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Association of chronic pain and fibromyalgia with cardiovascular risk factors and metabolic syndrome: the Norwegian HUNT study

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Abstract

Background: Chronic pain is a common condition, affecting a high percentage of the population. Fibromyalgia (FM) is a syndrome characterized by chronic widespread pain, fatigue and tenderness at specific anatomical locations (tender points), which affects more women than men. Chronic widespread pain has recently been associated with increased risk of mortality, and especially to death from cancer and cardiovascular diseases. The aim of this study was to explore if people who reported chronic pain or FM had more unfavourable levels of cardiovascular risk factors compared to people without pain, and thus a higher prevalence of metabolic syndrome. The effect of number of pain sites and physical activity level was also explored.

Methods: The study was based on cross-sectional data from 53 469 persons, 25 392 men and 28 077 women, who participated in the Nord-Trøndelag Health Study from 1995 to 1997 (HUNT 2). Levels of cardiovascular risk factors were compared using linear regression, and OR for metabolic syndrome (defined by the ATP III criteria) and the various components were calculated by logistic regression.

Results: Men and women with chronic pain and FM had higher waist circumference, body mass index, and triglyceride level, and lower high-density lipoprotein cholesterol compared to those with no pain. Lower values on both systolic and diastolic blood pressure were observed in the pain groups. The odds ratio (OR) for metabolic syndrome among those with chronic pain was 1.05 (95 % confidence interval, 0.98-1.12) in men and 1.18 (1.10-1.26) in women, and among those with FM it was 1.53 (1.14-2.04) in men and 1.66 (1.47-1.88) in women. There was a dose-response association between number of pain sites and the continuous measures of all outcome variables (all p-trends <0.01), except glucose (p-trend= 0.437 for men and 0.209 for women). Physically active persons had more favourable levels on most variables compared to the inactive within each pain group. The combination of FM and inactivity showed the strongest association with metabolic syndrome, with an OR of 2.05 (1.29-3.27) in men and 2.34 (1.95-2.81) in women.

Conclusion: In this population-based study, the prevalence of metabolic syndrome was higher among women with chronic pain, and among men and women with FM, compared to people without pain. There was a dose-response association between number of pain sites and metabolic syndrome and its components. Physical activity modified some of the observed association between chronic pain/FM and cardiovascular risk factors, resulting in more favourable risk factor levels.

Contents

Background

Musculoskeletal pain is a common complaint in the adult population, and affects a high percentage in a lifetime perspective (McBeth and Jones, 2007). Chronic musculoskeletal pain of at least 3 months duration during the last year was reported by 39 % of the men and 49 % of the women in a health study in Norway (Sirnes et al., 2003). Persons with musculoskeletal pain have a higher risk of absence from work due to sickness, and the risk is especially high among those with chronic widespread pain (Andersen et al., 2009). According to the American College of Rheumatology, pain is considered widespread when it is present on both sides of the body, above and below the waist, and the person also experience axial skeletal pain (Wolfe et al., 1990). Recently, the number of pain sites, rather than a cut-off between localized and widespread pain has been emphasised. A cross-sectional study from Norway found that number of pain sites was higher among women than men, and increased with age. A higher number was found among smokers, those who were less physically active, and those with a higher body mass index (BMI). There was a strong inverse relation between number of pain sites and overall health, sleep quality, and psychological health (Kamaleri et al., 2008b).

Fibromyalgia (FM) is a syndrome characterised by chronic widespread pain without known aetiology. The syndrome is, in addition to pain, associated with several systemic symptoms, such as fatigue, sleep deprivation, tenderness at specific anatomical sites (tender points), depression, cognitive dysfunction, morning stiffness, and headache (Russell and Raphael, 2008). The prevalence of FM is found to be approximately 3 % in the Norwegian population, and the syndrome is five- to six-fold more common in women than in men (Kurtze and Svebak, 2001).

Chronic widespread pain has recently been associated with an increased risk of mortality, and especially to death from cancer and cardiovascular diseases (McBeth et al., 2009). The increased risk is considered to be related to lifestyle factors (Andersson, 2009). Known modifiable risk factors for cardiovascular disease include hyperlipidemia, hypertension, diabetes, obesity (especially abdominal), depression, exercise, smoking, and consumption of alcohol, fruit, and vegetables (Haffey, 2009). The term metabolic syndrome describes a clustering of risk factors such as abdominal obesity, hypertension, dyslipidemia, and glucose intolerance (National Cholesterol Education Program, 2001), and is strongly associated with atherosclerotic cardiovascular disease and mortality (Malik et al., 2004; Galassi et al., 2006).

The prevalence of metabolic syndrome is known to increase with age, and with increasing adiposity and physical inactivity (Park et al., 2003; Hildrum et al., 2007; Yang et al., 2008). Studies assessing the physical activity level of people with chronic widespread pain or FM have shown inconsistent results. Physical inactivity as an approach to avoid pain is often considered a part of the clinical picture in persons suffering from FM and other chronic pain conditions, but there are few studies confirming this assumption. McLoughlin and co-workers (2011) observed that women with FM were less physically active than healthy controls, while others have observed that the average activity level among individuals with chronic pain or FM is similar to that of healthy controls (Kop et al., 2005; van den Berg-Emons et al., 2007), or even higher (Natvig et al., 1998). Although the average hours with activity are similar, the intensity of the activity may differ, with FM patients spending less time in high intensity activities than controls (Kop et al., 2005). According to McBeth and co-workers (2010), chronic widespread pain may predict physical inactivity. They suggest that chronic widespread pain is a causal factor rather than a mediating variable between physical inactivity and mortality. Physical activity on a regular basis is related to several beneficial effects that contribute to a protection against cardiovascular disease (Carroll and Dudfield, 2004).

In recent years, attention has been given to a possible relation between metabolic syndrome, chronic pain, and FM. Loevinger and co-workers (2007) observed that FM patients were five times more likely to have metabolic syndrome, compared with demographically similar women without chronic pain. Moreover, metabolic syndrome was present in 25 % of patients with chronic low back pain in a recently published study (Duruöz et al., 2010), and a 50 % higher prevalence of unilateral shoulder pain was observed in men with metabolic syndrome compared to those without in a Finnish population-study (Rechardt et al., 2010). Schultz and Edington (2010) found that American manufacturing employees who met the criterions for metabolic syndrome had both a higher prevalence of chronic pain and a higher likelihood of reporting new cases of chronic pain two years later.

A few studies have examined the relation between the various components of metabolic syndrome and chronic pain or FM. It has been reported that a large proportion of the FM patients are obese (Neumann et al., 2008; Okifuji et al., 2009), and unfavourable lipid levels among FM women (Gurer et al., 2006; Loevinger et al., 2007) and women with chronic low back pain (Heuch et al., 2010) have been found. Moreover, a three-fold higher risk of impaired glucose regulation and a six-fold higher risk of diabetes were found among those with chronic widespread pain in a Finnish population study (Mäntyselkä et al., 2009).

The main aim of this cross-sectional study was to explore if people who reported chronic pain or FM had more unfavourable levels of cardiovascular risk factors than those without chronic pain, and thus also a higher prevalence of metabolic syndrome. A second aim was to examine if there was a dose-response association between number of pain sites and prevalence of metabolic syndrome and its components. Finally, it was examined if physical activity could modify these associations.

Material and methods

Study population

Between 1995 and 1997, all inhabitants aged 20 years or more in the county of Nord-Trøndelag were invited to participate in the second Nord-Trøndelag Health Study (HUNT 2). In total, 66 140 persons (71.2 % of the population) accepted the invitation and participated in the study. Information was obtained from questionnaires and a clinical examination. A first questionnaire (Q1) was sent out together with the invitation. This was to be filled out and delivered upon participation. At the health examination, the participants received a second questionnaire (Q2) that was to be filled in at home and returned in a pre-stamped envelope (Holmen et al., 2003). Participation in HUNT was voluntary, and all the participants signed a written informed consent concerning the examination, subsequent control and follow-up, and the use of data and blood samples for research purposes. The study was approved by the Norwegian Regional Committee for Ethics in Medical Research (REK). A more detailed description about the population, procedures, and questionnaires can be found at www.hunt.ntnu.no.

The material used in this study contained data from 65 285 persons. After exclusion of 5696 persons with already developed cardiovascular disease (angina, myocardial infarction, or stroke), 605 pregnant women, and those with missing information on any of the variables fibromyalgia, pain/stiffness, height, weight, and the components of metabolic syndrome (5515 persons), 53 469 persons remained, 25 392 men and 28 077 women. In addition, 4207 persons who reported use of antihypertensive medication (or who had missing data on this question) were excluded from the analyses of blood pressure as a continuous variable, and those with missing data on physical activity (3797) or much reduced physical function (944) were excluded from the analyses concerning the effect of physical activity.

Data

Clinical measurements

Height and weight were measured without shoes wearing light clothing; height to the nearest 1.0 cm and weight to the nearest 0.5 kg. Waist circumference was measured to the nearest 1.0 cm with a steel band, horizontally at the height of umbilicus. BMI was calculated as kg/m^2. Specially trained nurses or technicians used a Dinamap 845XT (Critikon, Tampa, Florida, USA) to measure blood pressure three times at two minutes intervals, and after an initial five

minutes rest (Holmen et al., 2003). In this thesis, the mean of the second and third measure of systolic and diastolic blood pressure was used.

The blood sampling was done in a non-fasting or "random" state, whenever the participants attended. Serum samples were analysed at the Central Laboratory at Levanger, Hospital, using a Hitachi 911 autoanalyzer. An enzymatic hexokinase method was used to measure glucose. High-density lipoprotein (HDL) was measured by applying an enzymatic colorimetric cholesterolesterase method, and triglycerides by an enzymatic colorimetric method (Holmen et al., 2003).

Chronic pain and fibromyalgia

In Q1, participants were asked whether they had pain or stiffness in muscles and/or joints lasting for at least 3 months during the last year. If the answer was "yes" they were asked to indicate the location (neck, shoulders, elbows, wrists/hands, chest/abdomen, upper back, lower back, hips, knees, ankles/feet), and note the duration of the pain. Participants who answered "yes" on the question concerning pain or stiffness or reported at least one pain site on the subsequent question were defined as having chronic pain. Those who answered "yes" to the question about pain and stiffness, but had missing data on the subsequent question about pain sites were excluded from the analyses concerning number of pain sites. Identification of FM was based on the question "Have a doctor ever said that you have fibromyalgia?". The questions concerning musculoskeletal symptoms are adopted from the Standardized Nordic Questionnaire, and have been evaluated and found to give reliable estimates for low back pain, pain in upper limb, and neck discomfort (Kuorinka et al., 1987; Franzblau et al., 1997; Palmer et al., 1999). In the analyses exploring the effect of number of pain sites, participants were divided into five groups; no pain, 1-2 pain sites, 3-5 pain sites, 6 or more pain sites, and FM.

Metabolic syndrome

The metabolic syndrome variable was based on the National Cholesterol Education Program (NCEP ATP III) definition (National Cholesterol Education Program, 2001). Participants with at least three out of the five following criterions were defined as having metabolic syndrome; waist circumference ≥102 cm in men and ≥88 cm in women; serum triglycerides ≥1.7 mmol/L; HDL cholesterol <1.03 mmol/L in men and <1.29 mmol/L in women; systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg; and non-fasting plasma glucose ≥11.1 mmol/L (replacing the fasting glucose criteria of ≥5.6 mmol/L). A cut-off for

random glucose of 11.1 mmol/L has also been used in previous studies on the same cohort (Martin et al., 2009). In addition to the cut-off values for blood pressure, people who reported use of antihypertensive medication were classified as having high blood pressure.

Physical activity

Participants were asked to report their weekly duration of light (no sweating/being out of breath) and hard (sweating/being out of breath) leisure time physical activity, with the following response options for both items: 0 hours, <1 hour, 1-2 hours, and ≥3 hours. Based on this information, the participants were categorised into five groups combining light and hard activity: 1) no activity, 2) <3 hours light activity, and no hard activity 3) ≥3 hours light activity and/or <1 hour hard activity, 4) any light activity and ≥1 hour hard activity, 5) unknown. This variable was used to adjust for physical activity in analyses concerning the relation between chronic pain/FM and metabolic syndrome and its components. For the purpose of assessing the effect of physical activity on the estimated associations, six groups were created based on pain status and activity level. Here, inactive was defined as up to 2 hours light physical activity and no hard activity per week. Active was defined as 3 or more hours light activity or any hard activity per week. The following groups were created: 1) no pain and active, 2) no pain and inactive, 3) chronic pain and active, 4) chronic pain and inactive, 5) FM and active, and 6) FM and inactive. The physical activity questions in HUNT 2 have previously been validated, and the question for hard leisure time physical activity appeared to be a valid measure for vigorous activity (Kurtze et al., 2007).

Statistical analyses

Adjusted mean and mean difference of cardiovascular risk factors between individuals with or without chronic pain/FM was calculated using a generalized linear model (linear regression), whereas logistic regression was used to estimate prevalence odds ratios (ORs) for metabolic syndrome, or for having risk factors above the cut-off level for metabolic syndrome. Precision of the estimated associations was assessed by a 95% confidence interval (CI). To control for potential confounding, the final model was adjusted for age (20-30, 30-40, ..., 70-80, ≥80 years), education (primary school, high school, college, university <4 years, university ≥4 years, unknown), physical activity (no activity, <3 hours light activity and no hard activity, ≥3 hours light activity and/or <1 hour hard activity, any light activity and ≥1 hour hard activity, unknown), smoking (never, former, current, unknown), and alcohol consumption (0 times a

month, 1-3 times a month, ≥4 times a month, total abstainer, unknown). All analyses were stratified by sex. In analyses exploring the effect of number of pain sites, a linear trend test (dose-response) was performed by entering the pain group categories as an ordinal variable in the model.

Data analyses were performed with Statistical Package for the Social Sciences, version 17.0 (SPSS, Chicago, Illinois, USA).

Results

Characteristics of the study population

Participant characteristics are presented in Table 1 and Table 2 for men and women, respectively. Chronic pain of at least three months duration during the last year was reported by 40.4 % of the men and 42.4 % of the women. In total, 225 men (0.9 %) and 1647 (5.9 %) women had previously been diagnosed with FM. Both men and women who reported chronic pain or FM were on average older and had a higher BMI than those with no pain. There were a higher percentage of smokers and physically inactive, and a lower percentage with higher education in these groups, compared to those with no pain.

In total, 21.7 % of the men and 18 % of the women were defined as having the metabolic syndrome.

Table 1: Descriptive statistics men

Group	N	Mean age, years (SD)	Mean BMI, kg/m^2 (SD)	Higher ed., %	Smokers, %	Inactive, %	MetS, %	Median pain sites
All	25,392	46.7 (15.6)	26.4 (3.5)	21.0	28.6	30.5	21.7	0.0
No pain	14,906	44.7 (16.0)	26.2 (3.4)	24.1	26.4	28.4	20.4	NA
Chronic pain	10,261	49.6 (14.6)	26.6 (3.5)	16.5	31.6	33.4	23.4	2.0
1-2 pain sites	5,407	48.4 (15.2)	26.4 (3.4)	19.4	29.2	32.5	22.2	1.0
3-5 pain sites	3,826	50.8 (13.9)	26.7 (3.4)	14.0	33.7	33.8	24.1	4.0
≥6 pain sites	1,003	52.0 (13.4)	27.1 (3.0)	10.7	36.7	36.6	26.5	7.0
Fibromyalgia	225	49.6 (12.1)	27.4 (3.8)	12.4	38.7	38.7	32.0	6.0
No pain								
Active	9,808	42.5 (15.1)	26.0 (3.3)	28.9	22.8		17.6	NA
Inactive	4,206	46.3 (15.7)	26.6 (3.7)	17.1	33.4		25.3	NA
Chronic pain								
Active	6,065	47.9 (14.1)	26.4 (3.3)	21.2	29.1		21.0	2.0
Inactive	3,238	49.8 (14.2)	26.9 (3.6)	11.6	35.5		26.7	2.0
Fibromyalgia								
Active	106	46.5 (12.5)	27.1 (3.8)	19.8	35.8		31.1	5.0
Inactive	79	52.5 (11.3)	27.4 (3.7)	5.1	35.4		36.7	6.0

Abbreviations: N= number of participants, SD= standard deviation, BMI= body mass index, Higher ed.= higher education (university or university college), MetS= metabolic syndrome, NA= not applicable. Inactive was defined as up to 2 hours light activity, no hard activity.

Table 2: Descriptive statistics women

Group	N	Mean age, years (SD)	Mean BMI, kg/m^2 (SD)	Higher ed., %	Smokers, %	Inactive, %	MetS, %	Median pain sites
All	28,077	47.2 (16.1)	26.0 (4.5)	20.9	30.6	38.4	18.0	0.0
No pain	14,513	44.5 (16.6)	25.5 (4.3)	24.5	27.3	34.0	14.9	NA
Chronic pain	11,917	50.0 (15.5)	26.5 (4.6)	18.0	32.9	42.5	20.5	3.0
1-2 pain sites	4,950	49.5 (16.4)	26.2 (4.5)	20.6	29.2	40.0	19.0	2.0
3-5 pain sites	4,992	49.8 (15.0)	26.5 (4.6)	17.0	34.0	42.7	20.8	4.0
≥6 pain sites	1,938	51.7 (14.0)	26.9 (4.8)	13.4	39.6	48.2	23.4	7.0
Fibromyalgia	1,647	51.0 (11.5)	27.3 (4.8)	10.7	42.9	47.5	28.0	7.0
No pain								
Active	8,435	40.4 (14.7)	25.0 (3.9)	31.2	25.4		10.5	NA
Inactive	4,913	47.1 (16.1)	26.0 (4.6)	18.0	31.6		18.5	NA
Chronic pain								
Active	5,699	45.5 (14.1)	25.8 (4.3)	24.4	31.7		14.7	3.0
Inactive	4,815	51.6 (15.0)	26.9 (4.8)	14.1	35.3		23.5	3.0
Fibromyalgia								
Active	654	48.6 (11.8)	26.6 (4.8)	15.6	41.3		20.9	7.0
Inactive	710	51.1 (10.7)	27.7 (4.7)	9.2	44.8		31.4	7.0

Abbreviations: N= number of participants, SD= standard deviation, BMI= body mass index, Higher ed.= higher education (university or university college), MetS= metabolic syndrome, NA= not applicable. Inactive was defined as up to 2 hours light activity, no hard activity.

Chronic pain, fibromyalgia, and the metabolic syndrome

The association between pain status and components of the metabolic syndrome is presented in Table 2. The strongest associations were found among men and women with FM, who had statistically significant more unfavourable levels of cardiovascular risk factors compared to persons without pain. For men and women, respectively, mean difference (95 % CI) in waist circumference was 1.9 cm (0.8 to 3.0) and 3.1 cm (2.5 to 3.6), in BMI it was 0.8 kg/m^2 (0.3 to 1.2) and 1.2 kg/m^2 (1.0 to 1.4), for triglycerides it was 0.29 mmol/L (0.13 to 0.46) and 0.20 mmol/L (0.16 to 0.25), and in HDL cholesterol it was -0.06 mmol/L (-0.10 to -0.02) and -0.08 mmol/L (-0.10 to -0.06). For systolic blood pressure, both men and women with FM had lower values than people with no pain, but this was only statistically significant for women (-1.8 mmHg (-2.7 to -0.8)).

Women with chronic pain had statistically significant higher waist circumference (1.4 cm (1.2 to 1.7)), BMI (0.5 kg/m^2 (0.4 to 0.7)), triglycerides (0.06 mmol/L (0.03 to 0.08)) and lower HDL cholesterol (-0.02 mmol/L (-0.03 to -0.01)), compared to women with no pain. Men with chronic pain had higher waist circumference (0.4 cm (0.1 to 0.6 cm)) and BMI (0.2 kg/m^2 (0.1 to 0.3)) compared to men with no pain. Both men and women with chronic pain had lower values on both systolic (-1.6 mmHg (-2.0 to -1.2) in men and -1.5 mmHg (-2.0 to -1.1) in women) and diastolic blood pressure (-0.4 mmHg (-0.7 to -0.1) in men and -0.4 mmHg

(-0.6 to -0.1) in women), as well as glucose (-0.05 mmol/L (-0-08 to -0.01) in men and -0.04 mmol/L (-0.07 to -0.01) in women), compared to those with no pain.

Table 3: Effect of chronic pain and FM on components of the metabolic syndrome

Variable	No pain (ref.)	Chronic pain		Fibromyalgia	
	Mean[1]	Difference[2]	(95 % CI)	Difference[2]	(95 % CI)
Men					
Systolic BP, mmHg	137.6	-1.6	(-2.0 to -1.2)	-2.1	(-4.2 to 0.1)
Diastolic BP, mmHg	80.2	-0.4	(-0.7 to -0.1)	-0.2	(-1.6 to 1.2)
Waist circumference, cm	90.7	0.4	(0.1 to 0.6)	1.9	(0.8 to 3.0)
BMI, kg/m^2	26.2	0.2	(0.1 to 0.3)	0.8	(0.3 to 1.2)
Triglycerides, mmol/L	1.90	0.02	(-0.01 to 0.05)	0.29	(0.13 to 0.46)
Glucose, mmol/L	5.42	-0.05	(-0.08 to -0.01)	0.09	(-0.10 to 0.28)
HDL, mmol/L	1.25	-0.01	(-0.01 to 0.00)	-0.06	(-0.10 to -0.02)
Women					
Systolic BP, mmHg	130.4	-1.5	(-2.0 to -1.1)	-1.8	(-2.7 to -0.8)
Diastolic BP, mmHg	76.7	-0.4	(-0.6 to -0.1)	-0.5	(-1.0 to 0.1)
Waist circumference, cm	79.2	1.4	(1.2 to 1.7)	3.1	(2.5 to 3.6)
BMI, kg/m^2	25.5	0.5	(0.4 to 0.7)	1.2	(1.0 to 1.4)
Triglycerides, mmol/L	1.41	0.06	(0.03 to 0.08)	0.20	(0.16 to 0.25)
Glucose, mmol/L	5.25	-0.04	(-0.07 to -0.01)	0.01	(-0.05 to 0.07)
HDL, mmol/L	1.51	-0.02	(-0.03 to -0.01)	-0.08	(-0.10 to -0.06)

[1] Unadjusted
[2] Adjusted for age, education, physical activity, smoking, and alcohol consumption.
Abbrevations: BP= Blood pressure, BMI= body mass index, HDL= high-density lipoprotein, CI= confidence interval.

Table 4 and 5 show ORs (95 % CIs) for metabolic syndrome and for being above the cut-off value for each component of metabolic syndrome. Men and women with FM had a considerably higher prevalence of metabolic syndrome, compared to those without pain, with ORs of 1.53 (1.14-2.04) and 1.66 (1.47-1.88), respectively. Regarding the single components of the syndrome, men with FM had an OR of 1.84 (1.32-2.56) for high waist circumference (abdominal obesity), 1.61 (1.17-2.23) for obesity, 1.30 (0.99-1.70) for high triglyceride level, and 1.66 (1.26-2.18) for low HDL cholesterol. The corresponding ORs for women were 1.90 (1.70-2.13), 1.77 (1.56-2.01), 1.54 (1.38-1.72), and 1.42 (1.27-1.60).

Among women with chronic pain, a similar pattern as for FM was observed, although the ORs were somewhat weaker. Among men with chronic pain, only the OR for waist circumference was statistically significant higher than in men without pain. No association was found between pain and glucose. It was a tendency towards lower OR for high blood pressure in the pain groups, but the results were only statistically significant for men with chronic pain, who had an OR of 0.90 (0.85-0.96).

Table 4: Adjusted[1] prevalence OR with 95 % CI for metabolic syndrome/ being above the cut-off values for components of metabolic syndrome men

	Metabolic syndrome	Waist ≥102 cm	BMI (kg/m^2) ≥30	Glucose ≥11.1 mmol/L	Triglycerides ≥1.7 mmol/L	HDL <1.03 mmol/L	High blood pressure
No pain (ref.)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Chronic pain	1.05 (0.98-1.12)	1.12 (1.04-1.21)	1.07 (0.99-1.15)	0.99 (0.78-1.26)	1.01 (0.96-1.07)	1.04 (0.98-1.10)	0.90 (0.85-0.96)
1-2 pain sites	1.02 (0.94-1.10)	1.04 (0.94-1.15)	1.02 (0.93-1.12)	0.93 (0.69-1.26)	1.01 (0.95-1.08)	1.01 (0.94-1.08)	0.94 (0.87-1.01)
3-5 pain sites	1.06 (0.97-1.15)	1.13 (1.01-1.26)	1.05 (0.95-1.17)	0.99 (0.72-1.38)	1.00 (0.93-1.07)	1.04 (0.96-1.13)	0.85 (0.78-0.92)
≥6 pain sites	1.15 (0.99-1.34)	1.52 (1.28-1.80)	1.41 (1.19-1.67)	1.32 (0.81-2.15)	1.08 (0.95-1.23)	1.23 (1.07-1.41)	0.90 (0.77-1.04)
Fibromyalgia	1.53 (1.14-2.04)	1.84 (1.32-2.56)	1.61 (1.17-2.23)	0.67 (0.16-2.72)	1.30 (0.99-1.70)	1.66 (1.26-2.18)	0.82 (0.61-1.10)
P- trend	.005	< .001	.003	.808	.159	.010	< .001
No pain							
Active (ref.)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Inactive	1.43 (1.31-1.56)	1.60 (1.43-1.80)	1.39 (1.25-1.55)	1.22 (0.86-1.75)	1.30 (1.21-1.40)	1.31 (1.21-1.42)	1.02 (0.94-1.11)
Chronic pain							
Active	1.10 (1.01-1.19)	1.13 (1.02-1.27)	1.07 (0.97-1.18)	0.96 (0.68-1.35)	1.06 (0.99-1.13)	1.10 (1.02-1.18)	0.90 (0.84-0.97)
Inactive	1.42 (1.29-1.56)	1.81 (1.60-2.04)	1.49 (1.33-1.67)	1.32 (0.91-1.90)	1.25 (1.15-1.36)	1.24 (1.14-1.36)	0.95 (0.87-1.05)
Fibromyalgia							
Active	1.87 (1.23-2.85)	2.08 (1.25-3.46)	1.47 (0.87-2.45)	NC	1.61 (1.09-2.39)	1.87 (1.26-2.77)	0.61 (0.41-0.92)
Inactive	2.05 (1.29-3.27)	2.78 (1.66-4.64)	1.83 (1.07-3.13)	0.93 (0.13-6.84)	1.28 (0.82-2.01)	2.01 (1.28-3.16)	0.99 (0.58-1.68)

[1)] Adjusted for age, education, physical activity (except from analyses concerning physical activity), smoking, and alcohol consumption.
Abbreviations: OR = odds ratio, CI = confidence interval, BMI =body mass index, HDL= high-density lipoprotein, NC= not calculated.
High blood pressure was defined as systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg and/or current use of antihypertensive medication.
Inactive was defined as up to 2 hours light activity, no hard activity (weekly).

Table 5: Adjusted[1] prevalence OR with 95 % CI for metabolic syndrome/ being above the cut-off values for components of metabolic syndrome women

	Metabolic syndrome	Waist ≥88 cm	BMI (kg/m^2) ≥30	Glucose ≥11.1 mmol/L	Triglycerides ≥1.7 mmol/L	HDL <1.29 mmol/L	High blood pressure
No pain (ref.)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Chronic pain	1.18 (1.10-1.26)	1.31 (1.23-1.39)	1.29 (1.21-1.39)	0.98 (0.72-1.33)	1.14 (1.08-1.21)	1.12 (1.06-1.19)	0.94 (0.89-1.00)
1-2 pain sites	1.10 (1.01-1.21)	1.17 (1.08-1.27)	1.17 (1.07-1.28)	1.01 (0.68-1.50)	1.08 (1.00-1.16)	1.08 (1.01-1.17)	0.93 (0.86-1.00)
3-5 pain sites	1.21 (1.11-1.32)	1.35 (1.25-1.46)	1.34 (1.23-1.47)	0.97 (0.65-1.45)	1.17 (1.09-1.26)	1.13 (1.05-1.22)	0.97 (0.90-1.04)
≥6 pain sites	1.26 (1.12-1.42)	1.57 (1.41-1.75)	1.52 (1.34-1.71)	0.96 (0.55-1.68)	1.24 (1.12-1.38)	1.19 (1.07-1.33)	0.91 (0.82-1.02)
Fibromyalgia	1.66 (1.47-1.88)	1.90 (1.70-2.13)	1.77 (1.56-2.01)	1.53 (0.90-2.59)	1.54 (1.38-1.72)	1.42 (1.27-1.60)	0.93 (0.83-1.05)
P- trend	< .001	< .001	< .001	.924	< .001	< .001	.071
No pain							
Active (ref.)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Inactive	1.34 (1.20-1.49)	1.43 (1.31-1.57)	1.39 (1.25-1.54)	1.14 (0. 68-1.91)	1.23 (1.13-1.34)	1.30 (1.19-1.41)	1.00 (0.92-1.09)
Chronic pain							
Active	1.19 (1.07-1.32)	1.34 (1.22-1.46)	1.35 (1.22-1.50)	1.04 (0.61-1.78)	1.16 (1.07-1.27)	1.14 (1.05-1.24)	0.91 (0.84-0.98)
Inactive	1.55 (1.40-1.72)	1.81 (1.66-1.98)	1.80 (1.62-1.99)	1.11 (0.67-1.84)	1.40 (1.28-1.52)	1.40 (1.28-1.52)	0.98 (0.90-1.07)
Fibromyalgia							
Active	1.56 (1.27-1.92)	1.91 (1.59-2.29)	1.87 (1.52-2.30)	0.62 (0.15-2.62)	1.46 (1.22-1.74)	1.43 (1.19-1.71)	0.89 (0.74-1.06)
Inactive	2.34 (1.95-2.81)	2.64 (2.23-3.12)	2.42 (2.01-2.91)	2.75 (1.34-5.64)	1.90 (1.61-2.24)	1.89 (1.59-2.23)	0.93 (0.78-1.10)

[1)] Adjusted for age, education, physical activity (except from analyses concerning physical activity), smoking, and alcohol consumption.
Abbreviations: OR = odds ratio, CI = confidence interval, BMI =body mass index, HDL= high-density lipoprotein.
High blood pressure was defined as systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg and/or current use of antihypertensive medication.
Inactive was defined as up to 2 hours light activity, no hard activity (weekly).

Effect of number of pain sites

As illustrated in Figure 1, there was a significant dose-response relation between number of pain sites and all the components of metabolic syndrome (all p-trends <0.01), except glucose (p-trend= 0.437 for men and 0.209 for women). The values for waist circumference, BMI, and triglycerides were increasing, and HDL cholesterol decreasing with number of pain sites reported among women. Systolic blood pressure was decreasing with number of pain sites, but the FM group had a slightly higher value than those with 6 or more pain sites. Similar trends were found among men, but the values in some of the pain groups were not statistically significant.

Table 4 and Table 5 show a dose-response relation between number of pain sites and OR for the metabolic syndrome and its components. Among women there was a dose-response association for all single components, except high glucose and blood pressure, and, among men, a dose-response association was found for all components except high glucose and triglyceride level.

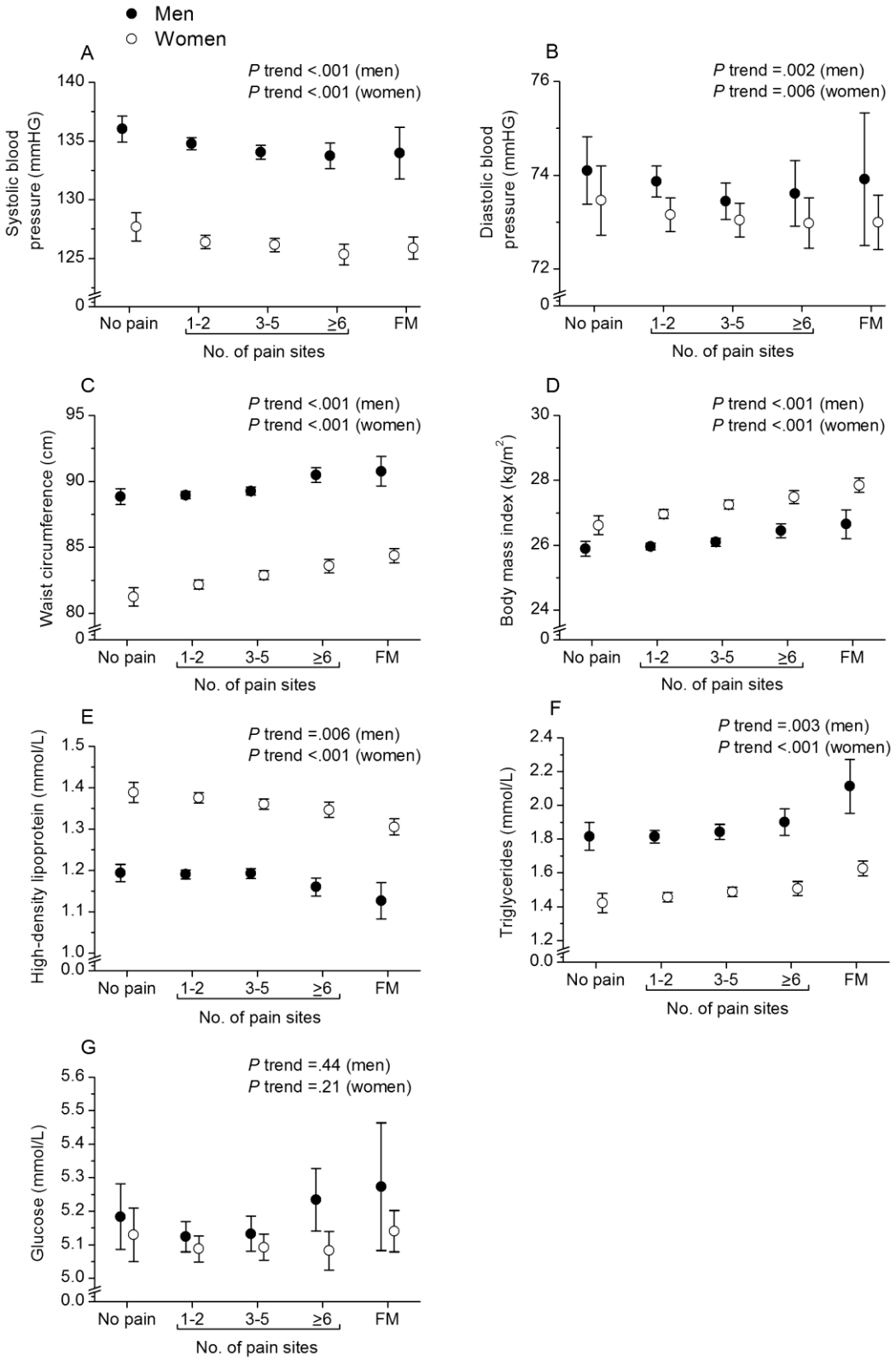

Figure 1: Number of pain sites and mean levels with 95 % confidence interval of various cardiovascular risk factors.

Effect of physical activity level

The effect of physical activity level on systolic blood pressure, waist circumference, BMI, triglycerides, and HDL is displayed in Figure 2. The active group within each pain group had more favourably levels than the inactive group on waist circumference, BMI, triglycerides and HDL. For systolic blood pressure, the tendency towards lower values among people with chronic pain and FM compared those with no pain that was observed in the main analyses persisted, but there were no consistent differences between the active and inactive within pain groups. There was no consistent effect of pain- and physical activity level on diastolic blood pressure and glucose (data not shown).

According to Table 4 and 5, the combination of FM and physical inactivity seems to be especially unfavourable, with an OR for metabolic syndrome of 2.05 (1.29-3.27) in men and 2.34 (1.9-2.81) in women, compared to the active persons without pain. Also the associations with the various components of metabolic syndrome were strongest in people with FM who were inactive.

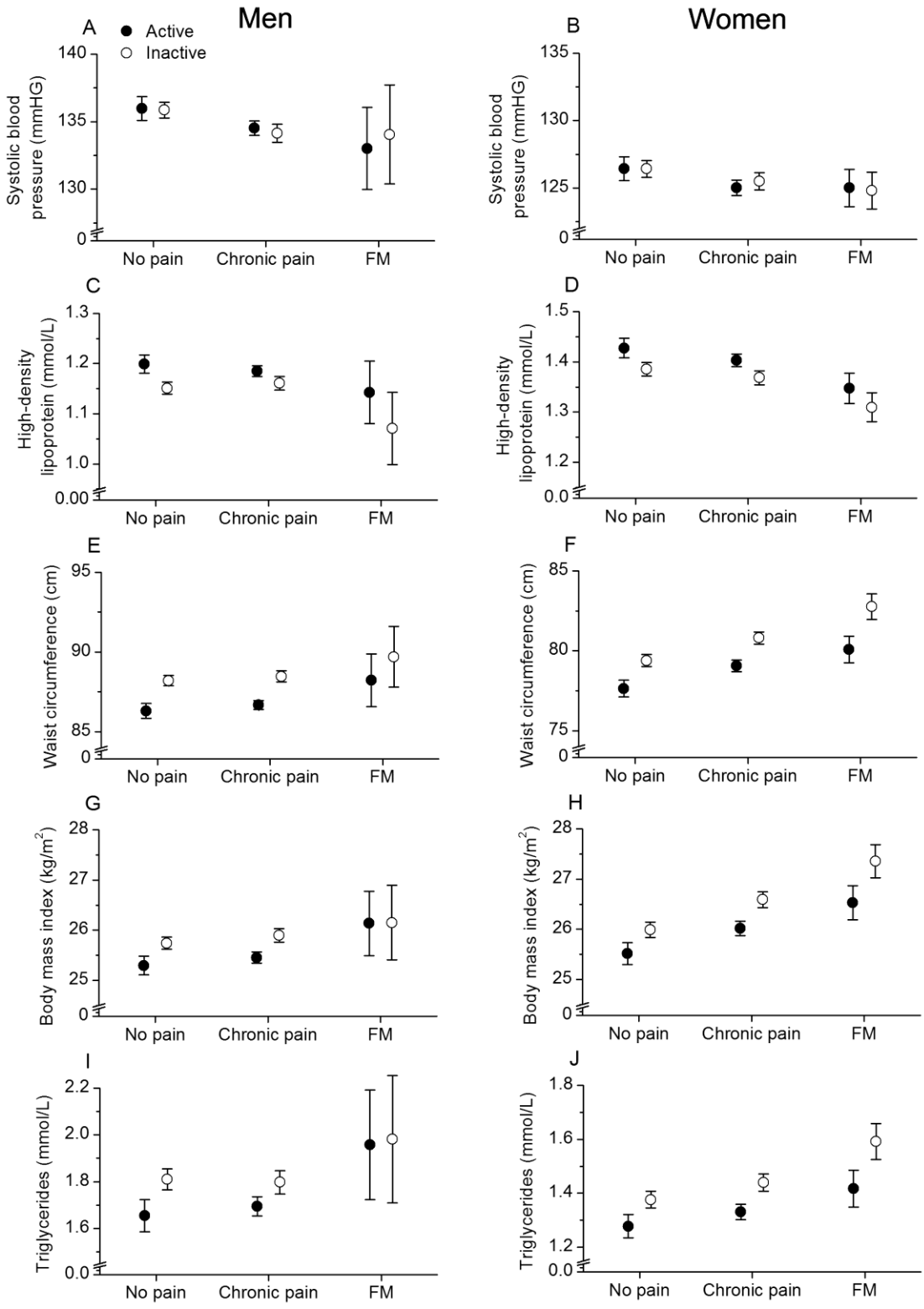

Figure 2: Pain- and physical activity groups and mean levels with 95 % confidence interval of various cardiovascular risk factors.

Discussion

Major findings

In this cross-sectional population study there was a strong positive association between FM and prevalence of metabolic syndrome, both among men and women, whereas the association between chronic pain and metabolic syndrome was weaker and only present among women. When exploring the relation between pain and the single components of the metabolic syndrome, several cardiovascular risk factors had more unfavourable levels in the pain and FM groups (e.g., obesity, triglycerides, and HDL cholesterol). However, a few risk factors showed no or even opposite associations, with more favourable levels among persons with pain (e.g., glucose and blood pressure). There was a dose-response association between number of pain sites and metabolic syndrome, and also with most of its components. In addition, being physically active had a beneficial effect on cardiovascular risk factors within each pain category.

Association between chronic pain, FM and metabolic syndrome

In line with our results, Loevinger and co-workers (2007) reported that women with FM were 5 times more likely than healthy controls to have metabolic syndrome. These results were based on the same definition of the metabolic syndrome as the present study, except the glucose level, which was measured as glycosylated hemoglobin (HbA_{1c}) instead of serum glucose. Fewer participants (109) and less statistical power could explain the higher OR found in Loevinger and co-workers study.

In the present study, both women and men with FM had higher waist circumference and BMI compared to those without pain. Loevinger and co-workers (2007) observed higher waist-to-hip ratio and waist circumference in women with FM, but not higher BMI and weight compared to controls, indicating that abdominal obesity might be a factor associated with FM. The OR for high waist circumference was only slightly higher than the OR for high BMI in all groups in our study, so it is not possible to decide whether one of the variables is more important than the other.

An association between hyperlipidemia and musculoskeletal symptoms has been suggested in the literature, but the pathogenesis behind this is not fully understood (Gurer et al., 2006). As in the present study, a higher triglyceride level in FM women was reported by

Loevinger and co-workers (2007). Gurer and co-workers (2006) compared lipid profiles of FM women with healthy women, and found no significant differences on triglycerides and HDL cholesterol, but significantly higher mean serum total-cholesterol and low-density lipoprotein cholesterol among those with FM. Abnormal lipid levels have previously been related to low back pain, through the process of atherosclerosis in the arteries supplying the lumbar region. Heuch and co-workers (2010) studied this relation in the HUNT 2 population and found that the prevalence of chronic low back pain was positively related to triglyceride level, and inversely related to HDL level. After adjustments, the results were only significant for women.

The findings of lower blood pressure among FM women, and both men and women with chronic pain, are contrary to Loevinger and co-workers' (2007) study, where women with FM had higher blood pressure than controls. This was a quite unexpected finding, due to the higher waist circumference and BMI in these groups, which in numerous studies have been associated with high blood pressure and hypertension (Gelber et al., 2007; Lakoski et al., 2011; Levine et al., 2011). The results might have been affected by the exclusion of those who reported current use of antihypertensive medication from the linear regression. There was a higher percentage of users in the FM group (9.3 %) and in the chronic pain group (8.2 %) compared to those without pain (5.8 %), and in the analysis of hypertension, where people using antihypertensive medication were included, the observed association was only statistically significant in men with chronic pain. A phenomenon referred to as hypertension-related hypalgesia, concerning an inverse relation between hypertension and pain sensitivity, has been described in the literature. Hagen and co-workers (2005) found that high systolic or diastolic blood pressure was associated with a lower prevalence of chronic musculoskeletal pain in the HUNT-population. On the other hand, heart rate variability is reduced in individuals with FM, and is a marker of autonomic dysfunction (Staud, 2008). Moreover, reduced heart rate variability has been associated with an increased risk of developing hypertension (Schroeder et al., 2003), and greater cardiovascular mortality (Dekker et al., 2000).

Impaired glucose regulation has been considered to be an important component of the metabolic syndrome (Carroll and Dudfield, 2004) so it was unexpected that the only difference observed on the glucose variable was in the chronic pain group, where both men and women had slightly lower glucose levels than those with no pain. However, biased results due to randomly (non-fasting) measured glucose cannot be ruled out.

Chronic pain had more pronounced influence on prevalence of metabolic syndrome and for meeting the criteria for the various components in women than in men. No association with metabolic syndrome was observed among men with chronic pain. Most of the literature concerning FM has focused on women, due to the low prevalence in men, but a few studies have evaluated gender differences in FM. Yunus (2000) reported that the major features of FM (e.g. fatigue, widespread pain, and number of tender points) were greater or more frequent in women, while pain severity and functional ability were similar. On the other hand, Buskila and co-workers (2000) found that men report more severe symptoms and more physical impairment than women. The extent of the material in HUNT made it possible to identify more than 200 men with FM. In this study, similar trends for men and women with FM were observed.

Possible mechanisms

Most of the observed association between chronic pain/FM and metabolic syndrome seems to be explained by obesity and unfavourable lipid levels. Although it is not clear whether the observed association is causal, possible mechanisms will be discussed. Overweight and obesity has been associated with an increased risk of developing FM in women (Mork et al., 2010). Even though there are currently no mechanisms explaining a causal relationship between obesity and widespread pain in FM, the conditions seem to share some etiological factors. Factors thought to contribute to the pain and associated disability in FM, such as dysregulated hypothalamic-pituitary-adrenal axis (Okifuji and Turk, 2002) and elevated serum levels of proinflammatory cytokines (Wallace, 2006), are also found in obesity (Vicennati and Pasquali, 2000; Khaodhiar et al., 2004).

An association between short sleep duration and elevated BMI and obesity has been suggested (Taheri et al, 2004; Bjorvatn et al., 2007). Short sleep duration has previously been associated with reduced leptin levels and raised levels of ghrelin. These hormonal changes are known to increase appetite, and might explain the increased BMI observed (Taheri et al., 2004). Bjorvatn and co-workers (2007) demonstrated an association between short sleep duration and different metabolic variables. Of interest, both triglyceride level, and HDL-cholesterol was related to sleep duration, with higher triglyceride levels, and lower HDL-cholesterol with shorter sleep durations (shorter than the reference of 7-8 hours). Sleep disturbances occur frequently among those with chronic pain (Menefee et al., 2000) and FM (Schaefer et al., 2003). Therefore, disturbed sleep/shorter sleep durations might be a possible

explanation for the association between chronic pain and FM and obesity, high triglyceride level, and low HDL cholesterol observed in this study.

Depression is often observed as a comorbid condition to chronic pain and FM (Bair et al., 2003; Fietta et al., 2007), and depression appears to be correlated with obesity (Gadalla, 2009; Faith et al., 2011). Hildrum and co-workers (2009) examined the associations of depression and anxiety with the metabolic syndrome within participants of HUNT 2, and found no consistent association. An initial weak positive association between depression and metabolic syndrome was entirely explained by confounders, most importantly physical activity and educational level. The analyses in this thesis was adjusted for these factors, thereby it is not very likely that the association with metabolic syndrome observed among those with FM and women with chronic pain are due to higher rates of depression or anxiety in these groups.

Association between number of pain sites and metabolic syndrome

Kamaleri and co-workers (2008a and 2008b) studied number of pain sites in relation to demographics, lifestyle, health-related factors, and functional ability, but to my knowledge, no previous study has evaluated the association between number of pain sites and cardiovascular risk factors. A strong negative association has been demonstrated between number of pain sites and functional ability (Kamaleri et al., 2008b). In this study, analyses concerning the effect of number of pain sites were adjusted for physical activity level, and it is therefore not likely that reduced functional ability have influenced the results to a large extent. Even though FM was used as the end of a continuum of number of pain sites, those with FM reported similar (women) or lower (men) median number of pain sites than the group with 6 or more sites. Still, the FM group had more unfavourable levels on most variables, indicating that there is an additional effect of having a FM diagnosis.

Effect of physical activity

There was a higher prevalence of metabolic syndrome among inactive compared to active persons with chronic pain and FM, both in men and in women. Carroll and Dudfield (2004) reviewed the literature concerning the effect of physical activity and exercise on metabolic abnormalities, and the overall evidence suggests that physical activity could modify each of the single components related to the metabolic syndrome. The findings in the present study are in accordance with the current knowledge of a favourable effect of physical activity on

body composition (Ekelund et al., 2011), triglyceride, and HDL level (Durstine et al., 2001). Unexpectedly, no significant association between physical activity level and high glucose or hypertension was observed, except for an increased OR for high glucose among inactive FM women, although such associations have been reported in numerous previous studies (Carroll and Dudfield, 2004; Fagard and Cornelissen, 2007).

In addition to the effect on the single risk factors, physical activity may reduce the risk of cardiovascular mortality in people with clustering of cardiovascular risk factors. In a prospective study of the HUNT 1 population, the risk of people with clustering of cardiovascular risk factors who achieved the highest level of physical activity (at least once a week, more than 30 min and moderate to vigorous intensity) was comparable to the risk of inactive individuals without clustering of risk factors (Tjønna et al., 2010).

Strengths and limitations

To our knowledge, this is the first large population-based study evaluating the association of chronic pain and FM with cardiovascular risk factors and metabolic syndrome. The HUNT 2 study aimed to include the whole adult population of Nord-Trøndelag County, which is stable and ethnically homogenous. In most respects, Nord-Trøndelag is fairly representative of Norway, for example when it comes to morbidity and mortality, geography, economy, and industry. The participation rate was high (71.2 %) (Holmen et al., 2003). A wide range of exposure data made it possible to adjust for potential confounding factors. Nevertheless, one cannot rule out that other possible confounders, for example diet, might have influenced the results. Recently, VanDenKerkhof and co-workers (2011) studied dietary habits of persons with chronic pain, and found that women with chronic widespread pain reported a more unhealthy diet (less fruit/vegetables and more fatty foods) than women without pain. Moreover, the cross-sectional design of the study limits the possibility to assess the temporal relation between exposure and effect, and thus, no causal effects can be inferred.

In comparison to Hildrum and co-workers (2007), who studied the age-specific prevalence of metabolic syndrome in HUNT 2, the total prevalence in this study was lower, i.e., 21.7 % compared to 26.8 % in men, and 18 % compared to 25 % in women, even though both studies were based on the ATP III definition of the metabolic syndrome. In the current study, those with already developed cardiovascular disease were excluded from the analyses, and this might have accounted for most of the difference in observed prevalence between the studies. Hildrum and co-workers adjusted their triglyceride and glucose level for hours since last

meal. In the present study, the glucose cut-off value was replaced by a higher (non-fasting) value, but for triglycerides, hours since last meal were not accounted for. However, there were no considerable differences between the groups with no pain, chronic pain, and FM in the distribution of hours since last meal, and thereby, the associations have not likely been affected by this. Hildrum and co-workers also included people with type 2 diabetes as having high glucose level, and this might have been a potential reason for the higher prevalence of metabolic syndrome observed in their study. Data from blood samples which identified cases having type 2 diabetes were not available in the current study. By defining those who were 20 years or older when they got diabetes as having diabetes type 2, and including these in the metabolic syndrome definition, the prevalence only increased slightly.

In the questionnaire used in HUNT 2, participants were asked about pain or stiffness in muscles or joints during the past 12 months. The use of this time period introduces the potential of recall bias, as inaccuracy in recall tends to increase with time (Feine et al., 1998). In most cases, the recall of pain experience is exaggerated (Gedney and Logan, 2006). Definition of FM was in this study based on the questionnaire. Participants who stated that the diagnosis of FM had been assigned by their doctor were included. The validity of self-reported diagnosis of FM is not known.

Information about physical activity level was collected through self-reported data from the questionnaire. Physical activity is a complex behavior, and thereby misclassification cannot be ruled out. The ability of persons with chronic pain or FM to accurately report physical activity has been questioned. Both under- and overestimating of activity level has been found when self-reported data has been compared to objective measures (McLoughlin et al., 2011; van Weering et al., 2011). The physical activity questions used in HUNT 2 has previously been validated on men between 20 and 39 years. Kurtze and co-workers (2007) found that the question for "hard" physical activity was a reasonably valid measure for vigorous activity, while the question for "light" physical activity did not correlate well with objective measures. Even though these question do not contain any information about type of activity, or can give specific information of important factors such as energy expenditure, self-reporting through questionnaires is the most practical data collection method in large population studies like HUNT, and have been found valid for classifying participants into broad categories of activity (Shephard, 2003).

Conclusion

In this population-based study, the prevalence of metabolic syndrome was higher among women with chronic pain, and among both men and women with FM, compared to those with no pain. Higher waist circumference and triglyceride level, and lower HDL cholesterol seems to account for most of the observed association. There was a dose-response association between number of pain sites, metabolic syndrome, and most of its components. Physical activity had a modifying effect on the observed association, with more favourable levels of risk factors and lower prevalence of metabolic syndrome in active compared to inactive persons. The combination of FM and physical inactivity was strongly related to a higher prevalence of metabolic syndrome, suggesting that physical activity should be promoted among persons with chronic pain or FM.

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