightly higher compared to similar levels of physical work demands. The difference was additionally to some extent larger in the combined analysis. This finding can be supported by Palmer and colleagues [48], who suggested that psychosocial work factors may be more important than physical factors when examining the association between prevalence of neck pain and occupational activities.

Although measurement of stress was not included in the current study, it may be possible that women who reported high psychosocial demands and almost always experienced excessive concentration and attention at work, also perceived stress as a central factor during working hours. Mechanisms underlying the increased risk of FM when exposed to high psychosocial work demands, may therefore find explanations in the pathology of FM. The etiology of FM is thought to involve deficits in the HPA axis [2,8,9], which is important in the regulation of responses to stress [49]. In numerous studies, the HPA axis has observed to be underactive in FM [49,50]. Additionally, FM patients have been described to have reduced cortisol levels [51-53], a characteristic which also has been found in people suffering from chronic fatigue and chronic psychological stress [54,55]. Consequently, these endocrinological studies can indirectly support the association between development of FM and high psychosocial work demands, indicating an increased risk of FM when exposed to psychosocial work factors.

Regarding mechanisms underlying musculoskeletal pain, it has been documented an association between high psychosocial work demands and development of low back pain [28]. Increased muscle tension has been related to an increased loading on the structures on the spine, further contributing to low back pain. In addition, it has been suggested that psychosocial work factors can reduce the pain threshold, and thereby influence the likelihood of reporting low back pain [28]. Workers' reaction to psychosocial work demands, such as job stress has further been found to be more consistently associated with musculoskeletal pain, than the psychosocial work demands themselves, such as work overload. However, this difference was not examined in the current study. Nevertheless, according to the abovementioned study [28], it is shown that high psychosocial work demands may contribute to the development of musculoskeletal pain. As persistent musculoskeletal pain can trigger the development of FM, the importance of reducing psychosocial work demands, and thereby reducing the risk of FM as observed in the present study, can be supported.

The protective effect of physical exercise on the risk of FM among workers with high psychosocial work demands as documented in the current study, has, as far as we know, not been investigated in any previous studies. However, a protective effect of physical activity was indicated through a study investigating physiological and psychological responses to a psychosocial stressor [56]. Among trained and untrained men, it was observed that cortisol levels after stress exposure were elevated. Nevertheless, the trained men (i.e., high aerobic fitness) exhibited significantly lower cortisol responses after the stress exposure than the untrained men, suggesting that physical activity provided a protective effect against stress-related disorders. In another study, different levels of physical activity were assessed in relation to adrenal responses when exposed to psychosocial stress [57]. It was found that those who exercised about 11 hours per week had the lowest cortisol responses after the psychosocial stress exposure, compared to those who exercised about 5 hours and <1 hour per week. The cortisol responses did not differ between the two lowest levels of physical activity. Although the results from the current study showed that 1.0-1.9 and ≥2.0 hours of exercise per week had a protective effect on the risk of FM among subjects with high psychosocial work demands, the study by Rimmele and colleagues [57] indicated an additional positive effect by a higher exercise level. However, as FM has been pointed out as a stress-related disorder [49], the results from the present study, which showed a protective effect of physical exercise on the risk of FM among subjects with high psychosocial work demands, may find support in the abovementioned studies.

When interpreting the results from the present study, awareness about causal relationships may be of importance. We found an increased risk of FM among inactive women, and FM patients are often reported to have limited physical fitness, both in terms of aerobic capacity [58] and muscular strength [59]. Further, high physical and psychosocial work demands were associated with an increased risk of FM in the present study, which has also been found in other studies [34,36]. However, it is unknown whether inactivity and low physical fitness may be contributing factors to the development of FM, or if they are consequences of the diagnosis [31]. The same assumption can be applied for work demands [21]. Although subjects in the current study did not have FM at baseline, time of the diagnosis for incident cases of FM during the follow-up is unknown. Furthermore, information regarding physical exercise and work demands was not collected during the follow-up, and consequently, it cannot be determined whether the observed associations are causal.

Strengths and limitations

Strengths of the current study includes the large population-based sample size, and the prospective and longitudinal study design, which is convenient in order to analyze changes in variables, like FM, related to a variety of exposures for the same population over a period of 11 years [60]. Nevertheless, some methodological limitations have to be considered. First, information concerning physical exercise and work demands was based on a self-reported questionnaire that allowed for subjective interpretations of the questions and subjective perception of physical exercise and work demands. Misclassification due to factors like age, seasonal variation and social situations must therefore be considered [61]. However, through validation studies, questionnaires have been found to be useful in classifying subjects into broad and few categories of physical exercise (e.g., low, medium, or high activity levels), as a large number of respondents may reduce problems related to misclassification [62]. Furthermore, validation of the questions related to intensity and duration of the physical activity in the present study has been performed against measured oxygen uptake and heart rate, and is found to perform well [63].

Second, physical exercise and work demands were measured at baseline without follow-up information, and possible changes in level of physical exercise and the perceived work demands are therefore not detected. However, we chose not to take follow-up measurements of exercise and work demands into consideration. This because it could have biased the results if subjects with incident FM reported reduced physical activity due to their disease, or alternatively, increased work demands. It is further considered noteworthy that the HUNT questionnaire does not include questions related to different types of exercise or fitness components (e.g., strength and cardiorespiratory fitness), which could be of importance when assessing the risk of FM. In this type of study, confounding by unknown or unmeasured variables resulting in biased estimates cannot be excluded. Controlling for factors often associated with FM, like familiar predisposition, traumatic life events [64], and additional work-related exposures (e.g., work place bullying, work stress, and decision latitude) could be of interest, but such information was not available. Furthermore, in the interpretation of the results, it should be noted that incident FM was measured at the follow-up at HUNT 2, and that these women both chose and were able to participate in both surveys. As a result, if subjects who were inactive or had high physical or psychosocial work demands were less likely to participate in HUNT 2, the estimated OR may be underestimated.

Conclusion

In this prospective longitudinal study of female workers, it was found that physical exercise during leisure time protected against the development of FM. Further, high physical and psychosocial work demands were associated with an increased risk of FM, whereas leisure time physical exercise seemed to reduce the risk of FM among women with high work demands. Thus, emphasizing the importance of leisure time physical exercise in relation with high physical and psychosocial work demands is important when recommending strategies for the prevention of FM.

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Appendix I

Har lege noen gang sagt at du har/har hatt noen av disse sykdommene:		JA	NEI
Beinskjørhet (osteoporose)	78		
Fibromyalgi (fibrositt/kronisk smertesyndrom)			
Leddgikt (reumatoid artritt)			
Slitasjegikt (artrose)			
Bechterews sykdom	82		
Andre langvarige skjelett- eller muskelsykdommer			

Appendix II

Hvor ofte driver du mosjon?
(Ta et gjennomsnitt)

Aldri..	12		1
Sjeldnere enn en gang i uka			2
En gang i uka			3
2–3 ganger i uka			4
Omtrent hver dag..			5

Dersom du driver slik mosjon så ofte som en eller flere ganger i uka:
Hvor hardt mosjonerer du?
(Ta et gjennomsnitt)

Tar det rolig uten å bli andpusten eller svett............	13		1
Tar det så hardt at jeg blir andpusten og svett.........			2
Tar meg nesten helt ut....................................			3

Hvor lenge holder du på hver gang?
(Ta et gjennomsnitt)

Mindre enn 15 minutter	14		1
16–30 minutter...			2
30 minutter–1 time			3
Mer enn 1 time			4

Appendix III

Hvis du er i arbeid (gjelder også heltids husarbeid), **ber vi deg fylle ut de neste spørsmålene:**

Er arbeidet ditt så fysisk anstrengende at du ofte er sliten i kroppen etter en arbeidsdag?

Ja, nesten alltid	45	1
Ganske ofte		2
Ganske sjelden		3
Aldri, eller nesten aldri		4

Krever arbeidet ditt så mye konsentrasjon og oppmerksomhet at du ofte føler deg utslitt etter en arbeidsdag?

Ja, nesten alltid	46	1
Ganske ofte		2
Ganske sjelden		3
Aldri, eller nesten aldri		4