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The relation between chronic musculoskeletal pain and obesity.

The HUNT Study, Norway

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ABSTRACT

Background

General obesity is a risk factor for fibromyalgia (FM), especially in physically inactive women, while abdominal obesity is a recognized risk factor for, and a feature in several metabolic diseases. Women with FM have shown higher prevalence of metabolic syndrome compared to healthy women. However, whether FM and chronic musculoskeletal pain are associated with abdominal obesity, independent of concurrent general obesity, is unclear.

Objective

To examine the association between FM and severity of chronic musculoskeletal pain and, 1) general obesity (i.e., peripheral or overall body fat distribution) and, 2) abdominal obesity (i.e., central body fat distribution). In addition, the impact of physical exercise on these associations was investigated in supplementary analyses.

Methods

A cross-sectional study was conducted on levels of Body Mass Index (BMI) and measures of abdominal fat layers (i.e., Waist Circumference [WC], Waist-to-Hip ratio [WHR], and Waist-to-Height ratio [WHtR]) in relation to the prevalence of FM in a large, unselected female population. First, healthy women and women with diabetes mellitus (DIA) and/or glucose level (GL) ≥11.1 mmol/l were used as references (n=28,788). Second, healthy women and women with localized chronic musculoskeletal pain were used as references (n=21,752). In analyses of influence of physical exercise, women with physical impairments were excluded (n=18,988).

Results

BMI and measures of abdominal fat layers showed positive associations to the prevalence of FM, DIA/GL ≥11.1 mmol/l, and FM with DIA/GL ≥11.1 mmol/l (*P* for trend <0.001), and dose-response relations to severity of chronic musculoskeletal pain (*P* for trend <0.001). Measures of abdominal fat layers were highly correlated with BMI in all subgroups. Women who reported highest exercise level had lowest BMI and measures of abdominal fat layers.

Conclusion

Both abdominal obesity (indicated by WC, WHR, and WHtR) and general obesity (indicated by BMI) showed a strong dose-response relation to severity of chronic musculoskeletal pain and FM. Physical exercise moderated these relations. Measures of abdominal fat layers were highly correlated with BMI, indicating that central body fat accumulation in women with FM and chronic musculoskeletal pain reflects concurrent overall body fat accumulation.

INTRODUCTION

Fibromyalgia (FM) is a chronic pain syndrome, defined by widespread pain and reduced pressure pain threshold at 11 or more of 18 anatomically defined tender points sites[1]. Pain should have been present for the past 3 months or more, and should be experienced in all four body quadrants as well as the axial body[1,2]. The clinical picture of patients with FM displays a wide range of variations, including comorbid symptoms like anxiety, depression, fatigue[2-4], cognitive deficits, headache[2,3], and insomnia[2]. The overall prevalence of FM in a representative Norwegian county population was found to be 5.2% for females and 0.9% for men[4]. In addition, the prevalence seems to increase with age up to approximately 70 years[2]. The pathogenesis of FM is poorly understood, but data support features with a dysregulation of the stress response system, including deficiencies in the hypothalamic-pituitary-adrenal (HPA) axis[5-8] and in the sympathetic nervous system (SNS)[5-7,9,10], with further altered pain perception and reduced capacity for endogenous pain inhibition[6,7].

FM, obesity, and associated features

Cross-sectional studies have found a higher prevalence of overweight and obesity among women with FM compared to healthy women[11-13]. Further, being overweight or obese is also associated with an increased risk of developing FM, especially in physically inactive women[14]. High Body Mass Index (BMI) is associated with some FM features, including poor sleep quality[11,15], physical impairment[11-13], and reduced pain pressure threshold and quality of life[13]. Conversely, weight loss among obese women with FM is associated with reduced pain and other FM related symptoms[16].

The prevalence of obesity has increased worldwide during the last decades[17,18]. It is well established that obesity has a major impact on the incidence of diseases like cardiovascular disease, diabetes mellitus type 2 (DIA), cancer, as well as physical disability[17,18]. Abdominal subcutaneous and visceral adipose tissue compartments exhibit physiological differences, whereby a high visceral fat layer is considered as a strong and independent risk factor for several metabolic diseases[19-23]. This association may be attributed to altered cortisol secretion and the high density of glucocorticoid receptors in visceral adipose tissue, together with inhibited sex steroids and growth hormones secretion leading to insufficient counteraction against cortisol effects [21-25]. Further, the visceral adipose tissue has a close anatomical relation to the hepatic portal circulation, as well as a specific propensity to mobilize free fatty acids[19,22,23]. In addition to secretion of adipokines and other lipid and

vasoactive substances in adipose tissue[19,21,22], this may then contribute to disturbances like the low-graded, systemic inflammatory state seen in obesity[19,21,26] and thereby increased risk of chronic pain development[7,27].

Metabolic syndrome comprise a clustering of vascular risk factors, and may indicate an early stage of DIA, whereby both conditions are characterised by impaired glucose regulation and abdominal obesity[19,28]. Loevinger and co-workers (2007)[29] reported increased prevalence of metabolic syndrome among women with FM, including higher prevalence of abdominal obesity measured as increased Waist Circumference (WC) and Waist-to-Hip ratio (WHR), compared to healthy controls. Since BMI or body mass did not differ significantly between women with FM and healthy controls, it was suggested that obesity in many women with FM[11-13] may include a bias toward central adiposity[29].

Neuroendocrine disturbances, often following undue stress exposure, may lead to the development of metabolic syndrome[21,24,30,31]. In coherence with this, SNS activation and HPA axis dysregulation in FM[5-10] have similarities to mechanisms which contribute to development of obesity in general, and visceral abdominal obesity in particular[21,22,24,30]. These disturbances may be seen as a dysfunction in the stress response system[5,6,21,22,24,32], exemplified by altered cortisol secretion[7,8,33] and increased sympathetic tonus and reduced sympathetic reactivity[7,9,10] reported in FM patients. Other chronic musculoskeletal pain conditions have been associated with the similar abnormalities as well, i.e., neuroendocrine disturbances[7,33], a low-graded inflammatory state[7,27], and total body fat accumulation[34,35].

The increased prevalence of obesity and related diseases is linked to the growing tendency of insufficient physical activity worldwide[17,36]. It is well-known that regular physical exercise has both a primary and a secondary impact on obesity, and obesity-related diseases[17,37], illustrated by its beneficial influence on physical fitness[37], body fat[38,39], and on immune and neuroendocrine perturbations[40-44]. Large-scale population-based studies have indicated associations between physical inactivity and increased risk of chronic musculoskeletal complaints[45], including symptoms in neck/shoulders and low back[46], as well as chronic widespread pain as observed in FM[14]. Contrary, regular physical exercise may decrease comorbid symptoms of FM[47-49], improve musculoskeletal health[37], and facilitate control of a healthy body mass[38,39].

Measurements of total body fat and body fat distribution

Different anthropometric measurements have different accuracy in estimating body fat distribution[50-52] and total body fat mass[50,53]. Measurements of abdominal fat layers most often

measure abdominal visceral and subcutaneous fat compartments as an unity, since these fat depots need multi-compartment methods to be distinguish. Such methods are reliable, but the costs are high in terms of time and resources, and more easily detected measures are often more practical[50,54]. BMI is thought to have moderate accuracy to measure total body fat mass, but has difficulties in predicting body composition or body fat distribution[50,53,55]. WC or ratio measures as WHR or Waist-to-Height ratio (WHtR) are likely to indicate central versus peripheral fat distribution, despite the inability to distinguish between the abdominal subcutaneous and visceral fat layers[50]. Alone, WC has been shown to be more strongly correlated with the abdominal visceral fat compartment than the WHR[51,52].

Study objectives

The main objective of the present study was to investigate the associations between the prevalence of FM, BMI and measures of abdominal fat layers in a large unselected population of adult women. A second objective was to investigate whether severity of chronic musculoskeletal pain is related to levels of BMI and measures of abdominal fat layers. In this analysis, severity of pain was expressed by number of chronic pain sites with FM as end point of the continuum. In additional analyses, it was investigated whether level of leisure time physical exercise influence the above mentioned relations.

To address the objectives, a cross-sectional analysis was conducted on levels of BMI and measures of abdominal fat layers in relation to the prevalence of FM. In addition to using healthy women, and women categorized by number of pain sites as references, women with DIA and/or hyperglycemia were included as an additional subgroup. Based on the discussed associations between FM, metabolic disturbances, and central adiposity, the primary purpose of including this subgroup was to elucidate the relation between FM and body fat distribution, independent of these related metabolic comorbidities. Data from the Nord-Trøndelag Health Study (HUNT 2) were used, which is an ongoing, comprehensive, population-based health study in one of Norway's 19 counties.

MATERIALS AND METHODS

Study population

In Nord-Trøndelag County in Norway, all inhabitants ≥20 years have been invited to participate in three waves of a large health survey (the HUNT Study). The first survey was carried out in 1984-86 (HUNT 1), the second in 1995-97 (HUNT 2), and the third in 2006-08

(HUNT 3). The HUNT Study was approved by the Regional Committee for Ethics in Medical Research and has been carried out according to the Declaration of Helsinki.

Among 46,709 eligible women, 34,751 accepted the invitation to HUNT 2. They filled out a questionnaire that was included with the invitation. The clinical examination included standardized measurements of body mass, body height, and circumference of waist and hip. The participants were given a second questionnaire to complete at home and return in a prestamped envelope. Briefly, information was collected on a range of lifestyle and health-related factors, including level of physical exercise, musculoskeletal pain, and various diseases. Details of the HUNT study are described at www.hunt.ntnu.no/.

The first part of the analyses focus on associations between FM, metabolic disturbances (i.e., DIA and hyperglycemia), and different measures of body fat. In these analyses, 1,008 women were excluded due to missing data on waist and hip circumference, body mass and/or body height. Furthermore, 4,916 women were excluded due to missing data on FM and DIA status (3,734 women), pregnancy (276 women), or hypothyroidism (906 women). Additionally, 39 women reported to have acquired diabetes before the age of 20 and were excluded from analyses (i.e., likely diabetes mellitus type 1). As a result, the first part of the analyses is based on data from 28,788 women.

The second part of the analyses focus on associations between number of chronic pain sites, FM, and different measures of body fat. Women without measurement of waist and hip circumference, body mass and/or body height were excluded from the analyses (1,008 women), as well as women with missing data on questions related to chronic musculoskeletal pain (8,018 women), and FM status (3,697 women). In addition, pregnant women were also excluded from the analyses (276 women). As a result, the second part of the analyses includes 21,752 women.

In analyses concerning an association with physical exercise level, additional 2,764 women were excluded due to reporting of moderate or severe physical impairments or due to missing data on physical exercise. As a result, analyses including physical exercise as an independent variable are based on data from 18,988 women.

Study variables

Body mass index and measures of abdominal fat layers

BMI was calculated as body mass (in kg) divided by the square value of body height (in meters) obtained at the clinical examination. BMI was further subdivided into four categories based on the cut points suggested by the World Health Organization (WHO)[56], i.e., ≤18.5

kg/m² (underweight), 18.6-24.9 kg/m² (normal weight), 25.0-29.9 kg/m² (overweight), ≥30.0 kg/m² (obese). WC, WHR, and WHtR were used as measures of abdominal fat layers. Standardized measurements of waist and hip circumference (in cm) were obtained at the clinical examination. WHR was calculated as the WC (in cm) divided by the hip circumference (in cm), and WHtR was calculated as the WC (in cm) divided by the body height (in cm).

Physical exercise

Weekly average duration of leisure time physical exercise during the last year was assessed with two questions: 1) reporting of the number of hours of light activity (no sweating or being out of breath) per week, and 2) reporting of the number of hours of hard activity (sweating or being out of breath) per week. Travel to work was counted as leisure time physical exercise. Both questions allowed 4 response options (0, <1, 1-2 and ≥3 hours/week).

Based on the information about frequency of light and hard activity, the participants were subdivided into categories of inactive to very low activity (<3 hours of light activity and/or 0 hour/week of hard activity) and low to high activity (≥3 hours of light activity and/or ≥1 hours/week of hard activity).

FM and chronic musculoskeletal pain

Information on FM was obtained from the questionnaire, where the participants were asked to respond (yes/no) to the question "Have a doctor ever said that you have fibromyalgia (fibrositis/chronic pain syndrome)?". Regarding chronic musculoskeletal pain the participants were asked to report whether they had suffered from musculoskeletal pain of at least 3 months' duration during the last year (yes/no) by the question: "During the last year, have you had pain and/or stiffness in your muscles and limbs that lasted for at least 3 consecutive months?". If "yes", they were asked to indicate pain localization, i.e., by ticking off one or several of the following nine body areas; neck, shoulders, elbows, wrist/hands, upper back, low back, hips, knees and/or ankles/feet. Based on number of pain sites, the participants were subdivided into four subgroups: 1) 0 pain sites/reporting no chronic musculoskeletal pain, 2) 1-2 chronic pain sites, 3) 3-5 chronic pain sites, and 4) ≥6 chronic pain sites.

Diabetes and hyperglycemia

The presence of DIA was measured by the question "Do you have, or have you ever had, diabetes?" with the response options "yes" or "no". In addition, women demonstrating

increased glucose level (GL) were included in the same subgroup. This inclusion was owed to the relation between DIA and obesity[19,22] and the report of high prevalence of metabolic syndrome among women with FM[29], together with different severity of impaired glucose regulation[57]. Hyperglycemia may indicate an early stage of DIA, and is a metabolic disturbance whereby excess abdominal body fat is likely[28]. Measurement of non-fasting GL was obtained with a venous blood sample at the clinical examination. The present study defines hyperglycemia as a random GL of ≥11.1mmol/l. This is a recommended cut-point for 2-hours oral glucose tolerance test in the diagnosing of DIA[57], and is previously used as a boundary for random glucose test in the determination of prevalence of DIA and hyperglycemia[58].

Statistical analyses

In the first part of the analyses, based on the information on FM, DIA, and GL, the participants were subdivided into four groups reflecting their pathological status: 1) reporting neither DIA and/or GL ≥11.1 mmol/l, nor FM (healthy), 2) reporting FM without DIA and/or GL ≥11.1 mmol/l (FM), 3) reporting DIA and/or GL ≥11.1 mmol/l without FM (DIA/GL), and 4) reporting both FM and DIA and/or GL ≥11.1 mmol/l (FM/DIA/GL).

Data were assessed using descriptive statistics. The distribution of variables across the different subgroups was analyzed using crosstabs. Mean and standard deviation of measures across the different subgroups were analyzed using frequencies. A general linear regression was applied to estimate mean differences with 95% confidence interval (CI) in BMI and measures of abdominal fat layers (i.e., WC, WHR, and WHtR as dependent variables) between the different subgroups. Potentially confounding factors were included in multiple linear regression analyses separately and together. Potentially confounding factors were age (10 years categories), smoking (never, former, current, unknown), leisure time physical exercise (low to high activity, inactive to very low activity, unknown), parity (no births, 1 birth, ≥2 births, unknown), education (<10 years, 10-12 years, ≥13 years, unknown), and psychological well-being (depressed, somewhat happy, happy, unknown), and all final analyses were adjusted for these factors. Trend tests across subgroups of FM, DIA, and GL, and of chronic pain affliction were done by threating the subgroups as ordinal variables in multiple linear regression analyses.

Distributions of comorbidities (i.e., athrosis, fatigue, insomnia, and functional restraining pain, illnesses or injuries) across the subgroups were analyzed using crosstabs. To evaluate whether levels of BMI and measures of abdominal fat layers among women in the

subgroups of FM and DIA/GL ≥11.1 mmol/l were independent of each other, additional general linear regression analyses were done, where crude measures of abdominal fat layers (i.e., WC and WHR) and BMI among healthy women and women in the subgroup of FM, DIA/GL, or FM/DIA/GL were compared. We conducted stratified (low to high activity vs. inactive to very low activity) analyses to evaluate the effect of physical exercise on the relations between number of chronic pain sites/FM, and BMI and measures of abdominal fat layers. Statistical analyses were done as in the main part, but without adjusting for leisure time physical exercise in the final analyses. To evaluate whether other conditions could affect the results of the second part, supplementary analyses were done. In addition to the primary excluding factors, women reporting other chronic diseases (i.e., DIA, osteoporosis, rheumatoid arthritis, arthrosis, morbus Bechterew, hypothyroidism, or the collective term "other long-term diseases") were excluded, and the same statistical analyses as in the main part were then done. P <0.001 was considered as statistical significant in all estimates. All statistical analyses were carried out using SPSS statistics (version 17.0).

RESULTS

Associations between FM, metabolic disturbances and body fat

Participant characteristics according to BMI are presented in Table 1.

Table 1. Participant characteristics categorized by body mass index*. Percentages are presented as proportions of study population for the subgroups, and as proportion within categories for remaining variables.

	Underweight		Normal weight		Overweight		Obese	
Age, mean (SD)	43.4	(19.7)	43.9	(15.8)	51.1	(16.4)	54.2	(16.4)
Women, % (no.)	1.1	(307)	45.5	(13,103)	36.0	(10,377)	17.4	(5,001)
Healthy[a], % (no.)	1.1	(287)	46.9	(12,235)	35.8	(9,349)	16.2	(4,226)
FM, % (no.)	1.0	(16)	34.4	(571)	39.5	(655)	25.2	(418)
DIA/GL, % (no.)	0.4	(4)	29.8	(288)	35.6	(345)	34.2	(331)
FM/DIA/GL, % (no.)	0.0	(0)	14.3	(9)	44.4	(28)	41.3	(26)
Inactive[b],% (no.)	41.0	(126)	34.6	(4,531)	40.3	(4,178)	47.2	(2,361)
Smoking[c], % (no.)	50.8	(156)	34.9	(4,578)	26.5	(2,755)	22.1	(1,103)
Higher educ.[d], % (no.)	33.2	(102)	39.6	(5,189)	26.7	(2,773)	17.6	(880)
Depressed, % (no.)	3.9	(12)	3.2	(425)	3.0	(315)	3.0	(151)
Parity, mean (SD)	2.5	(1.3)	2.4	(1.4)	2.4	(1.4)	2.4	(1.4)
WC, mean (SD)	64.5	(4.4)	73.1	(5.9)	83.5	(6.7)	97.5	(9.4)
WHR, mean (SD)	0.74	(0.05)	0.77	(0.05)	0.81	(0.05)	0.84	(0.06)
WHtR, mean (SD)	0.39	(0.03)	0.44	(0.04)	0.51	(0.04)	0.60	(0.06)

Abbreviations: FM = fibromyalgia without diabetes and/or glucose level ≥11.1mmol/l; DIA/GL = diabetes and/or glucose level ≥11.1mmol/l without fibromyalgia; FM/DIA/GL = fibromyalgia and diabetes and/or glucose level ≥11.1mmol/l; WC = waist circumference; WHR = waist-to-hip ratio; WHtR = waist-to-height ratio

*According to the cut points suggested by the World Health Organization

[a]Healthy defined as those who reported no fibromyalgia or diabetes and/or glucose level ≥11.1 mmol/l

[b]Inactive to very low activity

[c]Current smoker

[d]Reported an education of ≥13 years

Mean age increased along with increasing BMI. Most women in the study population were normal weight. Among the different subgroups, healthy women showed highest percentage of normal weight, whereas percentages of overweight and obese increased with FM, DIA/GL, and were highest in the FM/DIA/GL subgroup. Measures of abdominal fat layers (i.e., WC, WHR, and WHtR) increased with BMI. Percentages of current smokers decreased with increasing BMI. Apart from the category of underweight, percentages of women with higher education showed a similar trend, whereas percentages of inactive increased. The proportions of depression and parity were similar across BMI categories.

Table 2. Mean and mean difference (MD) of body mass index (BMI) and waist circumference (WC) between healthy women, and women with fibromyalgia (FM), diabetes and/or glucose level ≥11.1 mmol/l (DIA/GL), and fibromyalgia/diabetes and/or glucose level ≥11.1 mmol/l (FM/DIA/GL).

	No. of women	Mean value (SD)	Crude MD	Multi-adjusted[b] MD (95% CI)	P_{trend}
BMI, kg/m^2					
Healthy[a]	26,097	25.9 (4.4)	0.0	0.0 (Reference)	
FM	1,660	27.3 (4.8)	1.3	0.9 (0.7-1.2)	
DIA/GL	968	28.5 (5.7)	2.5	1.8 (1.5-2.0)	
FM/DIA/GL	63	30.0 (5.0)	4.0	3.1 (2.0-4.2)	<.001
WC, cm					
Healthy[a]	26,097	80.5 (11.1)	0.0	0.0 (Reference)	
FM	1,660	84.2 (11.8)	3.7	2.4 (1.8-2.9)	
DIA/GL	968	87.9 (13.9)	7.3	4.8 (4.1-5.5)	
FM/DIA/GL	63	91.2 (12.8)	10.7	7.7 (5.1-10.3)	<.001

[a]Healthy defined as those who reported no fibromyalgia or diabetes and/or glucose level ≥11.1 mmol/l
[b]Adjusted for age (20-29, 30-39, …, ≥70 years), physical exercise (low to high activity, inactive to very low activity, unknown), smoking (never, former, current, unknown), education (<10 years, 10-12 years, ≥13 years, unknown), parity (0, 1, ≥2, unknown), psychological well-being (depressed, somewhat happy, happy, unknown)

Table 2 presents mean values and adjusted mean differences of BMI and WC between healthy women, and women in the subgroups of FM, DIA/GL, and FM/DIA/GL. According to cut points of BMI, mean values for both healthy women, and women in the FM and DIA/GL subgroups were within the category of overweight (i.e., 25.0-29.9 kg/m²). Mean value for FM/DIA/GL subgroup were within the category of obese (i.e., ≥30.0 kg/m²). Correspondingly, both BMI and WC increased significantly in a dose-response manner between FM, DIA/GL, and FM/DIA/GL, referencing healthy women (*P* trend <.001). Using WHR or WHtR as measure of abdominal fat layers resulted in same trends with mean differences increasing significantly across the subgroups (*P* trend <.001 for both measures), i.e., the FM/DIA/GL subgroup showed the largest difference from healthy women (results not shown).

Associations between chronic musculoskeletal pain and body fat

Table 3 presents participants characteristics according to number of chronic pain sites and FM. Women with ≥6 pain sites and women with FM tended to be older than healthy women and women with ≤5 pain sites. The percentage of women with higher education decreased with increasing number of pain sites/FM, whereas the percentages of women who reported to be inactive, current smoker, and depressed increased with increasing level of pain affliction.

Table 3. Participant characteristics categorized according to number of chronic pain sites, and fibromyalgia (FM). Percentages are proportions within categories.

	Healthy[d]		1-2 pain sites		3-5 pain sites		≥6 pain sites		FM	
Women, no.	15,329		1,544		1,964		1,145		1,770	
Age, mean (SD)	45.4	(17.2)	47.7	(17.3)	49.1	(16.5)	52.4	(16.0)	52.1	(12.1)
Inactive[a], % (no.)	34.5	(5,296)	40.4	(624)	41.6	(818)	49.3	(564)	47.5	(840)
Smoking[b], % (no.)	26.8	(4,109)	28.9	(446)	35.0	(668)	39.8	(456)	41.2	(729)
Higher educ.[c], % (no.)	37.3	(5,718)	34.1	(526)	27.2	(535)	18.7	(214)	16.0	(284)
Depressed, % (no.)	1.9	(294)	2.8	(44)	4.7	(93)	4.6	(53)	8.2	(145)
Parity, mean (SD)	2.4	(1.4)	2.4	(1.5)	2.3	(1.4)	2.4	(1.6)	2.3	(1.4)

[a]Inactive to very low activity
[b]Current smoker
[c]Reported an education of ≥13 years
[d]Healthy defined as those who reported no musculoskeletal pain

Mean values and mean differences of BMI and WC between healthy women, women with different number of pain sites, and women with FM are presented in Table 4. Both BMI and WC increased significantly in a dose-response manner with increasing level of pain affliction, referencing healthy women (*P* for trend <.001).

Table 4. Mean and mean difference (MD) of body mass index (BMI, upper panel) and waist circumference (WC, lower panel) between categories with different pain affliction, i.e., healthy women, women with 1 to ≥6 chronic pain sites, and fibromyalgia (FM).

Categories of pain affliction	No. of women	BMI, kg/m^2, mean (SD)	Crude MD	Multi-adjusted[b] MD (95% CI)	P_{trend}
Healthy[a]	15,329	25.6 (4.3)	0.0	0.0 (Reference)	
1-2	1,544	26.1 (4.5)	0.5	0.4 (0.2-0.7)	
3-5	1,964	26.6 (4.8)	1.1	0.9 (0.7-1.1)	
≥6	1,145	26.9 (5.0)	1.4	0.9 (0.7-1.2)	
FM	1,770	27.4 (4.9)	1.8	1.3 (1.0-1.5)	<.001

Categories of pain affliction	No. of women	WC, cm, mean (SD)	Crude MD	Multi-adjusted[b] MD (95% CI)	P_{trend}
Healthy[a]	15,329	79.5 (10.8)	0.0	0.0 (Reference)	
1-2	1,544	81.5 (11.3)	2.1	1.6 (1.1-2.2)	
3-5	1,964	82.8 (12.0)	3.3	2.5 (2.0-3.0)	
≥6	1,145	84.0 (12.6)	4.6	2.9 (2.2-3.5)	
FM	1,770	84.5 (12.0)	5.0	3.2 (2.6-3.7)	<.001

[a]Healthy defined as those who reported no musculoskeletal pain
[b]Adjusted for age (20-29, 30-39, …, ≥70 years), physical exercise (low to high activity, inactive to very low active, unknown), smoking (never, former, current, unknown), education (<10 years, 10-12 years, ≥13 years, unknown), parity (0, 1, ≥2, unknown), psychological well-being (depressed, somewhat happy, happy, unknown)

Using WHR or WHtR as measure of abdominal fat layers resulted in same trends with mean differences increasing significantly across subgroups (*P* trend <.001 for both measures), i.e., the FM subgroup showed the largest difference from healthy women (results not shown).

Influence of physical exercise on chronic musculoskeletal pain and body fat

Participant characteristics categorized by level of physical exercise are presented in Table 5. Women reporting lowest physical exercise level were on average oldest, exhibit highest mean values of BMI and measures of abdominal fat layers (i.e., WC, WHR, and WHtR), and reported highest percentages of current smokers and depressed, as well as lowest percentage of higher education. The percentages of women with no or very low activity increased with increasing number of pain sites/FM.

Table 5. Participant characteristics categorized according to level of physical exercise. Percentages are presented as proportions of study population for the subgroups, and as proportion within categories for remaining variables.

	Low to high activity		Inactive to very low activity	
Age, mean (SD)	41.6	(14.9)	48.9	(16.1)
Healthy[a], % (no.)	62.6	(8,669)	37.4	(5,173)
Pain affliction, 1 to ≥6 pain sites, % (no.)	56.9	(2,201)	43.1	(1,668)
1-2 pain sites, % (no.)	58.3	(803)	41.7	(574)
3-5 pain sites, % (no.)	58.1	(966)	41.9	(697)
≥6 pain sites, % (no.)	52.1	(432)	47.9	(397)
FM, % (no.)	48.6	(621)	51.4	(657)
Smoking[b], % (no.)	27.5	(3,165)	33.4	(2,506)
Higher educ.[c], % (no.)	45.1	(5,184)	25.0	(1,877)
Depressed, % (no.)	2.5	(286)	3.3	(246)
Parity, mean (SD)	2.4	(1.4)	2.4	(1.4)
BMI, mean (SD)	25.3	(4.1)	26.4	(4.7)
WC, mean (SD)	78.3	(10.3)	82.1	(11.6)
WHR, mean (SD)	0.78	(0.06)	0.80	(0.06)
WHtR, mean (SD)	0.47	(0.06)	0.50	(0.07)

Abbreviations: FM = fibromyalgia; BMI = body mass index; WC = waist circumference; WHR = waist-to-hip ratio; WHtR = waist-to-height ratio

[a]Healthy defined as those who reported no musculoskeletal pain

[b]Current smoker

[c]Reported an education of ≥13 years

Figure 1 presents the combined effect of physical exercise and chronic musculoskeletal pain on multi-adjusted mean values of BMI (A) and WC (B). Overall, the most active women had lower BMI and WC than the least active women across all pain categories. Physical exercise showed curved linear relations between level of pain affliction, and BMI and WC among women at both activity levels. The subgroup of FM tended to have highest differences in mean BMI and mean WC between the different levels of physical exercise. Moreover, women with FM who were inactive or had a very low activity level had a markedly higher BMI and WC than women in the same exercise category without FM.

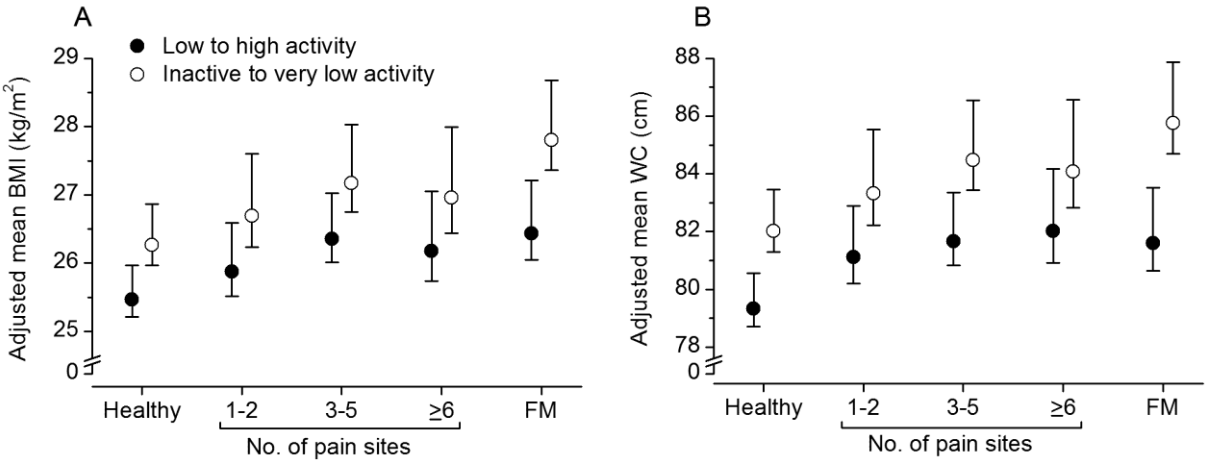

Figure 1. Multi-adjusted mean values of body mass index (BMI) and waist circumference (WC) between levels of physical exercise, categorized by number of chronic pain sites, and fibromyalgia (FM). Error bars indicate 95% CI. Values are adjusted for age (20-29, 30-39, …, ≥70 years), smoking (never, former, current, unknown), education (<10 years, 10-12 years, ≥13 years, unknown), parity (0, 1, ≥2, unknown), psychological well-being (depressed, somewhat happy, happy, unknown).

Using WHR or WHtR as measure of abdominal fat layers resulted in same trends as using WC (*P* trend <.001 for both comparisons) (results not shown).

Correlation between BMI and WC

A scatter plot showing the associations between crude BMI and WC within healthy women, women in the subgroups of FM, DIA/GL, and FM/DIA/GL are presented in Figure 2A. Separate regression lines for women in the different subgroups are shown in Figure 2B.

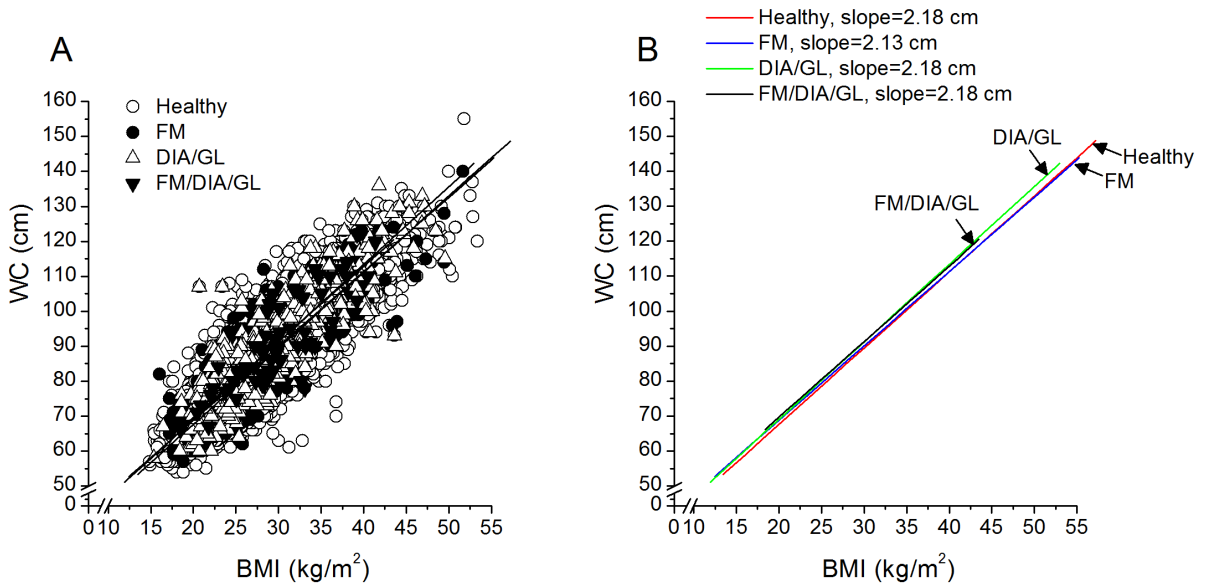

Figure 2. Scatter plot of the association between crude waist circumference (WC) and body mass index (BMI) among healthy women and women with fibromyalgia (FM), diabetes and/or glucose level ≥11.1 mmol/l (DIA/GL), and fibromyalgia/diabetes and/or glucose level ≥11.1 mmol/l (FM/DIA/GL) (figure 2A). Separate regression lines are shown for women in the different subgroups (indicated by arrows) (figure 2B).

The slopes of the regression lines were 2.13 cm for women with FM, and 2.18 cm for healthy women, and women in DIA/GL and FM/DIA/GL subgroups (figure 2B), indicating a similar body fat distribution within the different subgroups, and a high correlation between BMI and WC. Using WHR as measure of abdominal fat layers resulted in same trends as using WC (result not shown).

Distribution of comorbidities among women with FM

Table 6 presents the percentages of comorbidities among women with FM, categorized by level of physical exercise. Women with FM who were inactive or had a very low activity level, reported highest percentages of insomnia, fatigue, arthrosis, pain which reduces leisure time activity or working capacity, and of other long-term illnesses or injuries that impair everyday function. It should be noted that the percentages reflect different responding rate across exercise levels and across measured comorbidities.

Table 6. Percentage of comorbidities among women with fibromyalgia, categorized according to level of physical exercise.

	Low to high activity		Inactive to very low activity	
Insomnia, % (no.)	27.3	(169)	31.8	(209)
Fatigue, % (no.)	10.9	(68)	14.0	(92)
Reduced leisure time activity, % (no.)	81.4	(505)	88.0	(578)
Considerably reduced working capacity , % (no.)	42.1	(261)	50.4	(331)
Long-term illness or injury[a], % (no.)	62.5	(388)	65.2	(428)
Arthrosis, % (no.)	24.0	(149)	30.6	(201)

[a]Illness or injury of physical or psychological nature that impairs everyday function

DISCUSSION

The main objective of the present study was to investigate the associations between FM, BMI, and measures of abdominal fat layers. A second objective was to investigate whether severity of chronic musculoskeletal pain (i.e., defined by number of pain sites/FM) are related to levels of BMI and measures of abdominal fat layers. Additionally, it was investigated whether level of leisure time physical exercise may influence the above mentioned relations.

The analyses revealed positive associations between prevalence of FM, and levels of BMI and measures of abdominal fat layers. These associations were further independent of metabolic comorbidities of DIA or GL ≥11.1mmol/l, and the presence of FM together with one or both of these conditions resulted in even higher BMI and measures of abdominal fat layers. When examining the independent associations between prevalence of FM, DIA and/or GL ≥11.1mmol/l, and FM and DIA and/or GL ≥11.1mmol/l together, and measures of

abdominal fat layers or BMI, these associations showed no differences in body fat distribution, i.e., BMI and measures of abdominal fat layers increased in concurrence with each other in all subgroups.

Results also indicated dose-response relations between number of chronic pain sites, with FM as the extreme endpoint, and levels of BMI and measures of abdominal fat layers. Also here, high measures of abdominal fat layers within FM reflected concurrent high BMI. Assessing effect of physical exercise, these relations showed curved linear relations to number of chronic pain sites among women without FM, as the women with ≥6 pain sites tended to have lower or similar BMI and measures of abdominal fat layers, compared to women with 3-5 pain sites at the same activity level. Physical exercise moderated the dose-response associations, as women reporting the highest activity level in each subgroup had lowest BMI and measures of abdominal fat layers. This effect was particularly pronounced within the FM subgroup.

Given the cross-sectional design of the study, causalities cannot be inferred. However, chronic widespread pain is thought to be best represented as a continuum from localized to more generalized pain[7,59], whereby FM represent the severe end[7]. Then, the subgroups with different numbers of chronic pain sites can indicate different cross-sections of a continuum of chronic pain. Additionally, previous prospective[46,60,61] and cross-sectional studies[15,34,35,61] have reported positive associations between level of BMI, and the risk of and/or presence of pain and pain severity, including within FM patients[13,14]. Conversely, weight loss in women with FM seems to reduce pain[16]. A causal and linear relation between level of overall body fat accumulation and severity of chronic pain may then be hypothesized. Moreover, FM has been associated with higher prevalence of metabolic syndrome[29], and increased prevalence of FM is reported among DIA patients[62]. Metabolic syndrome may indicate an early stage of DIA, with impaired glucose regulation and abdominal obesity (i.e., WC ≥80cm among European women) acknowledged as important features of both conditions[19,28]. It is then possible that the subgroups of FM, DIA/GL, and FM/DIA/GL may indicate different cross-sections of a continuum with increasing involvement of metabolic disturbances. Accordingly, high BMI and/or abdominal fat layers has been reported as a risk factor for musculoskeletal pain[46,60,61], FM[14], and DIA[18,19,22].

FM, metabolic disturbances, and body fat distribution

Increased prevalence of metabolic syndrome has been reported among women with FM, including higher abdominal fat layers measured as increased WC and WHR, compared to

healthy controls[29]. Since BMI or body mass did not differ significantly between women with FM and healthy controls, Loevinger and co-workers (2007) [29] suggested that obesity in many women with FM[11-13] may reflect a bias toward central adiposity.

Based on the current findings, an independent association between FM and abdominal obesity is questioned as WC and WHR were highly correlated with BMI among women in the subgroups of FM and FM/DIA/GL. Further, the similar correlation within and between all subgroups of FM and DIA/GL ≥11.1mmol/l is noteworthy, since a strong relation between the pathophysiology of DIA and hyperglycemia, and centralization of body fat has been indicated [19,22,23,28]. Thus, independent body fat centralization does not seem to be a pathological feature of either FM, DIA and/or GL ≥11.1mmol/l, or the combination of these conditions, but rather reflects concurrent presence of overweight or obesity in general.

Chronic musculoskeletal pain, body fat, and related pathophysiological concomitants

Despite the precluded possibility to draw conclusions regarding causations, possible explanations of the current findings may be suggested. First, the mechanical forces on the weight-bearing joints will increase as a consequence of increasing body mass, which further is related to load-related chronic pain as back pain[15,34,46,60]. Together with the reports from Loevinger[29], there are findings of associations between high BMI and pain in nonweight-bearing body sites[34,35,61], and of a complex interplay between high BMI, pain, and FM comorbidities[11-13,15,16,59]. It is then likely that other pathophysiological mechanisms related to body fat accumulation overlap with those of pain and metabolic diseases. Among these, perturbations of the immune and neuroendocrine systems have to be considered.

Neuroendocrine perturbations

HPA axis dysregulation is assumed to be a feature in the pathogenesis of FM, with negative impact on pain perception and pain inhibition[5-8]. Further, this feature is tightly related to SNS activation and to a dysfunction in the stress response system[5-7,9,21,32,33]. Such dysregulation is thought to be part of the pathogenesis of other pain states as well, indicated by alteration of the physiologic responses required for adequate stress management and pain inhibition[6-7]. Finally, similar mechanisms are suggested to have an adverse impact on body fat accumulation, and on the development of metabolic disturbances like metabolic syndrome and DIA[21,22,24,30,31].

HPA axis dysregulation includes aberrant glucocorticoid signaling, and abnormal cortisol secretion is reported in obesity[22,25], as well as in other conditions of a dysfunctional

stress response system like chronic pain states and FM[5,7,8,32,33], and metabolic syndrome[21,24,31]. Prolonged increase in circulating glucocorticoids is related to higher energy intake/expenditure ratio, thereby increasing the probability of developing obesity and metabolic disturbances[21,24]. Accordingly, there are indications of close relations between HPA axis dysregulation, and increased BMI and/or abdominal fat layers[21,24], including in FM[11], despite seeming incongruous reports regarding the pattern of abnormal glucocorticoids secretion. Additionally, also dysautominia in FM[7,9,10] shows similarities to disturbances which likely promote positive energy ratio and development of obesity and metabolic syndrome[30,31]

Low-graded, systemic inflammation

Obesity has been referred to as an unconventional type of low-graded, systemic inflammatory state, with marked changes in the secretion functions of adipocytes and macrophages, and with elevated serum concentrations of inflammatory markers[19,21,26]. Likewise, chronic musculoskeletal pain[7,27] and FM[40,63] display signs of inflammatory conditions. It has even been hypothesized that the origin of all pain is inflammation and the inflammatory response[64], including inflammatory hypothesis of pain syndromes like FM[65]. SNS activation and disturbances of the HPA axis are closely associated with prolonged secretion and increased circulating levels of proinflammatory cytokines[21]. Elevated release of neurotransmitter substance P is thought to stimulate release of proinflammatory cytokines closely related to pain and FM[7,27,40,63,65], and may contribute to an up-regulation of painful stimuli and lead to widespread pain[2,5,64]. Proinflammatory cytokines have been found to induce or facilitate both inflammatory and neuropathic pain as well as hyperalgesia[27,40] and increased pain intensity in FM patients[63]. Several of these cytokines have been associated with obesity, metabolic syndrome, DIA, and chronic stress with derangement of the metabolic equilibrium[21,31,32,41]. Further, they have been associated with the presence of comorbid symptoms of FM like fatigue, depression, and sleep alterations[32,65]. Previous reports[21], including findings among FM patients[11], show relations between increasing circulating levels of inflammatory markers and accumulation of body fat. These reports may then substantiate the present associations between low-graded, systemic inflammation, obesity, chronic pain, and metabolic disturbances.

Taken together, obesity has been recognized to be a disease of energy regulation, rather than a simple consequence of a disadvantageous lifestyle[22,25,26,30]. Beside energy consumption, accumulation of body fat is likely dependent on the energy intake, which is further thought to be regulated by a complex interplay between factors as cytokines, insulin,

and several neurotransmitters [22,25,26,30]. Similarly, metabolic syndrome and DIA[21,22,24,30-32,41], as well as chronic pain and FM[6,7,27,32,33] are related to disturbances in the same interplay. Then, the current findings that increased body fat accumulation is associated with the presence of chronic musculoskeletal pain, FM, and DIA/GL ≥11.1mmol/l, are likely to partly be explained by common pathophysiological mechanisms of disturbances in the immune and neuroendocrine systems.

Furthermore, it has been proposed that these abnormalities are associated with accumulation of the abdominal visceral fat compartment in particular[20-25,30]. The anatomical location of the visceral adipocytes and their drainage by the portal vein system have been suggested to be critical[19,23]. This, in combination with their innate capacity to mobilize free fatty acids, and the secretion of inflammatory markers and other lipid and vasoactive substances in adipose tissue may then contribute to the relation[19,21-23]. In addition, altered cortisol secretion and the high density of glucocorticoid receptors in visceral adipose tissue, together with inhibited sex steroids and growth hormones secretion may lead to insufficient cortisol counteraction[21-25]. However, based on the present results, the idea needs further elucidation. Despite this view of the abdominal visceral fat layer as a relative high-risk fat depot, it amounts to only a lesser extent of the total adipose tissue mass[54,66]. Contrary, the abdominal subcutaneous fat compartment has a higher fat storage capacity, and the absolute risk attributed to this fat depot may then be greater[66]. Therefore, the question whether the effects of abdominal visceral and subcutaneous fat compartments actually differ in risk contributions may be ambiguous[20,25,50,54,66]. Similar, there are inconsistent reports regarding whether measures of abdominal fat layers (e.g., WC or WHR) are better, or make an additional contribution in the prediction of conditions related to the above-discussed disturbances[22,50,67-69], compared to measures of overall body fat (such as BMI)[70-72].

The current associations did not exhibit any relation to increased measures of abdominal fat layers independent of concurrent increased BMI. However, the measures do not reflect the independent contribution of each abdominal fat compartment. The linear relation between BMI and measures of abdominal fat layers within all study groups may then include bias toward different contributions of the subcutaneous and visceral fat layers between and/or within the subgroups. Therefore, future studies must be conducted to state whether a high abdominal visceral fat layer is an independent phenomenon in any of the subgroups, and/or whether such an increase has an additional risk enhancing beyond a high abdominal subcutaneous fat layer or general obesity. However, it can be suggested that neither central fat

accumulation nor peripheral fat accumulation are independent features of the examined conditions, but rather presence together.

Influence of physical exercise on body fat and chronic musculoskeletal pain

Previous studies have reported that regular, well-adjusted physical exercise can improve tender-point pain threshold and reduce pain in FM and other inflammatory states[40,47,48]. Conversely, inactivity increases the risk of chronic musculoskeletal pain[45,46] and FM[14].

The present study design prevents interference about causality, and the directionality of the relation between physical exercise and pain affliction cannot be determined. Regarding influence on body fat, the most active women within each subgroup had markedly lower BMI and measures of abdominal fat layers, compared to the least active. These findings imply a reverse impact of physical exercise on rate of body fat accumulation. Regular physical exercise has shown to affect body composition reflected by lower abdominal fat layers[38,39] and improved weight control[39]. Contrary, obesity may lead to inactivity[36]. Thus, differences in BMI and measures of abdominal fat layers between the most and the least active women in the current study may reflect impact on energy regulation brought about by exercise, and/or a restraining effect of overweight or obesity on exercise participation. However, a healthy body composition is likely to include more appropriate mechanical forces on weight-bearing joints and thereby lesser extent of load-related pain.

Moreover, since obesity may reflects a pathological process as well[22,25,26,30], it is likely that physical exercise influences pathophysiological resemblances of the investigated conditions. Independent reverse relation between level of physical exercise and degree of low-graded, systemic inflammation has been suggested[42]. Initially, exercise enhance production of inflammatory substances, whereby increasing circulating levels of anti-atherogenic and anti-inflammatory cytokines then restrict this inflammatory response by inhibition of inflammatory substances, inducing lipolysis and increasing fat oxidation[40-43]. Additionally, exercise training has the ability to modify regulation of the autonomic nervous system activity through increased parasympathetic tone, and decreased SNS activity[43,44]. Together, these events might also suppress appetite[26].

Thus, physical exercise may act directly on the pathophysiological features of chronic musculoskeletal pain, FM, and morbid body fat accumulation. The exact effect is likely to depend on type, frequency, duration and/or intensity of exercise[37,42,47,48], and on individual factors such as physical fitness[37] and disease characteristics[40,44,47].

Exercise effect within the FM group

The effect of physical exercise was particularly pronounced within the FM group. Differences in mean BMI and mean WC between the physical exercise levels in the three pain sites groups were 0.8 kg/m^2 and 2.1-2.8 cm, whereas FM showed differences of 1.4 kg/m^2 and 4.1 cm, respectively.

FM represents a complex pain syndrome, with several subgroups regarding comorbidities and pathological mechanisms[2-4,73]. Despite likely benefits of physical exercise[40,47-49], the effects as well as the exercise participation may differ according to the clinical picture. In inadequate doses and/or within certain FM subgroups, exercise may contribute to increased pain and other symptoms of FM[40,47,74,75], likely followed by restrained activity level and energy expenditure.

Based on the accessible information in the HUNT data, supplementary analyses investigated the distribution of comorbidities of athrosis, fatigue, insomnia, and functional restraining pain, illnesses or injuries within the current exercise subgroups. The prevalence of all these comorbidities were highest among the less active women, and thereby among women with highest BMI and WC, i.e., the differences in reported prevalence of the comorbidities range from 2.7% to 8.3% between the least and most active women with FM.

These findings are in line with current researches. In addition to a relation between high BMI, and risk of and/or presence of pain and pain severity[13,14,34,35,46,60,61], there are reported associations between presence of pain, and impaired psychological health[34,59], poor sleep quality, reduced physical activity[59], and lower quality of life[13]. Similar, a high BMI is associated with disturbed sleep[11,15], physical impairment[11-13], and low levels of physical activity[36] and quality of life[13]. At the contrary, weight loss, partly attributed to physical exercise, is found to improve pain and comorbid symptoms of FM[16]. Further, well-adjusted exercise has shown to bring about improvement in pain[40,47,48], functional status, and psychological and overall well-being[37,47-49], as well as to be related to a more healthy body mass[38,39].

Thus, it is possible that the current exercise levels reflect different pathological subgroups, whereby the most physically active women with FM represent a subgroup which is less affected by comorbidities. Compared to the least active, they may then be less influenced of any additional adverse impact of comorbidities on body fat accumulation, exercise participation, and/or benefits of exercise.

Exercise effect between levels of chronic pain sites

The curved relation between physical exercise, number of chronic pain sites, and body fat accumulation needs further elucidation. Women with ≥6 pain sites without FM may represent a subgroup with high prevalence of both known and unknown comorbidities, and with loss of body mass as a pathologic feature. Additional analyses with exclusions of other chronic diseases failed to identify a possible cause of the curved relation. An unmeasured, but relevant comorbidity in chronic pain states is cachexia, a wasting syndrome with detrimentally impact on several ongoing pathophysiologic processes[76-77]. Although the underlying pathophysiological mechanisms of cachexia are unclear, they likely involve disturbances in interplay among cytokines, neuropeptides, and neurotransmitters[76-77]. Unfortunately, no questions in the HUNT Study could be used to indicate whether prevalence of this or corresponding conditions were especially high among women with ≥6 pain sites.

Another interpretation is a level off in the dose-response relation between body fat accumulation and chronic pain at the level of ≥6 pain sites. However, if FM represents the severe end of the spectrum of chronic musculoskeletal pain, this explanation is unlikely to be valid. Thus, the exact explanation of the curved relation needs further investigations.

Strengths and limitations

The current study has some strengths and limitations, which should be considered in the interpretation of the results. Although the study found strong associations between chronic musculoskeletal pain, FM, conditions of metabolic disturbances, BMI, and measures of abdominal fat layers, the cross-sectional design prevent drawing conclusions about directionalities and causations. Thus, prospective studies must be performed to elucidate any causality of the associations.

The use of a large unselected population of adult women minimizes random errors, and the study sample is believed to represent a cross-section of the general female population in Norway. It is though not clear whether the results can be applied to other study populations differing in age, sex, or ethnicity.

The use of self-administered questionnaires in assessing independent variables as FM, chronic musculoskeletal pain, DIA, and physical exercise, may induce personal misclassifications as it allows for subjective interpretation of the questions, including individual perception of the physical exercise[78]. The HUNT data do neither include assessment of different exercise types nor fitness components, which could, in addition to impact of occupational physical workload, be important in the interpretation of the

results[37,78,79]. However, a validation study of the present physical exercise questionnaire showed that the "light" physical exercise question had poor reproducibility in a random sample of men, while the "hard" physical exercise question was found to be a useful measure of vigorous physical exercise in the same study population[79]. Likewise, the questions assessing chronic musculoskeletal pain have been shown to provide useful and reliable information on musculoskeletal symptoms[80]. However, none of the questionnaires are validated specific to the present study population of Norwegian women ≥20 years.

The division into subgroups of increasing pain affliction and metabolic disturbances may indicate different cross-sections of a continuum and thereby strengthen the confidence of the findings. Nevertheless, limitations in the analyses must be acknowledged. The subdivision of physical exercise levels is a merger of a previous used subdivision in HUNT 2[45], whereby the lowest activity level partly reflects WHO used boundary of insufficient activity in quantifying risk of health (i.e., <2.5 hours/week of light activity, <1 hour/week of vigorous activity)[17]. Nonetheless, attempt to investigate the effect of physical exercise on the associations between FM, metabolic disturbances, and measures of body fat accumulation failed, and the possibility of fallacious splitting cannot be ruled out.

In spite of using important excluding criteria and despite adjustment for several factors related to FM, pain, metabolic disturbances, and/or body fat accumulation, adjustment for additional comorbidities would be important. Bias due to confounding by unmeasured or unknown factors, such as genetic predisposition and sociopsychological factors cannot be ruled out. The supplementary analyses of any impact on body fat distribution had no adjustments. On the other hand, the crude measures of BMI and abdominal fat layers showed similar trends as their corresponding multi-adjusted measures, which strengthen the likelihood of similar results also among multi-adjusted measures.

The capability to estimate total body fat[50,53] and body fat distribution[50-52] differ between different anthropometric measurements. Here, BMI was used as a measure of total body fat, whereas WC was used as a measure of abdominal fat layers. Similar analyses with WHR and WHtR resulted in the same trends as with WC, but none of them distinguish between the abdominal subcutaneous and visceral fat compartments. As discussed, the associations do not reflect the independent contribution of abdominal visceral fat layer. Similar misclassification of overall body fat is possible, as BMI has limitations like the difficulty to predict body composition (e.g., inability to take into account contributions of fat-free mass versus fat mass)[50,53,55].

Conclusion

To summarize, there were dose-response associations between chronic musculoskeletal pain sites, FM, and levels of BMI and measures of abdominal fat layers. Physical exercise moderated these associations. However, the associations showed no differences in body fat distribution, as BMI and measures of abdominal fat layers increased in concurrence with each other among women with FM, DIA and/or GL ≥11.1 mmol/l, and FM and DIA and/or GL ≥11.1 mmol/l together, referencing healthy women. Therefore, based on the current cross-sectional study, the presences of chronic musculoskeletal pain and FM with or without metabolic comorbidities of DIA and/or GL ≥11.1 mmol/l are associated with increased BMI and measures of abdominal fat layers, whereby the accumulation of central fat seems to be dependent on concurrent overall body fat accumulation.

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