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FIBROMYALGIA:
BACKGROUND FACTORS AND
IMPACT ON MORTALITY AND ABILITY TO WORK

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ACADEMIC DISSERTATION

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To all Finnish twins

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ORIGINAL PUBLICATIONS

These studies are referred to in the text by their Roman numerals.

- I Markkula R, Järvinen P, Leino-Arjas P, Koskenvuo M, Kalso E, Kaprio J. Clustering of symptoms associated with fibromyalgia in a Finnish twin cohort. *Eur J Pain*. 2009;13(7):744-750.

- II Markkula R, Kalso E, Kaprio J. Risk factors for fibromyalgia-associated symptoms. (submitted)

- III Markkula, R., Kalso, E., Huunan-Seppälä, A., Koskenvuo, M., Koskenvuo, K., Leino-Arjas, P. & Kaprio, J. (2011) The burden of symptoms predicts early retirement: A twin cohort study on fibromyalgia-associated symptoms. *Eur. J. Pain*, 15, 741-747.

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ABBREVIATIONS

ACR	American College of Rheumatology
BDI	Beck Depression Inventory
BMI	body mass index
CI	confidence interval
COMT	catechol-O-methyltransferase
DNIC	diffuse noxious inhibitory control
DPN	diabetic polyneuropathy
DSM	Diagnostic and Statistical Manual of Mental Disorders
DZ	dizygote
EMG	electromyography
sEMG	surface electromyography
FM	fibromyalgia
HPA	hypothalamic pituitary adrenal (axis)
HR	hazard ratio
ICD	International Classification of Diseases
LC1	latent class 1 (in the twin sample of this study)
LC2	latent class 2 (in the twin sample of this study)
LC3	latent class 3 (in the twin sample of this study)
MZ	monozygote
NSAID	non-steroidal anti-inflammatory drug
OR	odds ratio
QST	Quantitative Sensory Testing
RA	rheumatoid arthritis
RR	risk ratio
SCID	structured clinical interview based on DSM IV criteria
SNP	single-nucleotide polymorphism
TTH	tension-type headache
WSP	widespread pain

ABSTRACT

Background and aims: Fibromyalgia (FM) is a syndrome with widespread pain (WSP), tenderness at specific points, and other symptoms such as fatigue and stiffness. Despite active research, open questions around FM remain. Competing theories as to its pathogenesis do not provide clinical tools for management or prevention. Though many studies have suggested that genetic factors play an obvious aetiological role, we do not know the extent to which heritability would affect occurrence of the syndrome. Neither do we know enough about other risk factors to be able to take preventive action. Because the diagnosis “fibromyalgia” is questioned, disliked, and even actively avoided by some clinicians, we cannot rely on registry data to reveal the prevalence of FM or in judging the effect of FM on work disability even in Finland, which has a comprehensive and trustworthy social insurance registry. Evidence is controversial concerning mortality associated with FM. The purpose of this study was to evaluate the prevalence, heritability, and other predictive factors of FM in a population-based sample. Another aim was to assess the impact of FM on work disability and mortality risk.

Material and methods: we used data of the older Finnish Twin Cohort, which originally comprised 17 357 twins born before 1958. The members of this cohort had participated in three surveys by replying to large health questionnaires in 1975, 1981, and 1990, with response rates of 89%, 84%, and 77%. Applying their responses to an FM question-set from 1990, we could classify this cohort into three latent symptom classes: LC1 with no or few FM-associated symptoms, LC2 with some symptoms, and LC3 with a high number of symptoms, resembling FM patients and thus serving as a proxy for FM (Study I). We then estimated the role of heritability as explaining the variance in this classification by using the data on zygosity of the twins and comparing twin pairs discordant for the classes (LC3 vs. LC1). To assess risk factors for LC3, we used data from the first two surveys. The variables for the regression analysis we chose from the literature. The participation of most twins in all three surveys enabled longitudinal assessment of these risk factors (Study II). Finally, we gathered the follow-up data on disability retirement and mortality by linkage of the twin cohort data with the data from the Finnish official pension registers, the Social Insurance Institution, and the Finnish Centre for Pensions. Respectively, linkage of our cohort data to the Population Register Centre (which covers all Finnish citizens) produced data on emigration and vital status of the twins (Study III).

Results: A total of 10 608 twins had replied to the FM-related questions in 1990 and could be classified in Study I. Their mean age was 43.4 ± 7.6 years. From each gender an almost equal 13% were classified into LC3. The statistical analyses estimated heritability in the three-category model as 50.5% (95% CI 44.9-55.9%) for additive genetic components and 49.5% (95% CI 54.1-55.1%) for unique environmental components, and in the four-category model as 45.6% (95% CI 40.4-50.4%) for additive genetic components and 54.4% (95% CI 49.6-59.6%) for unique environmental components.

In Study II, after the exclusions, 8 343 subjects remained in the analyses. All the putative risk factors for LC3 in the univariate analyses were statistically discernible, when adjusted for age and gender: back, shoulder, and neck pain, headache, migraine, poor sleep, high body mass index (BMI), physical passivity, infrequent exercise, and smoking. In the multivariable analyses, however, only headache, back and neck pain, poor sleep, and high BMI were significant. Frequent headache yielded the highest odds ratio (OR) of 6.8 (95% CI 3.7-12.4) and persistence of back pain yielded an OR of 4.7 (95% CI 3.3-6.7). In the pairwise analyses of twins, back pain and headache seemed independent of genetic confounding.

In Study III, a total of 9 760 individuals remained for the analysis of disability retirement and mortality, of whom 1 312 had already retired by 1990. During the 14-year follow-up, of the 8 448 at risk a total of 806 (9.5%) subjects retired due to disability. The cumulative incidence for disability retirement in general was 25.7% in LC3, 10.6% in LC2, and 6.8% in LC1. For disability retirement due to musculoskeletal disorders the cumulative incidences were 12%, 4%, and 2%. After adjustment for age, gender, body mass index, smoking, binge drinking, and depressive mode, the hazard ratio (HR) for general disability retirement in LC3 was three-fold and for disability retirement for musculoskeletal disorders five-fold. Work-related variables did not modify this effect.

During the 19-year follow-up (for 173 675 person-years) 744 deaths occurred among the twins. The cumulative incidence of death was 4.3/1 000 person-years. The age- and gender-adjusted HR for death was 1.4 (95% CI 1.2-1.8) in LC3 and 1.2 (95% CI 1.0-1.4) in LC2. The risk decreased, and the excess risk disappeared with further adjustment for the lifestyle factors smoking (HR = 1.3, 95% CI 1.1-1.6), alcohol intake (HR = 1.2, 95% CI 1.0-1.5), BMI (HR = 1.1, 95% CI 0.9-1.4), and depressive symptoms assessed with the Beck Depression Inventory (HR = 1.0, 95% CI 0.8-1.3).

Conclusions: Clustering of FM-like symptoms occurred in a substantial proportion of the Finnish population. Heritability explained approximately 50% of the variance, and other statistically discernible risk factors were headache, back pain, neck pain, poor sleep, and high BMI. Further research is necessary to clarify the optimal timing

and the possibility of preventing the development of FM symptoms by early active management of the known risk factors, even if, and especially when, a genetic liability is suspected. Subjects with a high number of FM-like symptoms seem to show a significantly increased risk for disability retirement and even a higher mortality risk explained by associated lifestyle factors.

Prompt attention and active management in their health care are thus warranted.

1. INTRODUCTION

Does fibromyalgia, a benign diffuse pain syndrome, require further study? After thousands of studies, no exact pathology is known, but with no destructive changes identified, either. The syndrome thus seems harmless, and its symptoms can be alleviated by medication and exercise.

Its estimated point prevalence has been around 1 to 5%, whereas the prevalence of widespread pain, a central feature of FM, has ranged from 7 to 13%. Theories as to its pathogenesis still lack robust evidence. Familial aggregation of FM has been confirmed, and this has raised interest in identifying more specific genetic factors related to FM. Studies on risk factors are few; they usually have focused on individual factors only, and need confirmation. Reliable information on risk factors is essential for preventive action.

Great variation exists in estimates of the impact of FM on the ability to work, because of variation in the social insurance systems and compensation criteria across countries and over the course of time. The practice of diagnosing FM may also vary, and the registered clinical diagnoses (as in statements for disability pension) may prove unreliable, because an FM diagnosis has not been generally accepted in all countries. Epidemiologic studies on mortality risk related to WSP have yielded inconsistent results. An updating among the Finnish population is needed.

2. REVIEW OF THE LITERATURE

2.1. FIBROMYALGIA (FM) AND WIDESPREAD PAIN (WSP)

2.1.1. DEFINITIONS

In the 1940s and 1950s, FM was called non-articular rheumatism, soft-tissue rheumatism, fibrositis, or fibrositis syndrome, among other names and later went by the names fibromyalgia or fibromyalgia syndrome. Because of the criteria for this condition, a need arose to standardise diagnostics. The first suggestion with physical signs included, in addition to the symptoms, was introduced by Smythe in 1979 (Wolfe, 1986). In the proposed criteria sets of Smythe in 1979, Bennet in 1981, Yunus *et al.* in 1981, and Wolfe *et al.* in 1985, widespread aching and pain was included by all four groups, and normal results in laboratory tests and different numbers of tender point sites and minimum counts, as well (Wolfe, 1986). Smythe and Bennet included disturbed sleep, morning fatigue and stiffness, Yunus and colleagues included a number of alternative minor criteria including poor sleep and general fatigue.

In 1989 Yunus, Masi, and Aldag published their suggestion of criteria for “primary fibromyalgia syndrome”. These included certain tender points and the so-called historical variables such as “hurt all over”, pain at seven sites (hands, shoulders, neck, lower back, hips, knees, and ankles, each either unilaterally or bilaterally counted as one site), general fatigue, poor sleep, anxiety/tension, and irritable bowel syndrome. Tender points should be located among possible bilateral locations: 1) mid upper border of the trapezius, 2) lower part of the sternocleidomastoid muscle, 3) lateral part of the pectoralis major muscle at the level of the fourth costo-chondral junction, 4) mid-supraspinatus muscle, 5) upper outer quadrant of the gluteal region, 6) posterior-superior aspect of the greater trochanter, and 7) medial fatty pad of the knee. The suggested preliminary criteria included “presence of pain or stiffness, or both, at four or more anatomic sites (counting unilateral or bilateral involvement as one site) for three months or longer” and “exclusion of an underlying condition which may be responsible for the overall features of fibromyalgia” as obligatory criteria. In addition to these, either major or minor criteria had to be fulfilled. The major criteria were presence of at least two of the six “historical variables” and at least four of the 14 tender points. The minor criteria were the presence of at least three of the six “historical variables” and at least two tender points (Yunus *et al.*, 1989).

The American College of Rheumatology (ACR) published in 1990 their criteria

for classification of primary and secondary FM (Wolfe *et al.*, 1990), but they suggested that the classification was in fact not needed, because the features of primary and secondary FM were the same. The ACR 1990 criteria defined FM as chronic widespread pain with at least 11 positive among the 18 specific tender points at palpation; the tender points in part differed from those suggested earlier by Yunus and colleagues. Chronic WSP was defined as pain that had lasted at least three months and occurred axially (in the region of the spine or anterior chest), on both right and left sides of the body, and both above and below the waist. Other symptoms connected to FM but not mandatory for the diagnosis included sleep disturbance, fatigue, morning stiffness of more than 15 minutes, and impact of cold, warmth, and weather changes on symptoms. Compared to the Yunus criteria, these “classification criteria” focused on pain and soreness, whereas in the Yunus criteria, spontaneous pain was not even obligatory. The possibility of diagnosing primary fibromyalgia syndrome with stiffness at four sites and only two tender points and “three historical variables” such as fatigue, poor sleep, and anxiety may have contributed to FMs being considered a disorder based on mainly psychological problems.

Criticism appeared regarding the central role of tender points in diagnosis of FM in the ACR 1990 criteria, since tender points occur even in individuals who have no pain. In population studies, painful tender points have occurred in individuals with no spontaneous pain. Their occurrence seems to correlate with somatic or psychological distress more than with pain qualities (Croft *et al.*, 1994; Wolfe, 1997; Petzke *et al.*, 2003; Schochat and Raspe, 2003; Huppe *et al.*, 2004).

In 2010, the ACR published new preliminary diagnostic criteria for FM with the aim of offering simple criteria which would be more usable and which would enhance the recognition of somatic symptoms (Wolfe *et al.*, 2010). The authors pointed out that these new criteria are not meant to replace the old ones, but to offer an alternative in diagnosing this syndrome. These criteria comprise scores on a new “widespread pain index” (0-19 sites) and a physician-rated symptom-severity scale including fatigue, waking unrefreshed, cognitive symptoms, and somatic symptom severity in general (all rated 0-3). The suggested new criteria either require scores of at least 7/19 on widespread pain index and at least 5/12 on symptom severity scale, or of 3 to 6/19 on the widespread pain index and at least 9/12 on the symptom-severity scale. These criteria have been criticized for their inaccuracy (Smythe, 2011). The requirement option of only three pain localisations and nine or more various somatic symptoms does not seem to identify the fibromyalgia pain syndrome as defined by the ACR 1990 criteria.

2.1.2. EPIDEMIOLOGY: PREVALENCE, INCIDENCE, AND CO-MORBIDITY

As “chronic WSP” is a key symptom of FM and a key part of the 1990 ACR criteria of this syndrome and is easily assessable, it became the object of many epidemiologic studies as an FM substitute. Population-based random sample surveys in the UK, the USA, Canada, and Israel that used the ACR criteria reported an estimated point prevalence of 7.3 to 13%, with a female predominance and higher prevalence in older middle age (Croft *et al.*, 1993; Wolfe *et al.*, 1995; Macfarlane *et al.*, 1999; White *et al.*, 1999a; Buskila *et al.*, 2000). A similar prevalence (12%) later emerged in Korea in a large population survey, with female preponderance and increase with age (Cho *et al.*, 2012), whereas in the Swedish Twin Registry Kato and colleagues (2006a) identified WSP in only 4.1%. That study used the ACR criteria, but the criteria were stricter than earlier, in that the pain was assumed to be continuous during the most recent three months. White and colleagues (1999a) asked about “widespread pain of at least one week’s duration over the preceding three months”, whereas Croft and colleagues (1993) asked about “any pain during the previous month which had lasted longer than 24 h” and that “any such pain had started more than three months ago”. In numerous studies since the appearance of the ACR criteria of WSP, the criteria have been interpreted in different ways: postulating pain either in all four body quadrants, in at least three of them, or in two crosswise quadrants. This results in great difficulties in comparing the results.

Two of the surveys targeted FM as well: Wolfe and colleagues (1995) found an age- and sex-adjusted prevalence of 2.0% (3.4% in women and 0.5% in men), and White and colleagues (1999a) found a prevalence of 3.3% (4.9% in women and 1.6% in men). In both of these surveys, prevalence increased with age. An earlier population-based study on “primary fibromyalgia syndrome”, diagnosed with the adapted 1989 preliminary criteria by Yunus and colleagues, used data from the Mini-Finland survey of 1977 to 1980 and found a prevalence of only 0.75% among a sample of 7 217 subjects, with a variance of 0.29 to 1.15% depending on the criteria modification set (Mäkelä and Heliövaara, 1991).

Among children and adolescents, population-based studies of FM are few, and they indicate inconsistent prevalence. Buskila and colleagues found a FM prevalence of 6.2% in Israeli school children, whereas Clark and colleagues with somewhat different protocols found a prevalence of only 1.2% in Mexican school children (Buskila *et al.*, 1993; Clark *et al.*, 1998). A Finnish study among 11-year-old twins found for WSP a corresponding point prevalence of 9.9% for both boys and girls (Mikkelsen *et al.*, 2001). Another Finnish study, a prospective one, among 1 756 school children showed a cumulative incidence from 7.5% at 1 year to 14% during a 4-year follow-up (Mikkelsen *et al.*, 2008). A similar report was a prospective English study of 1 081 school children, with a 14.6% point prevalence at the start, and a 7.7% cumulative incidence at its one-year follow-up (Jones *et al.*, 2003).

Methodological variation makes it difficult to draw conclusions as to the suggested difference in prevalence for both FM and WSP by gender. The tendency is, however, toward stricter screening criteria to select more women (Croft *et al.*, 1993; Macfarlane *et al.*, 1999; White *et al.*, 1999a; Buskila *et al.*, 2000). Clearly, the ratio of women to men increases in clinical settings when compared to population-based studies (Häuser *et al.*, 2011; Oh *et al.*, 2012; Rivera *et al.*, 2012). This is a general phenomenon among many pain conditions, probably depending on differences both in cultural aspects and in the sensory-affective system of pain.

Studies on clinical FM patient populations have shown considerable comorbidity with irritable bowel syndrome (IBS), migraine, tension-type headache, and depression (Marcus *et al.*, 2005; Kurland *et al.*, 2006; de Tommaso *et al.*, 2011). Two high-quality population-based studies have shown similar findings: an increased risk for chronic fatigue syndrome, rheumatoid arthritis, systemic lupus erythematosus, IBS, headache, depression, and anxiety among FM patients (Weir *et al.*, 2006). Among twins with WSP, Kato and colleagues (2006a) found an increased risk for chronic fatigue syndrome, joint pain (possible rheumatoid arthritis or osteoarthritis of hip or knee), migraine, tension-type headache, IBS, gastro-oesophageal reflux disease, urological diseases, allergy, psychiatric disorders, and overweight. In this same study, genetic and environmental effects shared by the family seemed to confound the association between WSP and psychiatric disorders, prolonged cough, possible asthma, and overweight, whereas the associations between WSP and other co-morbidities were statistically discernible also in the discordant monozygotic pairs; particularly the associations between WSP and migraine and tension-type headache showed no decrease at all.

Thus, based on the literature, the prevalence of FM and WSP seem to vary as a function of the criteria chosen. FM and WSP tend to co-occur with various painful conditions.

2.2. AETIOLOGY: AETIOPATHOGENIC THEORIES AND FINDINGS

2.2.1. MUSCLE TISSUE AS THE ORIGIN OF FIBROMYALGIA

Whereas the pain in fibromyalgia (as the name states) concentrates in the muscles, early research has focused on potential histological and metabolic changes in these structures. In general, the findings have been scarce. Many investigators found “a moth-eaten pattern” in the patients’ muscles, but, as Le Goff (2006) noted, this is found in healthy controls as well. In the 1980s, Bengtsson and colleagues (1986b) found ragged red fibres in FM patients but not in the controls. Several investigators

using electron microscopy for FM patients have found changes in structure and reduction in the number of mitochondria (Yunus *et al.*, 1986; Sprott *et al.*, 2004). Sprott and colleagues also found increased DNA fragmentation among FM patients (in 55% of the muscle-cell nuclei) when compared to age- and sex-matched healthy controls (in 16% of their nuclei). Gronemann and colleagues (2004) found no such changes in their patients, but they found lower amounts of intramuscular collagen compared to those in controls (sedentary, and undergoing knee arthroscopy), who were matched for age, sex, and physical activity.

Bengtsson and colleagues (1986a) calculated energy metabolism of FM patients by measuring levels of adenosine phosphates, phosphoryl creatine, creatine, lactate, pyruvate, and glycogen from muscle biopsies of the trapezius of patient-group 1 and of the tibialis anterior muscles of patient-group 2. They found a decrease in the levels of adenosine triphosphate, adenosine diphosphate and phosphoryl creatine, whereas the levels of adenosine monophosphate and creatine were increased in the painful trapezius muscles of group-1 patients compared to healthy controls and to the non-painful tibialis anterior muscles of the group-2 patients. However, these groups were not age-matched, and no exclusions were reported. No differences appeared in lactate or pyruvate levels. Later, Gerdle and colleagues (2010) studied the muscle energy metabolism with interstitial microdialysis in the trapezius muscles of FM patients and of healthy age- and sex-matched volunteers in a resting state. This method has served in investigations of regional myalgias (Sjogaard *et al.*, 2010). In FM patients, Gerdle and colleagues (2010) found higher interstitial lactate and pyruvate concentrations compared to controls, with a negative correlation with pressure pain thresholds of the trapezius.

That metabolic findings pose some problem in muscle energy metabolism in FM, and electromicroscopic studies have shown mitochondrial changes, both suggest a mitochondrial dysfunction (Le Goff, 2006; Gerdle *et al.*, 2010). The subjective fatigue and subjective reduced strength often reported by FM patients are also symptoms of mitochondrial myopathy. Ragged red fibres have been evident also in mitochondrial diseases (Suomalainen and Isohanni, 2010). Moreover, in many FM patients, the alleviating effect of exercise agrees with the idea of mitochondrial dysfunction, since exercise amplifies the number of mitochondria. The improvement after exercise can, of course, be due to many other mechanisms, such as enhanced inhibitory pain modulation caused by elevated levels of catecholamines (Pertovaara, 2006; Nijs *et al.*, 2012).

Studies of muscle function in FM have yielded inconsistent results. Most of the earlier published studies discovered decreased muscle strength (muscle force by voluntary contraction), and some of them also suggested slightly but non-significantly decreased endurance (repeated contractions at 50% of maximum strength). However, the study groups were mostly small, and it has

been impossible to conclude whether the changes were primary or secondary (Norregaard *et al.*, 1994; Borman *et al.*, 1999; Maquet *et al.*, 2002). On the other hand, exercise seems to improve functional capacity in FM patients in the same manner and to the same magnitude as in healthy controls (Häkkinen *et al.*, 2002; Valkeinen *et al.*, 2004).

Some findings suggest that FM patients use an aberrant means of activating their muscles, and that their subjective muscle fatigue has no equivalence in their muscle electrophysiology. Nilsen and colleagues (2006) found no differences in surface EMG (sEMG) amplitudes (root mean squares) between FM patients, shoulder-neck-pain patients, and healthy controls during a mental-stress task of 60 minutes. Pain was associated with their subjective tension but not with their muscle activity. After a stressful task (a two-choice reaction-time test of one hour on a monitor), both patient groups showed less pain recovery than did the controls. Casale and colleagues (2009), using sEMG in both maximal voluntary contraction and electrical stimulation of non-painful biceps brachii muscles, found no differences in muscle activation following electrical stimulation, whereas voluntary contractions at 60% of maximum voluntary contraction showed myoelectric signs of fatigue in the FM group, significantly differing from that of the control group. Bandak and colleagues (2013), using sEMG in an isometric contraction of the deltoid muscle with an abducted arm (90°), found that the FM patients were exhausted significantly earlier (ca. 250 seconds vs. 500 seconds to maximal fatigue, as assessed on the Borg rating scale¹) than were healthy controls. Their pain increased on a scale from 0 to 10 from 3.6 (SD 3.1) to 6.5 (SD 3.0), but the patients showed no increase during the task in normalized root mean squares as an objective sign of muscle fatigue (as did the controls). Their median frequencies in the anterior and posterior deltoid and control frequencies were similar. That these controls were younger than the patients may have affected median frequency values, but the investigators reported no changes with age included in the analyses. The groups were not matched for body mass index, however. In another recent study, FM patients showed higher muscle tension (particularly in the trapezius muscle) than did controls in sympathetic activation by a mental-stress test and breath-holding, and the rest-time of their muscles was shorter (Westgaard *et al.*, 2013), indicating a tendency for increased static muscle activity. A shorter relative rest-time of muscles has been associated with propensity to create musculoskeletal complaints (Thorn *et al.*, 2007).

This literature proposes that subjective muscle fatigue reflects an incapacity to properly activate the muscles, probably at least partly because of pain. This incapacity may be particularly related to reactions in stressful situations (Nilsen *et al.*, 2006; Thieme *et al.*, 2006; Westgaard *et al.*, 2013). Through rehabilitation, capacity may be restored (Lofgren *et al.*, 2008).

1 The Borg rating scale has five levels: 0 = "no fatigue", 3 = "moderate fatigue", 5 = "strong fatigue", 7 = "very strong fatigue", and 10 = "maximal fatigue".

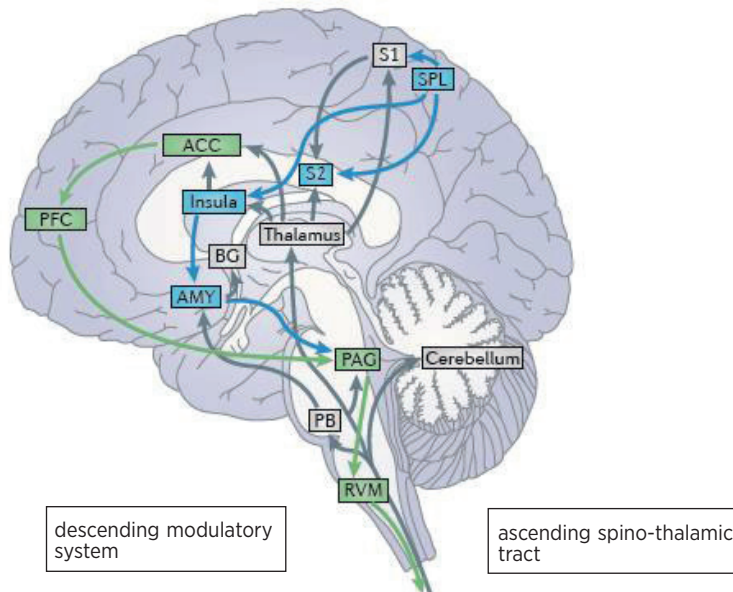
Evidence thus supports the idea that recurrent exaggerated regional muscle tension and persistent pain with characteristic pain referral and central sensitisation may progress to the widespread pain seen in FM (O'Neill *et al.*, 2007; Arendt-Nielsen and Graven-Nielsen, 2011; Ge *et al.*, 2011)

2.2.2. CHANGES IN THE NERVOUS SYSTEM

2.2.2.1. CHANGES IN CENTRAL PAIN MODULATION

The human central nervous system includes a pain modulation mechanism with both facilitatory and inhibitory descending pathways in the spinal medulla. These pathways originate supraspinally from the brain stem (Figure1).

Figure 1



Modified from Bushnell *et al.*, 2013 with permission of the Nature Publishing Group.

Activated by noxious stimuli most commonly: primary (S1) and secondary (S2) somatosensory cortex, anterior cingulate cortex (ACC), insula, prefrontal cortex (PFC), thalamus, and cerebellum and also activated: amygdala (AMY).

Modulatory system (both inhibitory and excitatory effect): periaqueductal grey (PAG) in the midbrain, rostroventral medulla (RVM) and locus coeruleus in the brain stem.

PAG receives input from higher regions: amygdala and prefrontal cortex involved in attentional and emotional control.

The function of the inhibitory pathways has been studied via analyses of the diffuse noxious inhibitory control system, first in animals and later in humans. Diffuse noxious inhibitory control (DNIC) is a phenomenon in which a new noxious stimulus reduces the pain first caused by another noxious stimulus. The function of DNIC can be studied in experimental pain settings (Pud *et al.*, 2009). Phenomena suggesting activation of the DNIC system occur in acute pain states, whereas findings suggesting dysfunction of DNIC appear in FM and other chronic pain states, such as chronic low back pain and temporomandibular disorder (Leffler *et al.*, 2002).

More recently the term “conditioned pain modulation” has described the protocols assessing the DNIC system in human beings. DNIC is probably mainly responsible for pain inhibition by conditioned pain modulation, but other supraspinal mechanisms may participate. A recent systematic review and meta-analysis on conditioned pain modulation in patients with chronic pain provides evidence for significant and clinically important dysfunction of the conditioned pain modulation in various pain states (Lewis *et al.*, 2012). The 30 qualified studies included in this meta-analysis comprised 42 comparisons between patients and healthy controls, with 29 comparisons showing a significant difference. Six of the studies compared FM patients with controls, five of them indicating reduced conditioned pain modulation in the FM patients. Other pain states were IBS (six studies), headache, arthritis, poststroke pain, temporomandibular joint disorder, Parkinson’s disease, neuralgia, vestibulodynia, and pancreatitis.

The facilitatory mechanisms have been studied by use of protocols for temporal and spatial summation (Staud *et al.*, 2007; Graven-Nielsen *et al.*, 2012), with increased temporal summation found in patients with both FM and whiplash-associated disorder, when compared to healthy control subjects (Flor *et al.*, 2006). For spatial summation in FM the study results have been contradictory (Staud *et al.*, 2007). FM patients have had high levels of glutamate and substance P in their cerebro-spinal fluid; these neurotransmitters have been associated with descending facilitation (Brummett and Clauw, 2011).

Another mechanism suggested to explain widespread pain in FM is central sensitisation or amplification of the neural nociceptive responses to sensory stimuli as a result of extensive functional changes in the central nervous system. This may be expressed as tactile allodynia, hyperalgesia, referred pain, and temporal and spatial summation of pain. Several studies (Arendt-Nielsen and Graven-Nielsen, 2003; Meeus and Nijs, 2007) have shown FM patients to have larger areas of referred pain than do healthy control subjects in experiments with evoked muscle pain, which refers to central sensitisation. This referred pain has been partly inhibited by ketamine, more strongly suggesting central sensitisation (Flor *et al.*, 2006). However, central sensitisation is not specific for fibromyalgia but occurs in other pain conditions as well. Kosek and colleagues (1996) found in FM patients an increased

sensitivity to heat, warmth, and cold pain (hyperalgesia), but also to cold pain and to warmth bilaterally in patients with one-side painful osteoarthritis (Kosek and Ordeberg, 2000). Leffler and colleagues (2002) found thermal sensitivity changes over inflamed joints and widespread pressure allodynia also in non-painful areas of rheumatoid arthritis patients of over five years' disease duration (but not with only one year's duration), with their normal DNIC function, thus suggesting either central sensitisation or increased descending facilitation.

Changes in the pain perception pathways: the spatial-discriminative and the sensory-affective perception, are also suggested. A noxious peripheral stimulus is mediated through the dorsal horn in the spinal medulla upwards mainly via the contralateral spino-thalamic tract to the thalamus and further to the somatosensory cortex (spatial-discriminative perception) as well as to the insular cortex, and from there to the prefrontal cortex, anterior cingular cortex, and amygdala (sensory-affective perception) (Fig. 1). This system, together with other regions participating in pain processing in the brain, is called the central pain network of the brain. Functional magnetic resonance imaging (fMRI) studies can show changes in the activation of different brain regions as a response to certain stimuli, with quite good spatial accuracy. These have suggested augmented responses to equal pain stimuli in several parts of the pain network of FM patients when compared to those of healthy control subjects (Gracely *et al.*, 2002; Cook *et al.*, 2004; Williams and Gracely, 2006). When the pain stimuli were stabilized so that the subjective pain ratings of the patients and control subjects were equal, no differences emerged between the groups, however (Williams and Gracely, 2006). This indicates that the patients are sensitised to peripheral noxious stimuli and that their subjective ratings of pain level correlate reliably with their neural central nervous system responses.

2.2.2.2. CHANGES IN THE PERIPHERAL NERVOUS SYSTEM

Some similarities exist in the symptoms of FM and pain in small fibre-predominant neuropathy such as burning pain, prickling, numbness, and touch-evoked allodynia. Koroschetz and colleagues (2011), surveying 1 434 clinical FM patients and 1 623 patients with diabetic polyneuropathy (DPN), identified by cluster analysis five subgroups which had differing symptom profiles. Within these subgroups, DPN and FM patients' reports of sensory symptoms did not differ. Distributions in the subgroups within the two diagnostic patient samples differed, however: two subgroups were more typical among FM patients and one among DPN patients. The symptom profile in these typical FM subgroups included light-pressure-induced pain and pain attacks as one group, and thermally evoked pain as the other, whereas among DPN patients, numbness and prickling were prominent symptoms in the

subgroup more frequent, suggesting that these patient groups' symptoms may have only partially overlapping mechanisms.

Three recent studies have explored small fibres in FM patients and verified neuropathic changes, two with skin biopsies (Oaklander *et al.*, 2013; Üçeyler *et al.*, 2013) and one with microneurography (Serra *et al.*, 2014). Üçeyler and colleagues (2013) found lowered intraepidermal nerve-fibre density, prolonged distal (in the feet) pain-related evoked potential latencies and reduction of amplitudes, and impaired function by Quantitative Sensory Testing (QST) in 8 of 20 FM patients, each of whom had at least one abnormal finding. As controls they had 10 patients with major depression and 35 healthy control subjects, none of whom had significant changes in QST, nor prolonged latencies, nor reduced amplitudes, nor reduced intraepidermal nerve density. Another 2013 study showed decreased intraepidermal nerve density in 14 of its 27 FM patients, but the changes in autonomic nervous function tests did not differ from those of the control group (Oaklander *et al.*, 2013). Serra and colleagues (2014) studied 30 FM patients, 17 small fibre neuropathy patients and 9 healthy controls with microneurography, involving approximately six nerves per subject. Microneurography is an electrophysiologic nerve-recording method for the small, unmyelinated C fibres. Nerve conduction measurement of myelinated fibres and QST were also performed. Aberrant function of C fibres emerged in 77% of the FM patients, in 65% of small-fibre-neuropathy patients, and in 2% of the controls. This aberrant function manifested as spontaneous activity, sensitisation, and slowing in C nociceptors of type I B, which are normally silent, mechano-insensitive nociceptors. Spontaneous activity in C nociceptors, associated with painful neuropathy, occurred in 31% of the FM patients and in 33% of the small-fibre-neuropathy patients (Serra *et al.*, 2014).

In conclusion, recent studies strongly suggest that pathological changes in peripheral nerves, namely small nociceptive fibres, play a role in FM. Further studies are needed to confirm these preliminary findings.

2.2.3. PSYCHOSOCIAL FACTORS

The term “psychological distress” refers to various symptoms related to socio-demographic, stress-related factors, and to internal and external personal resources (Drapeau *et al.*, 2012). These symptoms overlap with those related to depression and anxiety and may also include somatic symptoms. Several studies have examined associations between FM and psychological distress, assessed with differing questionnaires and standardized scales. Many have suggested an association in subpopulations of FM patients (McBeth *et al.*, 1999; Häuser *et al.*, 2009; Loevinger *et al.*, 2012; Salgueiro *et al.*, 2012; Wolfe *et al.*, 2013). The causal relationship

remains obscure, however, and may even be bi-directional. This very limited review is restricted to studies on the relationships between FM and depression (or depressive mode) or anxiety (or anxiety symptoms). Other psychosocial factors may be important as well, but are beyond the scope of this thesis.

Cross-sectional studies have shown a significant association between depression -- assessed by varying and debatable methods -- and FM. Significant association has also appeared between depression and other chronic pain problems (like chronic low back pain) and other chronic illnesses (Dersh *et al.*, 2002a). Prevalence of depression has been estimated at 30 to 60 % in chronic-pain patients (Bair *et al.*, 2008). In FM, major-depressive-disorder prevalence was reported at 22% in a population-based study with 115 137 participants (Kassam and Patten, 2006). In clinical studies from tertiary health-care clinics, the prevalence has been higher (Aaron *et al.*, 1996; Dersh *et al.*, 2002b; Thieme *et al.*, 2004). Aaron and colleagues (1996) compared three groups: rheumatology clinic patients, non-patients who met the ACR 1990 criteria for FM but had not sought medical treatment during the previous 10 years, and healthy controls with each other. They found that the tertiary clinic patients had significantly more psychiatric diagnoses (including depression and anxiety) than did the non-patients, who did not differ from the healthy control group. Even though a small study (64+28+28 subjects), this suggests that psychiatric diagnoses may not be related to FM itself but to “health-care-seeking behaviour”.

By means of a population survey of 1 953 subjects, Macfarlane and colleagues (1999) compared “consulters” and “non-consulters” with WSP: the consulters had visited primary care because of their pain complaints, and the non-consulters had never consulted a physician for their complaints, but reported them only in the survey questionnaire. It appeared that among women, the consulters reported high levels of psychological disturbance and a greater “effect of symptoms” on activities, whereas among men, the consulters reported more fatigue than did non-consulters.

With a structured clinical interview based on DSM criteria (SCID) and the Center for Epidemiological Studies Depression Scale among others, Thieme and colleagues assessed 115 female FM patients recruited from a rheumatology clinic. Their results suggested psychosocial subgroups, from which the “dysfunctional” subgroup (n=35) reported symptoms of anxiety, the “interpersonally distressed” group (n=38) mood disorders, but the “adaptive copers” (n=42) reported little comorbidity (Thieme *et al.*, 2004). These groups did not differ in terms of age, gender, number of pain areas, or in pain duration. The dysfunctional group reported more anxiety disorder symptoms than did the two other subgroups (68% vs. 15% and 20%) assessed with both the State-Trait Anxiety Inventory-Trait Scale and the SCID (structured clinical interview based on DSM criteria). Depression was the diagnosis for 80% of the “interpersonally distressed” group compared to 21% of the dysfunctional group, and only 2% of the “adaptive copers”.

Dersh and colleagues (2002a) have pointed out that more evidence exists for the theory that depression is a consequence of pain than for a relationship in the opposite direction. Assessing depression among pain patients with questionnaires such as the Patient Health Questionnaire, Beck Depression Inventory, or Zung self-rating depression scale is, to some extent, problematic. These questionnaires include questions about symptoms that are frequent in pain patients even in the absence of depression, such as somatic symptoms, sleep problems, fatigue, and disability. A recent retrospective study, in which depression was not assessed with the (in pain-patients) problematic questionnaires but with the clinical interview SCID, found the majority of depression disorders of 100 chronic pain patients to appear after the onset of their pain problem (Knaster *et al.*, 2012). According to Dersh (2002a), the diathesis-stress model of Banks and Kerns suggests that subjects' pre-existing characteristics may be augmented by a distress situation caused by chronic pain, with disability, losses, and the negative responses of the health care system. There is earlier empirical support for this model (Maxwell *et al.*, 1998; Dersh *et al.*, 2002a).

Evidence of the association between anxiety disorders and chronic pain, including FM, is also considerable. Specifically, prevalence rates of current anxiety disorders were higher in chronic pain patients than in the general population, but the lifetime prevalence was equal. This could be interpreted in two ways. First, anxiety could be a consequence of ongoing pain. Second, anxiety and chronic pain, or rather the chronification process of pain, could share a trigger (Dersh *et al.*, 2002a).

When considering any chronic pain, psychological processes such as thoughts and behaviours are most essential, because they are fundamental factors in directing and controlling a person's reactions to both physical and psychosocial distress. Börsbo and colleagues (2010) in a cross-sectional assay studied rehabilitation-clinic patients with pain related to spinal cord injury, whiplash-associated disorder, and FM to investigate interactions between self-efficacy, symptoms of depression, anxiety, and pain, catastrophizing, disability, quality of life, and health. Depressive and anxiety symptoms, catastrophizing, and disability were intercorrelated, and self-efficacy correlated positively with both general health and quality of life and negatively with disability. In the multivariate correlation analyses, no specific pattern for any of the diagnostic subgroups emerged, the post-traumatic-pain patients and the FM patients did thus not differ.

In summary, no convincing evidence exists that depression and anxiety are epidemiologically important in FM aetiology. In FM, as in other chronic pain conditions and other chronic diseases, these rather seem to co-occur or be consequences of the pain or the disease. Individually, however, a pre-existing susceptibility to depression or anxiety may be amplified by FM, as well as any chronic pain, to such an extent that clinical symptoms of this susceptibility occur. Personal behavioural, cognitive, and affective reaction patterns such as coping strategies,

levels of self-efficacy, and catastrophizing should be assessed and targeted in the care and rehabilitation of FM to avoid or reduce disability.

2.2.4. NEUROENDOCRINOLOGICAL CHANGES

Enthusiastic interest in endocrinological and neuroendocrinological changes occurring in regards to FM produced in the 1990s many studies on growth hormone, female sex hormones, and especially on the hypothalamic-pituitary-adrenal (HPA) axis. The study populations have usually been small and the results inconsistent. Earlier studies did not control for possible opioid use. In many reviews, the conclusions are confusingly contradictory, as well.

Neeck and Crofford provided evidence for an elevated basal cortisol level, while Van Houdenhove and Egle reported low basal levels, and Geenen and Bijlsma, on average normal basal levels of cortisol (Crofford, 2002; Neeck, 2002; Van Houdenhove and Egle, 2004; Geenen and Bijlsma, 2010). These discrepancies might be explained by differing phases in the painful condition and in the coping process. A reduced cortisol awakening response has occurred in FM patients even when controlled for confounders such as age, BMI, smoking, sleep, employment, duration of symptoms, and physical activity (Riva *et al.*, 2010). One trend was toward lower basal cortisol values with longer duration of FM symptoms when the patient group was analysed stratified, but the difference was not statistically discernible, maybe because of too-small groups (Riva *et al.*, 2010). A recent meta-analysis of HPA-axis activity in chronic fatigue syndrome, FM, and IBS found basal cortisol levels in these three functional disorders to be generally lower, but the differences were statistically discernible only in chronic fatigue syndrome analysed separately (Tak *et al.*, 2011). These researchers also made a meta-regression for the assumed moderators: type of functional disorder, gender, medication, physical inactivity, and co-morbid depression. Female gender emerged as a moderator that augmented the difference towards lower basal cortisol levels in the functional disorders when compared to control levels. The type of functional disorder was a significant moderator as well, explaining the heterogeneity. For FM, the result was non-significant, possibly due to the small total number of subjects in the FM studies.

The studies by Crofford (2002) and Geenen and Bijlsma (2010) both have shown in FM patients an exaggerated adrenocorticotrophin (ACTH) response to corticotropin-releasing hormone (CRH) stimulation compared to that in healthy controls. Geenen and Bijlsma also found ACTH and cortisol responses to stressors (like hypoglycaemia and IL-6) to be reduced, and CRH secretion reduced as well. These findings together would indicate a reduced hypothalamic stress function accompanied by normal pituitary function. According to Geenen and Bijlsma

(2010), among FM patients, growth hormone levels and IGF1 levels are slightly but significantly reduced, with changes also found in the function of the autonomic nervous system, including night-time hyperactivity and attenuated responses to stressors. The findings are suggestive of a role in FM for the central stress system, but the question remains open whether the changes are primary or secondary. Tak and colleagues (2011) argued that the small number of studies on HPA axis function after challenge tests, together with the large spectrum of tests, does not allow a reliable meta-analysis to date.

In conclusion, in FM, alterations occur in the stress system: both the HPA axis and the autonomic nervous system. These seem to differ from those in depression. Some controversies arise among findings. More research into this topic is essential, as no conclusions can be drawn as to causality.

2.2.5. HERITABILITY AND GENETIC FACTORS

Clinicians who meet many FM patients are well acquainted with familial aggregation of FM. Earlier studies have confirmed the clustering of FM in families (Arnold *et al.*, 2004; Buskila *et al.*, 2005). Mikkelsen and colleagues (2001) studied Finnish adolescent twins to estimate the genetic and environmental effects explaining WSP. They found both in boys and in girls that genetic factors play only a minor role. A study of WSP among participants in the Swedish Twins Registry utilized computer-assisted telephone interviews between 1998 and 2002. With rather strict criteria (“continuous pain during all the [previous] 3 months” and the ACR 1990 criteria) it found a prevalence of 4.1% among 44 897 individuals. Of the individuals reporting WSP with these criteria, 1 406 were women and only 370 were men. Among the 15 806 pairs with known zygosity, the estimated genetic proportion responsible for the total variance was 48 to 54% (Kato *et al.*, 2006b).

The growing literature on candidate genes has mostly targeted genes related to the neurotransmitters serotonin and catecholamines, and their degrading enzyme catechol-O-methyltransferase (COMT), and recently also to adrenergic receptors. Serotonin (5-hydroxytryptamine) is a central neurotransmitter that participates in many psycho-physiological functions such as sleep, mood, appetite, and pain perception. Catecholamines (norepinephrine, epinephrine, and dopamine) participate in the sympathetic regulation (norepinephrine and epinephrine) and reward-motivational systems (dopamine) among others. Serotonin, norepinephrine, and dopamine also participate in central pain modulation, particularly pain inhibition.

Earlier studies on serotonin-related genes have suggested a relationship between fibromyalgia and polymorphism of the serotonin transporter promoter

region, particularly between FM and the S/S allele, but this was not true among psychologically healthy FM patients (Offenbaecher et al., 1999; Gursoy, 2002). Several studies have connected chronic pain with functional changes in genes encoding COMT which lead to decreased COMT activity. A recent meta-analysis of candidate-gene studies (covering 17 genes and over 35 polymorphisms in 18 studies) found an association of the serotonin-2A receptor 102T/C polymorphism with FM vulnerability (Lee *et al.*, 2012), but no association of the serotonin transporter promoter regions S/L allele or COMT val158met polymorphism with such vulnerability. Another meta-analysis that also included studies on WSP revealed that the rs4680-type single-nucleotide polymorphism of the COMT gene seems to be associated with both FM and WSP, but depending on ethnicity: significant associations arose in studies among Hispanic-Caucasian (OR 1.69, 95% CI 1.17-2.46, n=350) or Middle Eastern populations (OR 1.38, 95% CI 1.07-1.79, n=1015) but not among non-Hispanic Caucasians (OR 1.06, 95% CI 0.93-1.20, n=2410) (Tammimäki and Männistö, 2012).

In a powerful, large association study among the 1958 British Birth Cohort assessing genotypes for nine single nucleotide polymorphisms (SNPs) across the beta2adrenergic receptor and eleven SNPs across COMT, Hocking and colleagues (2010) found no association between any of the COMT genotypes and chronic WSP. On the contrary, they found an association between two SNPs of the beta2adrenergic receptor (rs12654778 and rs1042713) and WSP.

In conclusion, genetic factors play a substantial role in FM and WSP, but more research is necessary to draw conclusions as to the pathogenesis of FM from gene studies.

2.3. SUGGESTED RISK FACTORS FOR FIBROMYALGIA AND WIDESPREAD PAIN

Several cross-sectional and retrospective studies have found numerous factors associated with FM and WSP, including increasing age, female gender, depression, obesity, neck pain, accidental trauma, and sexual or physical abuse in childhood, among others. The problem with cross-sectional studies is their inability to evaluate the sequential relationship of the associated factors and the phenomenon under examination. We therefore cannot judge which one precedes the other. Retrospective studies always offer the possibility of recall bias. The most relevant and reliable way to explore risk factors (predictors) is a prospective study, in which the phenomenon under examination is first excluded from the research sample, and these “naïve” individuals -- the sample at risk -- is then monitored after assessment of the risk factors at baseline and possibly during follow-up. Controlling for possible

confounding variables and other putative risk factors is also wise. It is worth noting, that for instance, in one prospective study when confounding factors were controlled for, the predictive effect of traumatic accidents was almost completely abolished (Jones *et al.*, 2011). An important issue is selection of the study sample. Because studying patients at a tertiary care unit adds bias through a selection effect, population-based random samples are preferable. It is also important that the number of individuals is sufficient. Few such studies on risk factors for FM or WSP exist (Table 1).

Table 1. Population-based studies assessing risk factors for (new-onset) widespread pain or fibromyalgi

reference	sample, number of participants	assessment method, time of follow-up	study variables	outcome	risk factors, increasing (+) or decreasing (-) the risk
Forseth <i>et al.</i> , 1999a, 1999b	sample of 217 women from a local female population (2 498), aged 20-49, 214 responders sample at risk: 175	interview and examination at baseline 1990 and in 1995	pain variables, associated symptoms, feeling depressed, socio-demographic variables	WSP	pain > 6 years, back pain, feeling depressed (+)
Bergman <i>et al.</i> , 2002	sample (every 18th) of 3 928 subjects from a local population (70 704), aged 20-74, 2 425 responders (62%), 1 852 evaluated	questionnaire survey, 1995 and 1998	chronic musculoskeletal pain, socio-demographic variables, alcohol consumption, smoking	WSP	age > 59, multiple pain sites, family history of chronic pain (+) weekly/daily alcohol consumption, personal support (-)
Mikkelsen <i>et al.</i> , 2008	local cohort of school children aged 10-12, 1 756 participants (83% of the age group), sample at risk: 1 624 children	questionnaire survey, 1995, after 1 and 4 years	headache, pain in certain regions, feeling down, day-time tiredness, sleeping problems, physical activity	WSP	age > 11 years, female gender, feeling down, regional pain in neck, upper/lower back (+)
Mork <i>et al.</i> , 2010	local population survey (HUNT 1-2), sample of 24 357 women aged ≥ 20 years, sample at risk: 12 350	questionnaire survey, 11 years (1984-1986 and 1995-1997)	age, BMI, physical activity, smoking, education	FM	overweight/obesity (+)
Hagen <i>et al.</i> , 2012	local population survey (HUNT 2-3), aged ≥ 20 , 26 197 completed replies of 41 766 subjects, sample at risk: 13 781	questionnaire survey, 9-13 years (1995-1997 and 2006-2008)	age, gender, education, smoking, physical activity, anxiety and depression (by HADS), musculoskeletal complaints, headache	WSP ^{a)}	headache dose-dependently, both migraine and non-migrainous headache (+)
Mork and Nilsen, 2012	local population survey (HUNT 1-2), sample of 24 357 women aged ≥ 20 , sample at risk: 12 350	questionnaire survey, 11 years (1984-1986 and 1995-1997)	age, physical activity, BMI, psychological well-being, smoking, education, sleep	FM	sleep problems dose-dependently (+) age moderating
McBeth <i>et al.</i> , 2014	local cohort 19 818 subjects aged > 50, 13 986 participants (71%), sample at risk: 4 326	questionnaire survey, 2004, 3 years follow-up	education, subjective financial strain, social networks, anxiety and depression (by HADS) and variables as in "risk factors"	WSP	age, baseline pain status, physical health-related quality of life, cognitive complaint, anxiety, non-restorative sleep (+)

^{a)} Chronic widespread musculoskeletal complaints: "pain and/or stiffness in muscles and joints for at least 3 months during the past year"

BMI= body mass index

FM= fibromyalgia, reporting physician's diagnosis

HUNT = Helseundersøkelsen i Nord-Trøndelag (Nord-Trøndelag Health Study)

WSP = widespread pain, according to the criteria of the American College of Rheumatology, 1990

As part of a cohort study in Arendal, Norway, Forseth and colleagues (1999a, 1999b) screened women with possible FM by means of a questionnaire. Of the possible candidates in 1990, a smaller sample was interviewed and examined, the ones fulfilling FM criteria were excluded, and the rest (175 women) were re-interviewed and re-examined 5 years later for any new-onset FM. Potential risk factors assessed at baseline included 1) pain variables like recurrent pain, chronic regional pain, multi-site but not WSP, and chronic WSP, 2) associated symptoms like effect on pain of modulating factors, fatigue, irritable bowel symptoms, headache, and numbness, 3) self-assessed depression (feeling depressed at least once a week), and 4) socio-demographic variables. In the multivariable analysis, risk factors were duration of pain over six years (OR 3.5 with 95% CI 1.0-10.4), back pain (OR 3.2 with 95% CI 1.1-9.7), and self-assessed depression (OR 6.3 with 95% CI 1.4-28.6). Alternating hard/loose stools, a central symptom in IBS, were also a risk factor (OR 3.0 with 95% CI 1.1-8.0). The cumulative incidence of FM was 25% in the sub-population reporting pain at baseline, but it was only 3% in the same cohort among the women who were pain-free at baseline. The small sample size limits the power of that otherwise qualified study.

Bergman and colleagues (2002) did a population-based study with 3 928 subjects, who received a questionnaire in 1995. With a response rate of 62%, they replied to questions on occurrence and location of chronic musculoskeletal pain, socio-demographic factors, alcohol consumption and smoking habits, and psychological support. In multivariable analysis, age over 59 years (OR 3.13 with 95% CI 1.47-6.69), multiple pain sites at baseline (OR 6.91-12.13) and a family history of chronic pain (OR 1.87 with 95% CI 1.14-3.07) were risk factors for WSP, while protective factors were weekly/daily alcohol consumption (OR 0.42 with 95% CI 0.21-0.85) and having personal support (OR 0.49 with 95% CI 0.28-0.85).

Mikkelsen and colleagues screened WSP in 1 756 school children in Lahti, southern Finland aged 10 to 12 years with a questionnaire assessing headache, pain in the abdomen, neck, chest, upper and lower limbs, and upper and lower back during the past three months. The questions also evaluated pain frequency, depressiveness (feeling sad or down), day-time tiredness, sleeping problems, and physical activity. Both children with and without WSP at baseline were assessed with new questionnaires after one and four years to evaluate risk factors for new WSP and prognosis of WSP, and 73% of the children replied to all questionnaires. In the multivariable analysis risk factors for (new) WSP were age over 11 years, female gender, depressiveness, regional neck, upper-back, or lower-back pain.

Mork and colleagues (2010) followed 15 990 women who participated in two surveys in 1984-1986 and in 1995-1997 as part of the Nord-Trøndelag Health Study (HUNT). They evaluated age, BMI, and physical activity as risk factors for FM, adjusted for smoking and education. A total of 380 women reported physician-

diagnosed FM, with symptoms that started during the follow-up (between the first and the second survey). Overweight and obesity were significant risk factors (RR 1.72 with 95% CI 1.1-2.8), and inactivity elevated this risk. Physical exercise level during leisure time had a statistically non-discernible but consistent inverse dose-response relation to FM.

Mork and Nilsen (2012) evaluated as part of the same study (HUNT 1-2) the relation between sleep problems and FM. In this study, they included only women who were supposed to be free of FM, musculoskeletal pain, or physical impairment (reported in HUNT 1) at baseline. Among the 12 350 participants, 327 women reported doctor-diagnosed FM during the follow-up, corresponding to a cumulative incidence of 2.6%. Their linear regression model, adjusted for age, physical activity, BMI, psychological well-being, smoking status, and education, showed a dose-dependently increasing risk ratio associated with sleep problems, and with greater risk for age over 45 years. The RRs for other controlled variables in the multivariable model went, unfortunately, unreported.

Hagen and colleagues (2012), using the HUNT survey 2 in 1995-1997 and the HUNT 3 in 2006-2008, examined the relationships in both directions between chronic daily headache and chronic musculoskeletal complaints (with criteria slightly differing from WSP). It appeared that not only headache, both migraine (OR 2.0 with 95% CI 1.6-2.4) and non-migraine (OR 1.7 with 95% CI 1.4-1.9), was a risk factor (OR 1.8 with 95% CI 1.5-2.0, with a dose-dependent effect) for widespread chronic musculoskeletal complaints. When controlled for age, gender, education, smoking, physical activity, anxiety, and depression assessed with the Hospital Anxiety and Depression Scale, widespread chronic musculoskeletal complaints also predicted headaches of many kinds. The predictive effect of headache on non-widespread chronic musculoskeletal complaints was somewhat smaller (OR 1.3 with 95% CI 1.2-1.4). The sample at risk for chronic musculoskeletal complaints included 13 781 individuals, of whom 1 284 (9%) experienced widespread chronic musculoskeletal complaints during the follow-up. Again, the other ORs went unreported.

McBeth and colleagues (2014) assessed "any ache or pain which had lasted for one day or longer" with a questionnaire survey in a cohort of 13 986 subjects aged at least 50. Among the 4 326 subjects originally reporting no pain or some pain but not WSP (on a manikin), 800 subjects (18.5%) reported new-onset WSP during the three-year follow-up. In the multivariate analyses, age, baseline pain status, physical health-related quality of life, cognitive complaint (OR 1.3, 95%CI 1.1-1.5), anxiety (OR 1.5, 95%CI 1.01-2.1), and non-restorative sleep (OR 1.9, 95% CI 1.2-2.8) all were associated with the new-onset WSP, even when adjusted for gender. Social variables (education, subjective financial strain, social networks) showed no such association. The relation between age and WSP was weakly inverse. Anxiety and depression were assessed with the Hospital Anxiety and Depression

Scale, revealing no association between depression and new-onset WSP. “Cognitive complaint” meant impairment of alertness and ability to concentrate, as assessed by the Sickness Impact Profile subscale.

All these prospective, population-based, mostly large studies found several, in part same risk factors for FM/WSP. Unfortunately, they were not assessed simultaneously or if assessed, not reported.

2.4. PROGNOSIS

2.4.1. NATURAL COURSE AND QUALITY OF LIFE

Most studies on the natural course of FM have been performed with small clinical samples.

A few prospective studies deal with population-based samples:

Forseth and colleagues (1999a, 1999b) followed a Norwegian population-based sample of 214 women with musculoskeletal pain during 5.5 years, from 1990 to 1995. Of the original sample of 2 498 women aged 20 to 49, 2 038 (81%) replied to a pain screening questionnaire in 1990, and 1 168 (57%) reported chronic pain. Of these women, 242 were invited to participate in the study, and 217 of them participated in a structural interview and a physical examination. Based on these results, they were classified into four groups: non-chronic pain, chronic regional, chronic multifocal, and chronic widespread pain. At follow-up, of the original chronic WSP group of 57 women, 35 still had WSP but 22 met the criteria of the other three groups, and a total of 46 from the other groups had moved to the chronic WSP group. At baseline, the groups did not differ in regards to age, duration of symptoms, or modulation of pain when mental stress, anxiousness, or self-assessed depression were the variables. However, across the groups, together with pain sites and tender points, also general complaints (such as pain at night, poor sleep, modulation of pain/stiffness by weather, fatigue, paresthesia, and gastro-intestinal symptoms) increased. This agrees with the theory that WSP and FM represent an end of a pain continuum.

White and colleagues (2002) followed a Canadian population-based sample of 100 individuals with FM, of whom 72 were newly diagnosed, in order to evaluate the impact of the diagnostic label of FM. At the follow-up of 18 months, of the original 72, 56 subjects were available, and at 36 months 43 were available. Non-participants were disproportionately male, but in other respects, participants and non-participants did not differ. At 18 months, the participants reported more symptoms on a 41-item symptom checklist (both major and minor problems) than at

baseline, but at 36 months they reported fewer symptoms. At baseline, however, the 72 newly-diagnosed subjects had less severe symptoms than did the 28 previously diagnosed ones, perhaps affecting outcome.

Hughes and colleagues (2006) explored FM diagnosis as well, but its impact on health-care incidents. They used the Full Feature General Practice Research Database, a collection of data from over 350 general practices in the United Kingdom representing approximately 4.6% of the UK population. The research cohort comprised patients with a recorded FM diagnosis (codes based on ICD-9) in January 1998, and available records from at least two years previous to that, before the receiving the diagnosis (index date), and a control group (10 controls per one patient) matched for the index day, age, gender, and general practice. Data were collected of total general-practice visits, visits due to depression, fatigue, chest pain, headache, sleep disturbance, prescriptions for tricyclic antidepressants, and non-steroidal anti-inflammatory drugs (NSAID), all up to ten years prior to and four years after the index date. The total rate of general-practice visits increased sharply prior to the index date and continued to increase, but the rate for the matched controls also increased. Visit rates of FM patients were considerably higher than those of controls. The visit rate for depression treatment was higher for FM patients as well, but decreased after the index date, and the same happened with visits due to IBS symptoms. The rate of prescriptions of tricyclic antidepressants was slightly higher before the index date, and after the diagnosis, declined to become the same as for controls. However, the rates of NSAID prescriptions and visits due to sleep problems increased continuously, also after diagnosis. According to these results, receiving the diagnosis would seem to relieve symptoms of depression but not sleep problems or pain. However, the subjects with FM diagnoses represented only 0.18% of the whole Full Feature General Practice Research Database population, which is not comparable to generally estimated prevalences, and they may have had more complicated situations and co-morbidity than is usual for FM patients, as the researchers pointed out.

Mikkelsen and colleagues (2008) examined onset, prognosis, and risk factors for WSP in 1 756 children aged 10 to 12, in a 4-year follow-up. A total of 1 282 children (73%) participated both in 1-year and 4-year follow-ups. Of the 93 children who reported WSP at baseline, only 29 (31%) reported it at the 1-year follow-up, and only 9 (10%) at the 4-year follow-up. At the 4-year follow-up, of these 93, 9% reported no pain, 30% reported WSP (two-thirds of them new-onset), and the rest reported other pain.

In conclusion, based on two large prospective studies, the diagnosis “fibromyalgia” itself does not seem to have a negative impact on patients’ life quality; rather, the trend was in the opposite direction. Widespread pain is not necessarily a persistent condition in adults and particularly not in children.

2.4.2. ABILITY TO WORK

As FM often causes pain on or after exercise and physical effort, it can also affect physical function and work ability. The population-based studies of White and colleagues (2002) and Forseth and colleagues (1999b) and the twin study of Aaron and colleagues (2002) showed variable work disability. In the latter, among 221 twin pairs assessed as with both regional and widespread chronic pain, when compared to 82% of their pain-free co-twins, only 52% of the twins with WSP were employed. For chronic regional pain, the respective figures were 77% and 46%. In the study of White and colleagues (1999b) in Canada, based on the same population-based sample of FM patients as in their 2002 study, of their 100 FM patients, 26 reported receiving a disability pension compared to 10.5% of the 76 in the WSP non-FM group and 2.2% of the 135 general controls. Of these 26 FM patients, only 15 were in the new-onset FM group of 72 subjects, and 11 were in the pre-diagnosed group of 28. In follow-up of the new-onset FM group, at 18 months 11 (19.6%) of the 56 participants, and at 36 months 9 (20.9%) of the 43 responding participants received disability pensions.

In the Norwegian study of Forseth and colleagues (1999b), as many as half of the 81 subjects with WSP, reported being either on long-term sick leave or receiving a disability pension; of the 39 subjects with chronic multifocal pain, 12 (31%), of the 46 subjects with chronic regional pain, 5 (11%), and of the 48 subjects with non-chronic pain, only 2 (4%) reported the same at 5-year follow-up.

Wolfe and Michaud (2009) gathered data on 2 046 FM patients and 20 374 RA patients from the National Data Bank for Rheumatic Diseases in Wichita, Kansas, in the USA, from 1999 to 2008 to explore relationships between variables of illness severity and three outcome variables: disability, depression, and opioid use. The principles of the National Data Bank for Rheumatic Diseases are not reported in the article, but according to its homepage, patients with a physician-diagnosed rheumatologic disease are free to participate in the data bank and complete questionnaires for research purposes. In that study, when compared to the RA patients, FM patients had significantly more disability, self-reported depression, health dissatisfaction, sleep disturbance, pain, and fatigue, and higher scores on the Regional Pain Scale, Health Assessment Questionnaire Disability Index, Symptom Intensity scale, comorbidity index, and symptom count, and lower scores for mental health assessed with the Medical Outcomes Study Short-Form 36. Analysed by fractional polynominal regression, these variables predicted work disability quite similarly in FM and RA patients and predicted opioid use similarly but with a slight difference for sleep, mood, and fatigue in the lower range of the variable scale. In prediction of depression, the curves were of the same shape for both patient groups, but for all variables except for symptom count, FM patients' curves were shifted upwards (depression more probable).

In conclusion, fibromyalgia and widespread pain appear to associate with considerable work disability, but more population-based studies must to further elucidate their effect. Because criteria for disability pensions vary, both between countries and as a function of time, comparison of results is difficult.

2.4.3. MORTALITY

Results of the studies on any association between mortality and WSP are inconsistent. Of the four large population-based studies, the first two, using the same two cohorts from 1991 and 1992 until 1999, suggested increased mortality (Macfarlane *et al.*, 2001; McBeth *et al.*, 2003) and the next two found no difference from results in pain-free subjects or subjects with regional pain (Macfarlane *et al.*, 2007; Andersson, 2009).

In the first study in northwest England (Macfarlane *et al.*, 2001) with approximately 50 500 person-years, subjects diagnosed with cancer only before the baseline were excluded. Adjustments were made for age, gender, smoking, and psychological distress but not for social class. The odds ratio for crude all-cause mortality was 1.31(95% CI 1.05-1.65) among the subjects with WSP, with the pain-free group as the reference. Excess mortality was mostly due to malignancies: the mortality rate ratio for cancer was almost double in the WSP group (1.91, 95% CI 1.04-3.49), but rates for cardiovascular problems (the most common cause) were equal. In the second study (McBeth *et al.*, 2003), among individuals with WSP at baseline, the total incidence of cancers was double that of pain-free individuals (11.9 vs. 5.7 per 1000 person-years). The total adjusted mortality rate ratio for cancer was 1.82 (95% CI 1.18-2.80).

In the report by Macfarlane and colleagues (2007) among the Mini-Finland cohort, between 1979 and 1994 with 88 870 person-years, relative risk of death when adjusted for age, gender, education, smoking, and distress, was even lower, 0.64 (95% CI 0.46-0.91) in the WSP group than in the pain-free group. No exclusions at baseline or shortly thereafter were made. In the Swedish random-sample study from 1988 till 2002, deaths that had occurred during the first 2 years of the follow-up were excluded (Andersson, 2009). An increased risk for mortality with a hazard ratio 1.88 (95% CI 1.17-3.02) was apparent in the WSP group, although adjustment for age, gender, smoking, and physical activity abolished this excess (HR 1.09, 95% CI 0.62-1.91). WSP prevalence was comparable in the studies (15%, 16%, 9.4%) even though somewhat stricter criteria were used in the study by Andersson. The slightly differing WSP criteria probably do not account for the discrepancy in mortality risk, because if a true connection existed, the study group with the strictest criteria would likely have the worst outcome.

Dreyer and colleagues (2010) and Wolfe and colleagues (2011) followed up clinically diagnosed FM patients, Dreyer's group reaching 5 295 person-years and Wolfe's 60 413. The former used the 1990 ACR criteria, the latter the preliminary 2010 criteria approved by the ACR. No increased standardised mortality risk emerged in either of the studies compared to that of the general population.

3. AIMS OF THE STUDY

The purpose of this study was to evaluate in a Finnish twin cohort

1. the prevalence of fibromyalgia-like symptomatology as a proxy for fibromyalgia (Study I)
2. the role of heritability behind these symptoms (Study I)
3. prospectively other risk factors for fibromyalgia symptoms (Study II)
4. the prospective impact of fibromyalgia symptoms on ability to work (Study III)
5. the prospective impact of fibromyalgia symptoms on mortality risk (Study III)

4. MATERIALS AND METHODS

4.1. STUDY DESIGN

Study I

- a cross-sectional assay in 1990
- creation and validation of a classification method to screen the subjects with fibromyalgia-associated symptoms
- assessment of heritability behind the distribution of subjects into symptom classes

Study II

- a longitudinal cohort starting in 1975
- cross-sectional assessments in 1975 and 1981 for base-line variables
- cross-sectional assessment in 1990 for outcome, with the same classification method into symptom classes as in Study I

Study III

- a longitudinal cohort study
- baseline assessment in 1990 with the same classification method as in Study I registry linkage for cumulative disability and mortality data

4.2. THE FINNISH TWIN COHORT

4.2.1. QUESTIONNAIRE SURVEYS OF THE OLDER FINNISH TWIN COHORT

In all studies, our research group used data from the older Finnish Twin Cohort. Until 1996, it consisted of twin pairs of the same gender born before 1958 with both twins of the pair alive in 1975, when the first health questionnaire was mailed cohort-wide. In 1981 a second, comprehensive health questionnaire was mailed to the cohort (Kaprio and Koskenvuo, 2002). Both of these questionnaires contained a question on occurrence of pain during recent years in the back, neck, or shoulders that would

have disturbed performance of work. They also gathered data on height, weight, sleep, smoking, alcohol use, medication, education, and work-related questions, among others. In 1990 a third, follow-up, questionnaire was mailed to twins who had replied to either of the first two questionnaires. A total of 16 179 twins could be contacted (Hublin *et al.*, 2001). These twins were admirably active in replying: response rates were 89% for the first, 84% for the second, and 77% for the third questionnaire (Hublin *et al.*, 2001).

4.3. MEASURES

4.3.1. MEASURES OF FIBROMYALGIA SYMPTOMS IN THE TWIN SURVEYS, AMONG CLINICAL PATIENTS, AND IN THIS STUDY

The third questionnaire, sent in 1990, included a set of questions intended to detect individuals with possible fibromyalgia. Its design was based on the primary criteria for FM syndrome by Yunus and colleagues (1989). As the American College of Rheumatology (ACR) criteria were not published by the time of its design, this set did not include elements for categorizing WSP.

From the FM-question set of the 1990 questionnaire, these questions that would characterize possible FM patients served in this study:

How often have you had these symptoms during the previous year?

- 1) stiffness in your limbs and trunk in the morning
- 2) stiffness in your limbs and trunk in the evening
- 3) pain and stiffness in your neck
- 4) soreness with touch in your neck, back, trunk, or limbs
- 5) numbness in your extremities
- 6) daytime tiredness

Choices 1 to 6 were provided with the alternatives “never”, “daily or nearly daily”, “3 to 5 times per week”, “1 to 2 times per week”, “about once a month”, and “less often”.

- 7) Does the stiffness in your limbs and trunk in the morning last “less than 15 minutes”, “about half an hour”, “about 1 to 2 hours”, or “over 2 hours”?
- 8) Does low air pressure (rain, snow, storm) worsen the pain in your trunk or limbs?

The same health questionnaire was used by a rheumatologist (Pentti Järvinen), who gave it to 56 consecutive FM patients visiting the outpatient rheumatology clinic of Kiljava Hospital, Nurmijärvi, Finland, in 1992, with 49 (88%) patients

responding. P.J. had diagnosed the first patients according to the Yunus criteria (Yunus et al., 1989), and the later FM patients according to ACR criteria. Patient records of 43 of the 49 responders were still available in 2007, and in 42 of them the ACR criteria could be confirmed based on the records. The duration of their FM symptoms ranged from 2 to 29 years, with a mean duration of 8.1 years \pm 5.7. Their answers to the eight questions allowed classification in the twin sample.

4.3.2. OTHER COVARIATES ASSESSED IN 1975, 1981, AND 1990

Measures of other characteristics of the twins and FM patients

Further analysis of how closely the group with FM-associated symptoms (“FM-substitute class”) resembled our clinical FM patients required assessment of other characteristics and co-morbidity of the twin sample from the 1990 questionnaire and the clinical FM patients: age (from reported birth date), gender, depressive symptoms (assessed with the Finnish version of the Beck Depression Inventory, BDI (Varjonen *et al.*, 1997)), night awakenings (with six alternatives from “usually none” to “at least five times a night”), abdominal pain, flatulence, diarrhoea (these three with six alternatives from “never” to “daily”), arthrosis/osteoarthritis, rheumatoid arthritis, sciatica, migraine (these four, diagnosed by a physician, expressed with the alternatives “yes” or “no”), and current use of medication (frequency of use assessed with five alternatives from “none” to “on more than 180 days” last year).

Risk factors for fibromyalgia

The second study was a prospective cohort study based on the FM-symptom-classified twin sample of the first study and evaluating putative risk factors (from 1975 and 1980) for FM-associated symptoms (classification into the FM-substitute class). Risk factor variables were selected based on the literature on associated factors or suggested risk factors for FM or WSP. Variables chosen were regional pain in the back, shoulders, or neck, headache, migraine, sleeping problems, physical (in)activity, overweight/obesity (BMI), and smoking. The variable data from the baseline situation both in 1975 and in 1981 were included (Table 2).

Table 2 Putative risk factors for fibromyalgia symptoms used in analyses and confounding variables

Variable	Assessing question and reply alternatives
age	birth date
gender	male/ female, self-report
education	eight alternatives from elementary school to college or university degree
back pain shoulder pain neck pain	“In the recent few years, have you had pain that has impaired your working capacity in your back, shoulders, or neck?” yes, no (separately for each region)
sleep	“Do you usually sleep well?” “well”, “fairly well”, “fairly badly”, “poorly”, and “cannot answer”
BMI (kg/m ²)	calculated from reported height and weight
physical activity	“Which alternative best describes your year-round leisure-time physical activity?” “I rarely exercise in my leisure time at all”, “a bit”, “fairly”, “fairly much”, and “much”
exercise frequency	“How many times a month have you lately been exercising in your leisure time?” “less than once”, “1-2 times”, “3-5 times”, “6-10 times”, “11-19 times”, and “more than 20 times a month”
smoking	Several questions concerning lifetime and current smoking habits, allowing classification into four classes: “never”, “occasionally”, “former”, and “current”
migraine	“Has a physician ever said that you have or have had a...” “migraine” (as one of the alternatives)
headache	“Do you have headaches?” “daily or almost daily”, “many times a week”, “about once in a week”, “about once a month”, “many times a year (but not every month)”, “once a year or less” and “practically never”

Because of the small number of individuals reporting sleeping “poorly” at baseline (36 /52 in 1975/1981), the first two alternatives went into the category “good sleep” (reference category) and the next two into “poor sleep”; the number of “cannot answer” replies was small as well (44/48 in 1975/1981) and were handled as missing data.

Two questions were on leisure-time physical activity. To look at physical passivity as a possible risk factor and activity as a potential protective factor meant re-classifying replies on leisure-time physical activity into three categories: physically inactive (1-2), physically active (4-5), and average (3), which served as the reference. Leisure-time exercise frequency was originally assessed by six alternatives. This study re-categorized these also as three alternatives: 1) at most twice, 2) 3-10 times (reference category), and 3) at least 11 times a month.

BMI values from both 1975 and 1981 went into four categories: at least 30 (obese), at least 25 but less than 30 (overweight), under 18.5 (underweight), and at least 18.5 but under 25 (normal weight, reference category) based on World Health

Organization criteria.

For smoking status, subjects were classified into four groups: “never”, “occasionally”, “former”, and “current” (Kaprio and Koskenvuo, 1988), with “never” as the reference category.

Reported gender, age, and education were potential confounders. Education was originally reported with eight alternatives from elementary school to college or university degree. For this study, calculation was of the mean of the formal education years for each alternative to form a continuous variable.

Impact on ability to work and mortality

In order to prospectively evaluate the influence of FM-associated symptoms on disability retirement and mortality in the twin cohort, other baseline variables from 1990 also required inclusion.

As potential confounders known to predict risk for disability retirement or mortality or both and which are also associated with FM symptoms, I controlled for age, BMI (calculated from reported height and weight), smoking status, alcohol (ab)use, depression, working status, education, and social class. Smoking status was assessed with the alternatives “never”, “occasionally”, “former”, and “current” (Kaprio and Koskenvuo, 1988); alcohol use was assessed with two questions. The question “Do you drink at least once a month more than one bottle of wine, half a bottle of spirits, or the equivalent amount of other alcoholic beverages on one and same occasion?” defined binge drinking and divided the subjects into two groups. The second question on frequency of passing out as a result of excessive alcohol intake, included 5 response categories (“never”, “once”, “2-3 times”, “4-6 times”, and “at least seven times” during the previous year).

Possible depression was assessed with the Finnish version of the Beck Depression Inventory (BDI), and the subjects were classified into three groups: none or minimal depression (BDI score 0-9), mild depression (more than 9 but less than 17), and moderate to severe depression (at least 17) (Varjonen *et al.*, 1997).

Working status was assessed in seven categories: “working outside the home” / “housewife / farmer’s wife / working at home” / “on disability pension” / “on other pension” / “student / being re-educated” / “unemployed” / “and other”. Education had been reported in the earlier questionnaire in 1975 with eight alternatives from elementary school to college or university degree. Social class was classified based on reported occupation into six categories: upper and lower white-collar workers, skilled and unskilled blue-collar workers, farmers, and unclassified/other (Central Statistical Office of Finland, 1972).

Work-related variables as well as history of sciatica or osteoarthritis were analysed

as potential effect-modifiers. Physical workload was assessed with questions that classified the subjects into two groups: light or variable work (sitting / standing and walking / standing, walking, lifting and carrying) and heavy physical work. Questions on working hours categorized the subjects either into a regular work group (“regular day work”, “regular night work”, “two-shift work without night-shift”, “never employed”), or the shift-work group (“two-shift work with night-shift”, “three-shift work”). Questions on working rate divided the subjects into two groups: forced-rate work (“I am working at a forced rate or nearly a forced rate”), and free-rate working (“I can freely or somewhat freely regulate my work rate”, or “I am not working at the moment”). Questions on working methods categorized the subjects into two groups: not having or having a chance to influence their working methods (“freely choosing methods”, “some choice”, and “not working at the moment”). Questions about specific diseases and conditions diagnosed by a physician included sciatica and osteoarthritis.

4.3.3. ZYGOSITY

Zygoty was defined with a validated questionnaire that asked questions about similarity in appearance and confusion by strangers (Sarna *et al.*, 1978).

4.3.4. OUTCOME VARIABLES FOR WORK ABILITY AND MORTALITY

The outcome variable for ability to work was a disability pension, and for mortality the vital status. The data came through register linkages described in detail in the next section.

4.4. DATA ANALYSES AND STATISTICAL METHODS

4.4.1. PREVALENCE ANALYSES OF FIBROMYALGIA-LIKE SYMPTOMATOLOGY

We performed a latent class analysis with the Latent Gold (Vermunt and Magidson, 2005) statistical analysis program used to classify multivariate categorical data into subgroups. It classifies subjects into groups based on underlying profiles of their characteristics, so that the clusters are as homogenous as possible; within clusters, the variables are as uncorrelated as possible. The aim is to achieve the smallest number of clusters that accounts for all the associations between variables.

The replies of the 49 clinical FM patients from Kiljava Hospital (see p.44) to the

eight questions chosen to characterize FM formed a profile which then served to classify the twins according to their replies into symptom classes with the latent class analysis. In this way we could estimate the prevalence of FM-associated symptoms in the twin population and then analyse whether any genetic effect appeared behind the symptom set.

To find the optimal model, i.e. the optimal number of clusters, we used the likelihood ratio chi-square statistic L_2 . We started with a one-cluster model and added successively, one by one, clusters to each successive model. The percentage reduction in likelihood ratio chi-square decreased until the 4-cluster model, after which proportional improvement was quite equal as the number of classes increased. After comparing the models with three and four clusters, we concluded that three latent classes best represented the data. The three-class model categorized the twins in class one with no or few symptoms, class two with a moderate number of assessed symptoms, and class three with a high number of symptoms, resembling FM patients. The four-class model only divided the second class into two. The genetic analyses used both three- and four-class models. We called the final three clusters latent class 1 (LC1), with no or few FM-associated symptoms, latent class 2 (LC2), with some symptoms, and latent class 3 (LC3), with many symptoms. To validate this classification method, we analyzed the clinical FM patients, who were all classified into the highest symptom class.

4.4.2. QUANTITATIVE GENETIC MODELLING

Heritability is defined as the proportion of variance in the phenotype, in this case the liability to FM-associated symptoms that is due to genetic factors. It can be estimated by comparing the discovered and estimated resemblance of relatives. A twin population allows comparison of MZ and DZ twin pairs. These pairs most often, when reared in the same family, share most environmental factors in their childhood and youth. The effect of this shared environment on variance in the phenotype of MZ and DZ twins is assumed to be the same (which actually is just an estimation). DZ pairs, however, share only approximately 50% of their genes, like any full siblings, whereas MZ pairs are genetically nearly identical. This difference can be used in the mathematical modelling. The assumption, reasonable for a presumably polyfactorial trait, is that an underlying normally distributed liability exists for this disease (in this case accumulation of FM-associated symptoms), and it becomes observable when a threshold is exceeded.

First, we studied the distributions of symptom class using maximum likelihood estimation. This method allows for missing data and operates on all available data, including that from pairs from which only one of the twins had replied. These

initial tests were needed to obtain evidence that all twins came from the same base population. They also produced the polychoric correlations which are estimates of twin similarity by zygosity and gender.

Phenotypic variance is divided into four components: additive genetic effects (A), non-additive genetic effects (D), shared environmental effects (C), and non-shared environmental effects (E). We tested whether the pairwise distribution of the three categories (latent classes) was compatible with an underlying bivariate normal distribution in liability to see whether the relative contribution of genetic and environmental factors could be estimated.

Genetic models can be tested with structural equation modelling based on different combinations of these four components: ACE, ADE, AE, CE, and E. However, non-additive genetic (D) and shared environmental (C) effects cannot be modeled simultaneously with data limited to that from twins reared together (Neale and Cardon, 1992); likewise, a DE model is biologically unrealistic. We assessed the fit of each model by the goodness-of-fit chi-square test. Based on the best-fitting model, it is possible to estimate the proportion of total variance that is attributable to additive genetic effects (a^2), non-additive genetic effects (d^2), shared environmental effects (c^2), and individual, non-shared environment (e^2); a , d , c , and e are the path coefficients from the latent variables (A,D,C, and E) to the phenotypic value.

4.4.3. ANALYSES OF OTHER RISK FACTORS

To select out the population presumed free of widespread pain or fibromyalgia and diseases that might produce symptoms similar to FM, i.e. the population at risk, meant first excluding individuals with inflammatory rheumatic diseases and incident malignancy. This then meant using the data from the Special Refund Category in the Drug Reimbursement Register held by the Social Insurance Institution and excluding those subjects with a diagnosis from ICD-9 group 202 or ICD-10 blocks or categories M05-M14, M30-M36, or M45-M46. Subjects with malignancies were excluded by use of data on incident cancers from the Finnish Cancer Registry until 1993. We then designed the requirements to exclude any individuals with possible FM or WSP at baseline. Because the first questionnaires did not consider WSP or the FM symptoms assessed in the 1990 questionnaire, we excluded individuals reporting pain both in their neck and shoulders and in their back or reporting use of analgesics for at least 180 days per year in either 1975 or 1981. In Study I, our research group had already revealed that analgesic use of this magnitude was accumulated in latent class three.

We assessed the relationship between the chosen potential risk factors and FM-

associated symptoms using multinomial regression analysis. Outcome variables were thus the three latent symptom classes, LC1, LC2, and LC3, among which the reference category was LC1 (the class with no or few symptoms).

We first checked the bivariate associations for all the chosen variables (regional pain in the back, neck, or shoulders, headache, migraine, sleeping problems, physical (in)activity, overweight/obesity (BMI), and smoking, all adjusted for age and gender. As all the chosen variables were significant in these analyses, they were included in the multivariable model analysis, adjusted for age, gender, and education.

We analyzed further the multivariable model with the data stratified for the confounders. The data collected at two baseline time points with in part the same variables offered the possibility to assess the effects of persistence as well as new onset of certain risk factors.

To assess the possible effect of familial factors, either genetic or environmental, shared by the family, we analysed the twin pairs discordant for latent class position, that is LC3 vs. LC1 (one twin classified into LC1 and the co-twin classified into LC3). If the association between the presumed risk factor and classification in LC3 depended on familial factors, no association (or at least one much weaker) would exist in this analysis between the risk factor variable and LC3. If the association depended specifically on genetic factors, we would presumably find some association among the DZ pairs (who share approximately 50% of their genes) but not in the MZ pairs (with an almost identical genotype). For this assessment we used conditional logistic regression analysis.

4.4.4. IMPACT OF FIBROMYALGIA SYMPTOMS ON ABILITY TO WORK AND MORTALITY

Analogically to the study of risk factors, individuals with inflammatory rheumatic diseases or malignancy were excluded from the sample, because these conditions can share symptoms similar to those of FM and also elevate the risk for disability or death. This procedure was carried out in the same manner as in the previous study, using the data from the Special Refund Category in the Drug Reimbursement Register held by the Social Insurance Institution and the data on incident cancers from the Finnish Cancer Registry until 1993. Individuals retired up to 1990 were excluded as well, to include only the population at risk.

For the disability outcomes we linked the twin cohort data with data from the Finnish official pension registers, the Social Insurance Institution, and the Finnish Centre for Pensions. In Finland, a disability pension can be granted on the basis of a medically confirmed illness, disease, or injury that makes an individual incapable of working or essentially diminishes the individual's ability to earn a reasonable

living by work. An insurance physician confirms the final diagnoses (coded during the follow-up as ICD-9 or ICD-10), based on comprehensive medical documents; this leads to disability retirement.

Linkage of the cohort data to the Population Register Centre (which covers all Finnish citizens) produced data on emigration and vital status of the twins.

Follow-up started from the date of the questionnaire response (in 1990) for each individual and continued till the day of start of disability compensation, emigration, death, or end of follow-up (December 31, 2004) for disability retirement, and until emigration, death, or end of the follow-up (May 1, 2009) for mortality.

For data analyses, subjects with missing data for the covariates chosen were first excluded. Data were missing for only 2% of responses as to smoking status, for 1% as to alcohol use, and 0.6% as to BMI. We analyzed hazard ratios across latent symptom classes for disability retirement and mortality using the Cox proportional hazard model and adjusting for age, gender, BMI, depression, smoking status, and alcohol drinking, as described in detail in Study III. We also made further adjustments for education, social class, and working status.

For possible effect modification, we controlled for the association between symptom class and disability retirement for depression, work-related variables, and co-morbidity with sciatica or osteoarthritis.

As in the previous study, we also assessed the possible effect of familial factors, to test the hypothesis that disability depends more on these factors than on FM-associated symptoms. For this we analysed all pairs discordant for disability retirement (one twin retired for disability and the co-twin not) to control the association of FM symptoms and disability, analogously to the method of the analysis in the previous study.

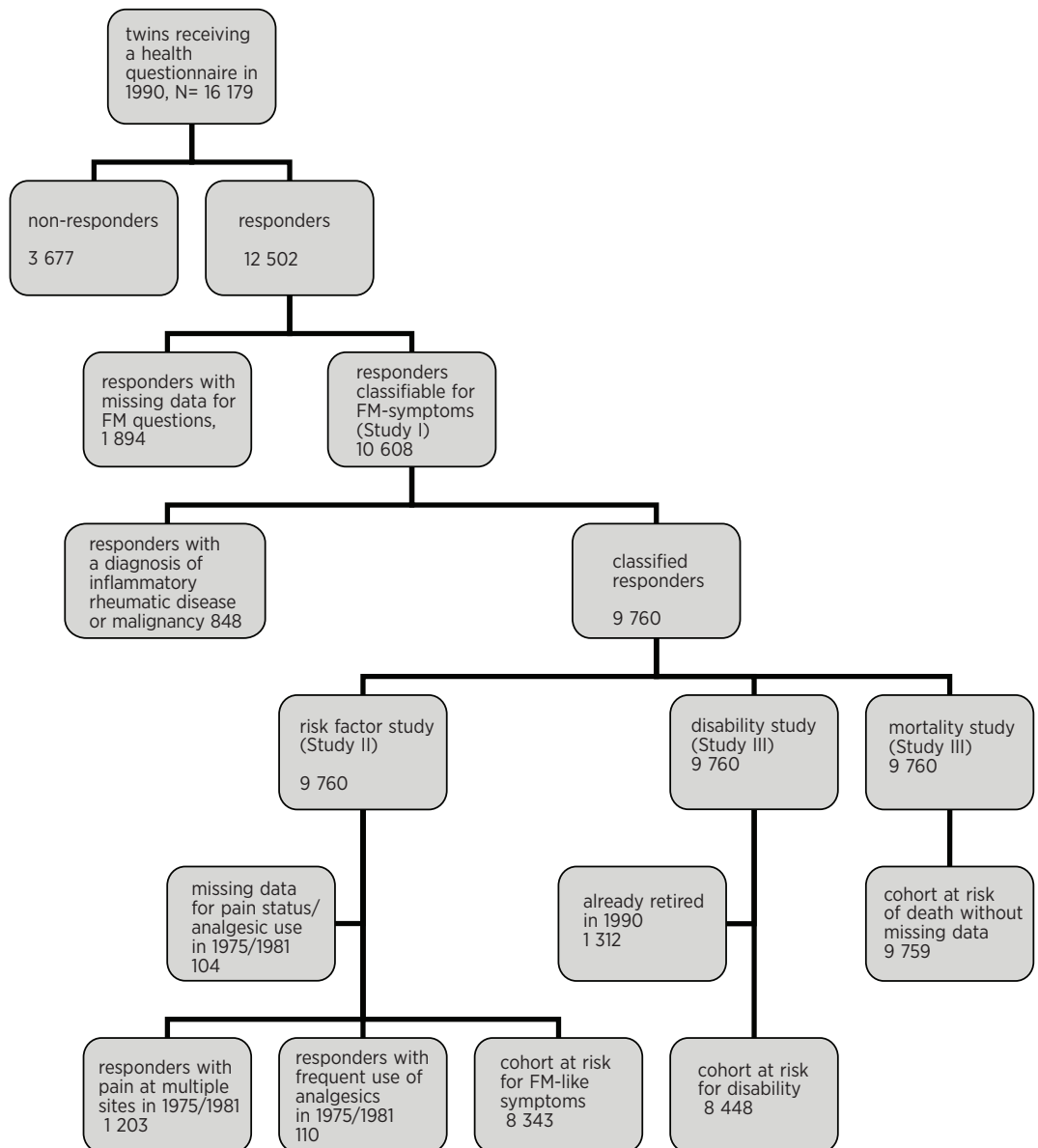
4.4.5. STATISTICAL SOFTWARE

All analyses except the pair-wise analyses in Study II used SPSS version 19, for all other analyses, Stata version 12 served as the statistical software.

5. RESULTS

Phases of the study and numbers of subjects at each phase are in Figure 2.

Figure 2 Flow chart of the study



5.1. PREVALENCE OF FIBROMYALGIA-LIKE SYMPTOMATOLOGY (STUDY I)

The mean age of the 10 608 respondents was 43.4 ± 7.6 years: for men, 43.8 ± 7.6 , and for women, the majority at 54.2%, mean age was 43.1 ± 7.6 years. Mean ages of the clinical FM patients were higher, 52.2 ± 4.9 for the 5 men and 48.3 ± 7.6 for the 44 women.

Three latent classes categorized the data with best fit. An almost equal proportion of men (12%) and women (13%) were classified in latent class three (LC3), the class in which a great majority reported many FM-associated symptoms resembling FM patients' (Table 3). In that group, men and women were surprisingly similar in their replies to the FM-question set, unlike the intermediate group LC2. To questions on other symptoms and diagnosed diseases, both genders in LC3 also replied quite similarly, except for migraine, for which there existed a general female predominance.

Table 3. Point prevalence (as percentage of individuals with a positive report) of reported symptoms and lifestyle factors and reported diseases (diagnosed by a physician) in 1990 across the latent symptom classes of twins and among the clinical FM patients, based on data collected in 1990-1992

Variable	LC1 Men	LC1 Women	LC2 Men	LC2 Women	LC3 Men	LC3 Women	FM patients
Number of subjects	2 850	3 078	1 431	1 920	582	747	49
Mean age	42.8	41.6	44.4	43.8	47.0	43.1	48.7
Morning stiffness	0.0	0.0	13.7	11.6	83.3	83.8	100.0
Evening stiffness	0.0	0.0	2.0	1.4	58.4	53.0	67.0
Neck pain & stiffness	3.4	5.6	14.0	24.3	60.0	68.5	85.7
Tender points	1.1	1.9	8.5	18.4	53.3	62.1	97.9
Numbness	2.0	2.0	11.4	12.9	59.5	51.8	85.7
Daytime tiredness	5.5	7.4	14.0	19.7	45.7	49.9	85.7
Duration m.s. <2 h ^a	0.0	0.0	56.7	51.4	84.9	89.3	83.7
Duration m.s. ≥2 h ^b	0.0	0.0	0.5	0.2	14.6	10.0	16.3
A.p.e. ^c	0.0	0.0	33.5	45.0	59.5	66.5	97.9
Night awakenings ^d	4.4	5.8	7.7	9.9	18.8	18.5	57.1
Depression mild ^e	5.7	9.5	12.0	17.3	21.0	24.4	69.4
Depression (moderate/severe) ^e	1.5	2.4	3.4	6.3	11.3	14.3	30.6
Abdominal pain	1.5	2.0	4.9	6.0	15.9	16.9	51.0
Flatulence	11.9	10.4	21.1	19.9	35.4	39.7	65.3
Diarrhoea	0.9	0.9	3.0	2.0	6.2	5.3	22.4
Osteoarthritis	2.5	1.9	9.3	10.2	27.1	33.6	59.2
Rheumatoid arthritis	0.5	0.7	2.1	2.6	9.8	10.2	10.2
Sciatica	10.8	8.8	21.5	19.5	40.3	37.7	48.9 ^f
Migraine	7.5	17.6	8.4	24.6	14.4	32.3	49.0
Never smoker	38.3	58.3	32.5	55.9	27.7	60.4	n.a.
Occasional smoker	4.4	3.0	4.1	2.4	2.1	2.9	n.a.
Former smoker	27.1	18.2	33.0	18.5	31.6	14.8	n.a.
Current smoker	30.3	20.5	30.5	23.2	38.6	21.9	n.a.
Binge drinking	43.8	11.6	45.0	13.6	49.8	12.6	n.a.
BMI (mean, SD)	25.0±3.0	23.2±3.5	25.6±3.3	24.3±4.1	26.0±3.4	25.4±4.5	n.a.

Minimum frequency set at three times per week for morning stiffness, evening stiffness, neck pain and stiffness, occurrence of tender points, daytime tiredness, abdominal pain, flatulence, and diarrhoea. Osteoarthritis, rheumatoid arthritis, sciatica, and migraine assessed by the question: "Has a physician ever said that you have or have had a..."

^a duration of morning stiffness less than 2 hours

^b duration of morning stiffness at least 2 hours

^c atmospheric-pressure effect

^d at least three times per night

^e depression assessed with the Finnish version of the Beck Depression Inventory, with the classification: 0-9 points none or minimal depression, 10-16 points mild depression, at least 17 points moderate to severe depression (Varjonen *et al* 1997)

^f number of individuals only 47

5.2. ROLE OF HERITABILITY (STUDY I)

The pairwise (polychoric) correlation tests for the three-category latent class model yielded a correlation of 0.52 for male MZ pairs, 0.16 for male DZ pairs, 0.49 for female MZ pairs, and 0.28 for female DZ pairs. The corresponding correlations for the four-category model were 0.47, 0.17, 0.45, and 0.24. The greater correlation for MZ pairs than for DZ pairs is suggestive of a genetic effect on the clustering of symptoms.

Based on this, we tested quantitative fitting of the genetic models for both three-category and four-category models, first allowing different variance components in men and women. The initial model ADE with genetic effects, both additive (A) and dominant (D), and unshared environmental (E) and gender-specific components, did not give a better fit than did the more restricted ADE and AE models, for which the variance components were confined to be equal in men and women: changes in the model fit relative to the change in degrees of freedom were non-significant ($p = 0.17$ and 0.28 for the three-category model and $p = 0.62$ and 0.34 for the four-category model). Estimates of heritability (proportion of variance due to genetic effect) in the three-category model were 50.5%, with a 95% confidence interval (CI) 44.9-55.9%, for additive genetic components, and 49.5% (95% CI 54.1-55.1%) for unique environmental components; and in the four-category model 45.6% (95% CI 40.4-50.4%) for additive genetic components, and 54.4% (95% CI 49.6-59.6%) for unique environmental components.

5.3. OTHER RISK FACTORS FOR FIBROMYALGIA (STUDY II)

Of the 8 343 subjects in the final sample analyzed for risk factors for FM-associated symptoms, 47.3% were men and 52.7% women. Their mean age in 1975 was 27.7 ± 7.3 years. Some expected gender differences for the variables occurred: in 1975, men (23.8%) reported slightly more back pain than did women (19.1%), and in 1981, this difference grew to 27.7% vs. 19.8%. Women reported more shoulder pain (7.1%) than did men (4.7%) in 1975, and this difference grew as well: to 27.7% vs. 19.8%. Men tended to be more frequently physically active than were women (17.4-18.2% vs. 9.1-10.6%). Current smokers were more numerous at both time-points among men (36.1-31.8% vs. 25.5-19.9%), with more non-smokers among women (58.2-56.4% vs. 37.6-35.6%). In 1981, 12.3% of women reported migraine, but only 4.6% of men. All the following analyses were adjusted for gender.

In 1990, 700 individuals (8.4%) in this sample were classified into LC3, a total of 2 501 individuals (30.0%) into LC2, and 5 142 individuals (61.6%) into LC1. For some variables, obvious differences emerged across these latent classes at baseline (Table 4).

Table 4. Baseline characteristics of the 8 343 subjects in 1975 and 1981 across the fibromyalgia-associated symptom classes based on latent class analysis

	In 1975			In 1981		
	LC1 %	LC2 %	LC3 %	LC1 %	LC2 %	LC3 %
back pain	7.0	25.9	36.3	18.8	28.4	37.3
no back pain	80.6	72.0	61.0	71.1	56.1	40.7
missing data	2.4	2.0	2.7	10.1	15.6	22.0
shoulder pain	4.2	8.0	11.4	9.0	17.1	23.0
no shoulder pain	93.4	89.8	85.9	73.4	59.1	47.3
missing data	2.4	2.1	2.7	17.6	23.8	27.9
neck pain	5.0	11.1	14.9	10.1	17.6	25.4
no neck pain	92.5	86.8	82.4	73.2	59.6	46.7
missing data	2.5	2.2	2.7	16.7	22.8	27.9
poor sleep	2.9	4.0	6.7	3.1	5.7	9.9
good sleep	94.3	93.6	90.1	92.5	89.7	84.7
missing data	2.8	2.4	3.1	4.4	4.6	5.4
BMI						
≥ 30	1.3	1.9	3.1	2.1	3.1	4.6
25.0 – 29.9	12.0	16.2	25.6	16.9	22.4	31.1
18.5 – 24.9	76.8	74.1	63.9	72.2	67.5	57.1
< 18.5	6.9	5.1	4.0	4.4	2.6	1.1
missing data	3.0	2.8	3.4	4.4	4.5	6.0
education (years)	8.6±3.0	8.1±2.8	7.3±2.2	9.0±3.4	8.4±3.1	7.4±2.4
missing data (per cent)	2.4	1.9	2.6	3.8	3.9	5.4
physical activity						
passive	51.9	53.7	59.3	45.6	48.2	51.6
average	31.4	32.9	28.4	34.9	35.5	32.6
active	14.3	11.2	9.7	15.6	12.4	10.4
missing data	2.4	2.2	2.6	3.9	3.8	5.4
exercise frequency/month						
at most 2 times	28.4	30.6	31.1	22.3	23.1	25.9
3-10 times	47.4	48.9	47.6	51.4	52.5	48.0
at least 11 times	18.7	15.6	14.1	20.6	18.5	18.1
missing data	5.5	4.9	7.1	5.7	5.9	8.0
smoking						
current	29.9	31.1	32.9	24.4	26.8	29.0
former	14.7	15.9	14.9	19.9	20.8	18.6
occasional	3.5	3.9	2.4	3.1	2.8	2.6
never	49.4	47.0	47.0	47.9	44.8	43.3
missing data	2.4	2.1	2.9	4.7	4.8	6.6
migraine	n.a.	n.a.	n.a.	7.6	9.4	13.6
no migraine				88.3	86.3	80.4
missing				4.1	4.2	6.0
headache frequency	n.a.	n.a.	n.a.			
daily to some days/week				1.6	3.9	7.9
once/week to once/mo				24.2	31.5	33.1
sometimes / year				42.8	43.4	39.3
never				27.4	17.0	13.9
missing data				4.1	4.2	5.9

LC1 = latent class 1 with few or no symptoms,

LC2 = latent class 2 with some symptoms,

LC3 = latent class 3 with a high frequency of FM-associated symptoms in 1990

In the bivariate analyses adjusted for age and gender, all the potential risk factors chosen significantly predicted classification into LC3, with odds ratios from 1.22 (95% CI 1.02-1.46) for physical inactivity in 1981 to 12.16

(95% CI 8.02 – 18.42) for frequent headache in 1981. In the multivariable model, only the regional pain problems (headache, back, shoulder, and neck pain), poor sleep, and high BMI remained significant risk factors (Table 5).

Table 5. Risk factors from 1975 and 1981 for fibromyalgia-associated symptoms in 1990: multivariable analyses.

	OR (95% CI) LC2 1975 variable data	OR (95% CI) LC3 1975 variable data	N	OR (95% CI) LC2 1981 variable data	OR (95% CI) LC3 1981 variable data	N
age (years)	1.02 (1.01-1.03)	1.06 (1.05-1.07)	8 343	1.02 (1.01-1.03)	1.06(1.05-1.08)	8 343
gender(female/male)	1.34 (1.20-1.50)	1.41 (1.17-1.70)	8 343	1.08 (0.94-1.23)	1.16 (0.89-1.49)	8 343
back pain (yes/no)	1.56 (1.38-1.76)	2.26 (1.88- 2.72)	8 149	1.73 (1.47-2.04)	2.99 (2.31-3.88)	7 281
shoulder pain (yes/no)	1.42 (1.14-1.77)	1.84 (1.36-2.49)	8 146	1.77 (1.41-2.21)	1.75 (1.23-2.48)	6 636
neck pain (yes/no)	1.94 (1.60-2.35)	2.34 (1.79-3.07)	8 144	1.23 (0.98-1.54)	1.76 (1.26-2.46)	6 718
poor sleep good sleep	1.27 (0.96-1.66) 1.00 (reference category)	1.78 (1.22-2.60) 1.00	8 116	1.58 (1.17-2.14) 1.00	2.34 (1.49-3.67) 1.00	7 966
BMI (kg/m-squared) ≥ 30 25-29.9 18.5-24.9 < 18.5	1.19 (0.78-1.80) 1.20 (1.03-1.40) 1.00 (reference category) 0.80 (0.64-1.00)	1.86 (1.09-3.17) 1.60 (1.28-1.99) 1.00 0.86 (0.55-1.33)	8 056	1.19 (0.81-1.76) 1.32 (1.12-1.56) 1.00 0.62 (0.44-0.88)	1.65 (0.91-3.01) 1.67 (1.27-2.20) 1.00 0.56 (0.25-1.25)	7 913
education (years)	0.96 (0.94- 0.97)	0.86 (0.83-0.90)	8 134	0.97 (0.95-0.98)	0.89 (0.85-0.92)	7 754
physical activity passive moderate active	0.94 (0.83-1.07) 1.00 (reference category) 0.90 (0.76-1.08)	1.15 (0.93-1.43) 1.00 1.00 (0.73-1.38)	8 148	1.04 (0.90-1.21) 1.00 0.88 (0.72-1.08)	1.08 (0.82-1.41) 1.00 0.87 (0.58-1.30)	8 007
exercise frequency/ month 1-2 times 3-10 times > 11 times	1.02 (0.90-1.16) 1.00 (reference category) 0.856 (0.7- 1.00)	0.98 (0.79-1.20) 1.00 0.91 (0.69-1.18)	7 889	0.96 (0.82-1.13) 1.00 1.01 (0.85-1.20)	0.94 (0.70-1.26) 1.00 1.01 (0.73-1.40)	7 849
smoking current former occasional never	1.10 (0.97-1.24) 1.14 (0.98-1.32) 1.27 (0.97-1.66) 1.00 (reference category)	1.20 (0.98-1.47) 0.97 (0.75-1.25) 0.90 (0.53-1.52) 1.00	8 146	1.11 (0.95-1.29) 1.05 (0.90-1.24) 1.12 (0.79-1.58) 1.00	1.21 (0.91-1.59) 0.95 (0.70-1.30) 0.83 (0.40-1.72) 1.00	7 936
migraine (yes/no)	n.a.	n.a.		0.86 (0.68-1.08)	1.17 (0.82-1.67)	7 986
headache frequency many/week 1-4/month some/year never	n.a.	n.a.		3.35 (2.19-5.13) 1.95 (1.62-2.35) 1.64 (1.40-1.93) 1.00 (ref. category)	7.22 (4.03-12.95) 2.22 (1.56- 3.15) 1.64 (1.19- 2.26) 1.00	7 767

The reference category for the outcome is LC1, i.e. those with no or very few fibromyalgia-like symptoms (see Study I). Odds ratios (OR) and 95% confidence intervals (CI) are provided for LC2 (with some fibromyalgia-like symptoms) and LC3 (with many fibromyalgia-like symptoms), based on latent class (LC) analyses. Risk factors are assessed from 1975 and 1981 with the exception of migraine and headache frequency, as from 1981 only.

We tested interactions of gender, age, and education with the risk factors for FM-associated symptoms in order to learn whether differences would arise in the strength of association between risk factor and outcome by strata of the covariate (men/women; under/over median age; high school education yes/no). We had no hypothesis that such interactions exist specifically for any of the risk factors. Only two of the age-group vs. regional-pain interaction comparisons were nominally significant at the $p < 0.05$ level, but neither existed after adjustment for multiple testing. Hence we have no evidence that the predictive value varies by level of any of these three covariates.

To assess the effect of persistent vs. non-persistent regional pain, we first identified a sub-sample of subjects who had replied to the questionnaires in both 1975 and 1981. They represented a great majority of our cohort at risk, a total of 5 894 individuals. The majority of them reported no pain at either time-point; more specifically, 86.9% reported no neck pain, 87.9% no shoulder pain, and 74.1% no back pain. In contrast, only 5.9% (349 individuals) reported back pain, 2.1% (123) reported neck pain, and 1.5% (89) reported shoulder pain at both time-points. Despite the small number of subjects reporting persistent pain, in a multivariable model analysis (Table 6) with all the pain variables, adjusted for age and gender, persistent back/neck/ shoulder pain yielded odds ratios approximately twice as high as the corresponding transient pain (occurring at either of the time-points). However, when headache was added to the model in the multivariable analyses of 1981, the significance of neck and shoulder pain dropped. In contrast, poor sleep (OR=2.23, 95% CI 1.39 – 3.58) and high BMI (obesity OR= 1.72, 95% CI 0.94 – 3.2 and overweight OR=1.55, 95% CI 1.17 – 2.05) remained significant risk factors.

Table 6. Risk factors for fibromyalgia-associated symptoms in 1990 in the sub-sample with regional pain data from both 1975 and 1981 (5 894 individuals): odds ratios (OR) and 95% confidence intervals (CI) for classification in LC3

	Univariate analyses a)	Multivariable analyses	
	OR (95% CI) for LC3	OR (95% CI) for LC3 1975 variable data	OR (95% CI) for LC3 1981 variable data
headache frequency 1981			
many /week	11.33 (6.63-19.35)		6.79 (3.73-12.37)
1-4 /month	2.66 (1.91-3.69)		2.06 (1.44-2.94)
some/year	1.78 (1.31-2.41)		1.53 (1.11-2.13)
never	1.00 (reference category)	not assessed	1.00
back pain (yes/no) both 1975 and 1981	6.33 (4.55-8.81)	5.20 (3.67-7.38)	4.67 (3.28-6.67)
either 1975 or 1981	2.28 (1.77-2.94)	1.97 (1.51-2.59)	1.85 (1.41-2.44)
never	1.00 (reference category)	1.00	1.00
shoulder pain (yes/no) both 1975 and 1981	4.65 (2.41-8.97)	2.10 (1.02-4.34)	1.89 (0.89-4.02)
either 1975 or 1981	2.38 (1.77-3.19)	1.56 (1.12-2.16)	1.51 (1.08-2.12)
never	1.00 (reference category)	1.00	1.00
neck pain (yes/no) both 1975 and 1981	5.78 (3.42-9.75)	3.80 (2.11-6.83)	3.32 (1.83-6.02)
either 1975 or 1981	2.23 (1.66-2.99)	1.69 (1.22-2.33)	1.51 (1.09-2.09)
never	1.00 (reference category)	1.00	1.00

The reference category for the outcome is LC1, i.e. those with no or very few fibromyalgia-like symptoms (Study I)). Odds ratios and 95% confidence intervals are provided for LC3 (with many fibromyalgia-like symptoms), based on latent class (LC) analyses. Risk factors are assessed from 1975 and 1981 with the exception of headache frequency from 1981 only.

To assess the effect of more recent pain we analysed another sub-sample by inclusion of only those subjects reporting no pain (back, shoulder, or neck) in 1975. This sample included 5 691 individuals, only 4.8% of whom were later classified into LC3. In the univariate analyses all variables except exercise frequency were significant. The number of missing answers ranged from 228 to 924 (4-16%). In multivariable analysis, ORs of the regional pain variables from 1981, including headache, decreased compared to those of the original sample. Regional back pain, sleep problems, overweight, and headache, however, still remained significant predictors. The OR for frequent headache diminished from 7.10 in the univariate analysis to 5.01 in the multivariable analysis, and for back pain, the OR diminished from 2.99 to 2.32; other changes in OR estimates varied by 20% at most.

Of the 2 345 twin pairs in this sample, 802 pairs were monozygotic (MZ), 1 401 pairs dizygotic (DZ), 142 pairs were of uncertain zygosity, and 3 653 were individual twins without their pairs. Of the 161 pairs discordant for classification in LC3 vs. LC1, 33 were MZ, 118 DZ, and 10 were of uncertain zygosity. In the pairwise analyses, we found significant associations between risk factor variable and LC classification within pairs for back pain, shoulder pain, neck pain, and headache, but not for sleeping problems or BMI. The associations identified were equally strong within DZ pairs, but with smaller statistical significance due to smaller sample sizes. Within MZ pairs, none of the associations were significant (Table 7).

Table 7. Pairwise analyses of odds ratios for classification into latent class 3 (LC3) in 1990 with FM associated symptoms in twin pairs discordant for this classification (LC3 vs. LC1)

Risk factor	Odds ratios for classification in LC3 by zygosity (with 95% confidence intervals)					
	All discordant twin pairs		Dizygotic twin pairs		Monozygotic twin pairs	
	OR (95% CI)	N	OR (95% CI)	N	OR (95% CI)	N
back pain (yes/no)	2.7 (1.4-5.2)	117	2.3 (1.1-4.6)	86	5.0 (0.6-42.8)	23
shoulder pain (yes/no)	3.1 (1.3-7.4)	91	8.0 (1.8-34.8)	64	1.0 (0.3-3.5)	23
neck pain (yes/no)	4.0 (1.5-10.7)	92	5.0 (1.4-17.3)	64	2.0 (0.4-10.9)	24
poor sleep good sleep	1.4 (0.4-4.4) reference category	144	1.3 (0.3-6.0) reference category	104	1.5 (0.3-9.0) reference category	31
BMI overweight underweight normal weight	1.9 (1.0-3.8) 0.5 (0.0-5.5) reference category	143	1.6 (0.8-3.3) 0.5 (0.0-5.5) reference category	103	5.0 (0.6-42.8) omitted ^a reference category	31
headache (yes/no)	2.1 (1.0-4.1)	132	2.2 (1.0-4.9)	97	2.5 (0.5-12.9)	27

LC1 is latent class 1 with no or very few fibromyalgia-like symptoms, LC3 is latent class 3 with many fibromyalgia-like symptoms, based on latent class (LC) analysis. All the variable data are from the year 1981.

^a The number of individuals in this category was too small for an adequate analysis.

5.4. IMPACT ON ABILITY TO WORK (STUDY III)

As shown in the flow chart of the study (Fig. 2), a total of 9 760 individuals remained for the analysis of disability retirement and mortality. Of these, a total of 1 312 were already retired in 1990, and thus the population at risk for disability retirement numbered only 8 448.

As to lifestyle factors and other potential confounders, the latent classes differed from each other. As in Table 2, men in LC3 more often reported current smoking than in the other classes, whereas across the latent classes no difference emerged in the smoking habits of women. Noticeably more men in LC3 also reported binge drinking and passing out from excessive alcohol intake than in the other classes. Again, this did not occur among the women. Both genders in LC3 were slightly older and had significantly higher BMI.

In the population at risk for disability retirement, a total of 4 952 subjects (58.6%) were classified in LC1, 2 653 (31.4%) in LC2, and 843 (10.0%) in LC3. During the 14-year follow-up, a total of 806 (9.5%) subjects retired due to disability, and for 287 subjects (36%) among these, their disability pension were granted based on musculoskeletal disorders. In LC3, the respective numbers were 217 and 104 (48%). The cumulative incidence for disability retirement in general was 25.7% in LC3, 10.6% in LC2, and 6.8% in LC1, and for disability retirement due to musculoskeletal disorders, respective cumulative incidences were 12%, 4%, and 2%. Among the diagnoses for disability retirement, fibromyalgia was rare, even among the musculoskeletal diagnoses.

After adjustment for age, gender, BMI, smoking, binge drinking, and depressive mode assessed with BDI, the hazard ratios (HR) for disability retirement in LC3 were many times that for LC1 (Table 8). Further adjustment for working status, education, and social class had minor effects: HR for disability retirement due to musculoskeletal disorders in LC3 decreased from 5.76 to 4.91 (95% CI 3.6-6.7) when education was added into the multivariable model. When adjusted for social class, that effect was even smaller (HR = 5.13, 95% CI 3.8-6.9).

Table 8. Risk for disability retirement for all causes and for musculoskeletal disorders in the three latent symptom classes of the twin cohort

	LC1 (reference class) HR (95% CI)	LC2 HR (95% CI)	LC3 HR (95% CI)
Individuals (N=8448)	4 952	2 653	843
Disability retirement			
adjusted for age and gender	1.00	1.66 (1.41-1.95)	4.08 (3.35-4.83)
multivariate model	1.00	1.59 (2.98-4.35)	3.60 (2.98-4.35)
multivariate model including BDI	1.00	1.47 (1.24-1.74)	2.93 (2.39-3.59)
Disability retirement for musculoskeletal disorders			
adjusted for age and gender	1.00	1.97 (1.47-2.64)	6.38 (4.75-8.55)
multivariate model	1.00	1.89 (4.25-7.79)	5.76 (4.25-7.79)
multivariate model including BDI	1.00	1.82 (1.35-2.47)	5.00 (3.62-6.91)

LC1 = latent class 1 with few or no symptoms,
 LC2 = latent class 2 with some symptoms,
 LC3 = latent class 3 with a high frequency of FM-associated symptoms in 1990
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In the analyses for effect modification by depressive symptoms, work-related variables, or co-morbidity with other musculoskeletal diseases, no significant changes in the HRs in the latent classes emerged.

Of the 509 twin pairs discordant for disability retirement for all causes, we found 212 (42%) retired for musculoskeletal disorders. Of all discordant pairs, most were DZ pairs (n=367), 136 were MZ pairs, and the rest were of unknown zygosity. In the pairwise analyses, the same associations between FM-associated symptom profile and disability were obvious. For all-cause disability, the HR in LC3 was 3.71 (95% CI 2.43-5.65) and for musculoskeletal disability, 5.19 (95% CI 2.74-9.87). In both of these categories, MZ pairs had corresponding HR of the same magnitude (HR = 7.2 and HR = 6.5) as DZ pairs (HR = 3.26 and HR = 4.88).

5.5. IMPACT ON MORTALITY (STUDY III)

We had to exclude one individual with missing vital status, so actually 9 759 were left for the follow-up analysis of mortality. During the 19-year follow-up (in 173 675 person-years) the twins suffered 744 deaths. The cumulative incidence of death was thus 4.3/1000 person-years. The age- and gender-adjusted HR for death was 1.43 (95% CI 1.17-1.75) for LC3 and 1.16 (95% CI 0.99-1.37) for LC2. With further adjustment for the lifestyle factors smoking (HR = 1.28, 95% CI 1.05-1.57), alcohol intake (HR = 1.18, 95% CI 0.96-1.45), BMI (HR = 1.12, 95% CI 0.91-1.37), and depressive symptoms assessed with BDI (HR = 1.01, 95% CI 0.81-1.25) risk decreased and the excess risk disappeared totally.

6. DISCUSSION

6.1. MAIN RESULTS

In this thesis we found that the prevalence of fibromyalgia-related symptoms in a large population-based sample, the older Finnish Twin Cohort, was considerable (12.5%) and was equal in both genders. As much as 50% of the variance in FM-symptom classes was explainable by heritability. These FM-related symptoms cause a substantial burden by increasing risk for work disability and by being associated with increased mortality. In this large cohort with its long follow-up, we could confirm many previously suggested risk factors for these symptoms. Regional pain, particularly frequent headache, is a strong risk factor, and its predictive strength appears to increase with the persistence or frequency of the pain. Poor sleep and high BMI are also risk factors, the effect of which is dependent on familial factors.

6.2. RESULTS IN RELATION TO PREVIOUS STUDIES

6.2.1. PREVALENCE OF FIBROMYALGIA SYMPTOMATOLOGY

This was the second epidemiologic study to assess the prevalence of fibromyalgia among Finnish adults. The fact that the study was carried out among twins, given that the genetic effect behind FM and FM-related symptoms is considerable, may have raised the prevalence to some extent. The prevalence of 12 to 13% is, however, comparable to that of most population-based epidemiologic surveys studying WSP in different countries (Croft *et al.*, 1993; Wolfe *et al.*, 1995; Macfarlane *et al.*, 1999; White *et al.*, 1999a; Buskila *et al.*, 2000; Cho *et al.*, 2012). These studies used more or less differing sets of assessments of WSP, but they can be considered to deal with the same phenomenon as our study (assessing FM-associated symptoms) with acceptable accuracy.

The finding of a similar prevalence across genders is in line with the study by Mikkelsen and colleagues (2001) among adolescent Finnish twins and also with the GP-registry study in the UK, where the WSP prevalence was 14.7% among women and 10.5% among men (Macfarlane *et al.*, 1999). In all other of these studies, differences between genders were greater. Such a difference seems to grow with stricter pain criteria, which would be in concordance with the greater pain sensitivity of women (Gazerani *et al.*, 2005; Pool *et al.*, 2007; Schmidt-Hansen *et al.*, 2007). Some differences may also reflect cultural issues.

6.2.2 ROLE OF HERITABILITY

Fibromyalgia has been considered a diffuse syndrome, the diagnosis of which has been debatable, making the estimation of FM based on an epidemiologic survey problematic. After screening for FM with epidemiologic classification methods, however, we estimated a notably high heritability explaining the variance between the classes. The role of genetic factors in FM susceptibility has long been strongly suggested based on familial occurrence. One twin study of heritability behind WSP showed results very similar to ours (Kato *et al.*, 2006b).

The considerable suggested heritability is in concordance with the results of our study on risk factors: in our analysis of discordant twin pairs, the number of MZ pairs was small in relation to the cohort at risk. Associations between regional pain problems and risk for FM symptomatology were strong, but that was not the case with poor sleep and BMI. Notably, even frequent headache was an independent risk factor, but in contrast to the whole cohort analysis, its odds ratio was smaller than for other pain variables. This agrees with the high estimated heritability rates for tension-type headache (Russell *et al.*, 2007).

Sleep problems often co-occur with FM and are suggested risk factors for FM as well. Sleep problems vary, but twin studies on insomnia in adults show a heritability of 28 to 46% for overall insomnia symptoms (Barclay and Gregory, 2013). Insomnia consists of several symptoms: difficulty in initiating or maintaining sleep, early awakening, and non-refreshing sleep. When the symptoms have been assessed individually, heterogeneity in the heritability estimates has ranged from 21% for “awaking tired” to 42% for “trouble staying asleep” and 46% for “nocturnal awakening” (this last, as was assessed in our study). Obesity and BMI are likewise highly inheritable, but their genetic predisposition can be counteracted or modified by environmental factors such as high physical activity (Naukkarinen *et al.*, 2012). Pairwise analyses in our study suggested that the association between risk for FM and poor sleep as well as high BMI could be explained by familially shared environment or heritability.

6.2.3. OTHER RISK FACTORS

Our strongest risk factor for FM symptoms was headache, in a dose-dependent manner. The association between headache and FM has appeared in cross-sectional settings: FM co-occurred particularly with chronic migraine and chronic tension-type headache (TTH) (de Tommaso *et al.*, 2011). The rather small cohort study by Forseth and colleagues (1999a, 1999b) found headache as associating with no higher FM risk. Recently a larger population-based survey explored relations between chronic musculoskeletal complaints and chronic daily headache. In that

study, headache (both migraine and non-migraine) predicted widespread chronic musculoskeletal complaints more than it did regional complaints (Hagen *et al.*, 2012). Generalized muscular hyperalgesia has been connected with frequent episodic TTH (Schmidt-Hansen *et al.*, 2007), and a recent study demonstrated chronic TTH to lead to increased peripheral pain sensitivity in skin, muscles, and nerves (Bendtsen and Fernandez-de-la-Penas, 2011). However, in contrast to findings of Hagen and colleagues (2012), here, migraine did not predict FM symptoms. Our prevalence of reported migraine (8 to 14%) is comparable with prevalences of other epidemiologic studies (Merikangas, 2013; Radtke *et al.*, 2009). Moreover, a self-report of physician-diagnosed major chronic disease has been shown to correlate well with data in medical records (Haapanen *et al.*, 1997). Our assessment in this regard can therefore be considered reliable.

Our other strong predictor of FM symptoms was back pain, consistent with the findings by Forseth and colleagues (1999a) and Mikkelsen and colleagues (2008). Shoulder and neck pain were also significant predictors, with somewhat smaller odds ratios, in line with the results of the Mikkelsen-group study among schoolchildren. Risk for FM symptoms was multiple if back pain was reported both in 1975 and 1981, thus representing either persistent or recurrent back pain. This is consistent with findings of the small cohort study by Forseth and colleagues, in which pain duration over six years was predictive of FM.

Numerous studies have shown the association between sleep disturbance and increased sensitivity to painful stimuli and also an increased intensity level of chronic pain (Chiu *et al.*, 2005; Moldofsky, 2010; Okifuji and Hare, 2011; Palma *et al.*, 2013). We therefore expected poor sleep to predict FM symptoms, which it did. This is in line with the recent report of Mork and Nilsen (2012), in which the risk ratio for clinical FM increased dose-dependently in association with sleep problems. That study also found an increased risk for women (all participants were women) aged over 45. We found no effect-modification by age, but the mean age at baseline was much lower than for Mork and Nilsen.

High BMI elevated risk for FM symptoms among those overweight by BMI. In our sample population at both baseline time-points, few individuals were obese, in concordance with Finland's relatively low prevalence of obesity, and obesity thus lost its significance as a predictor. In the Nord-Trøndelag Health Study (Mork *et al.*, 2010) overweight and obesity were both significant risk factors, but the proportion and the number of obese subjects was markedly larger than ours.

Smoking theoretically causes muscle pain through its vascular effects, and addiction problems and pain sensitivity share some background mechanisms. Even though smoking is a suggested risk factor for back pain (Shiri *et al.*, 2010), the predictive effect of smoking was lost in the multivariable analysis.

Physical activity variables, based on both self-assessment and report of exercise

frequency, also lost their association with FM symptoms in the multivariable analysis, opposite to our expectations and the results of Mork and colleagues (2010). This may have several explanations. Firstly, the effect may be greater for a more strictly defined outcome (clinical FM) than for our symptom class. Secondly, our primary parameters for physical activity may have been insufficiently accurate. Thirdly, other, more powerful factors diminished the effect in the final model. These factors were not included in the Mork-group study.

To our knowledge, this is the first analysis of risk factors for FM assessing also the role of confounding by genetic background. Given the role of genetic effects behind the variance in the symptom classification, the small number of discordant twin pairs and the decreasing proportion of MZ pairs among them were to be expected. In the pairwise analyses, associations between LC3 and the pain variables: headache, back, shoulder, and neck pain, remained significant. However, this was not the case between LC3 and sleep or BMI, suggesting confounding by genetic or environmental familial factors. Others have shown the role of heritability as well as environmental familial factors in obesity (Silventoinen *et al.*, 2010; Xia and Grant, 2013). Sleep is a complex process in which both genetic and environmental factors, including familial environmental factors, are likely to be important (Barclay and Gregory, 2013). Confounding is not improbable. None of the associations in our MZ pairs was significant, but this may be solely a consequence of our small sample. It may also be a consequence of full adjustment for genetic background. Although some loss of statistical significance occurred, because of the small number of pairs, associations for headache and back pain were equally strong in all pairs and in DZ pairs analysed separately, which could suggest an independent association.

6.2.4. IMPACT ON ABILITY TO WORK

The risk for disability retirement was markedly increased in LC3, that is, the group with the most FM-associated symptoms when compared to the other two latent classes. Though few fibromyalgia diagnoses emerged as the main diagnosis for disability retirement in this group, the proportion of musculoskeletal diagnoses was distinctly larger than in the other latent classes. Many potential reasons exist for the rarity of FM diagnoses: Firstly, fibromyalgia has been neither very well known nor recognized among physicians. Even specialists such as rheumatologists and physiatrists may not recognize it when focusing on other diseases that would need specific treatment. Pain as such is still underestimated and undertreated. Secondly, other underlying diseases (like lumbar disc degeneration) and secondary diseases (like depression) may be more prominent and obvious reasons for the patient's functional decline and were therefore automatically chosen as the main and final

diagnoses for the disability retirement. Thirdly, because FM has rarely been accepted as the main cause of disability retirement in Finland, physicians may avoid this diagnosis and use other coexisting diagnoses instead. Fourthly, the considerable overlap of FM with other pain diseases, both degenerative and inflammatory, may make it difficult to judge these alternatives' relative importance.

Pain per se has proved to be disabling: in several studies, multi-site pain has been associated with reduced work ability, with a trend toward correlations between number of pain sites and disability (Miranda *et al.*, 2010), and even in a predictive manner with a dose-dependent effect correlated with number of pain sites (Kamaleri *et al.*, 2009; Haukka *et al.*, 2013).

High depression-symptom scores mediated some of the effect of the symptoms. The assessment tool, the Beck Depression Inventory (BDI), includes subunits related also to sleep problems and pain, which can raise the score. The highest scores associate well, however, with clinical depression also in subjects with pain. A major depressive disorder markedly enhances the risk for work disability (Holma *et al.*, 2012), but subjects in LC3 with BDI scores indicative of moderate or severe depression amounted to only approximately 13%. The proportion with clinical major depressive disorder is probably even smaller. As much as 19% of the subjects in LC3 reported at least three night-time awakenings. This actuality raises their BDI scores, and the sleep problem eventually impairs their functional ability. Insomnia or night-time awakenings as such can lead to transient work disability ("sick leave"). A study among Finnish public-sector employees revealed that sleep disturbance predicted disability based on musculoskeletal-disorder diagnoses (Salo *et al.*, 2010).

A genetic liability may contribute to total disability retirement (Harkonmaki *et al.*, 2008) as well as to FM (this study). However, according to our analyses among the twins discordant for disability retirement, both MZ and DZ twins, the association between FM symptoms and disability retirement remained strong. This contradicts the hypothesis that familial factors would mediate this association.

Work-related variables have been identifiable risk factors for disability retirement (Karpansalo *et al.*, 2002; Kärkkäinen *et al.*, 2013). We could not affirm this in our study, and analysis of our sub-population who worked outside the home did not change these results. Of the clinical FM patients who had even more symptoms, only 20% were retired due to disability. What thus seems unlikely is that their unbearable symptoms would have selected the most disabled subjects out of the workforce at baseline. One possible explanation is that those subjects with a heavy symptom load had chosen physically light work more suitable for their health status. Another explanation is that the symptoms were equally harmful during all work tasks.

An important conclusion is that FM symptoms have a major impact on functional capacity and should be actively treated and considered in rehabilitation.

6.2.5. IMPACT ON MORTALITY RISK

The very long follow-up in this twin study was able to show an increased mortality risk among the latent class with many FM symptoms. This was, however, fully accounted for by life-style factors, mainly smoking. Further adjustment for alcohol intake, depression, and BMI abolished any increase in hazard ratio. Related to studies on WSP and mortality, our results are in line with the Swedish study by Andersson and colleagues (2009) with its increased risk which was abolished by adjustment mainly for age, gender, and smoking. That study dated from approximately the same time period as ours and had the same kinds of exclusions at baseline. The study using MiniFinland data from 1979 to 1994 also found no increased mortality risk after extended adjustment (Macfarlane *et al.*, 2007). Cumulative incidences of death seemed to decrease across these studies as a function of study time period, probably reflecting a general positive development in public health and medical care.

None of the later studies could repeat the findings of Macfarlane and colleagues as to their UK findings from 1991 to 1999 of increased mortality risk specifically due to malignancy in the WSP group. Relationships between smoking, alcohol intake, depression, BMI, and pain are complex. All of them but pain have in several studies been strongly associated with increased mortality risk. Focusing on lifestyle factors and depression in addition to the pain problem in health care would be very important in order to improve patients' quality of life and to prevent higher mortality.

6.3. LIMITATIONS AND STRENGTHS OF THE STUDY

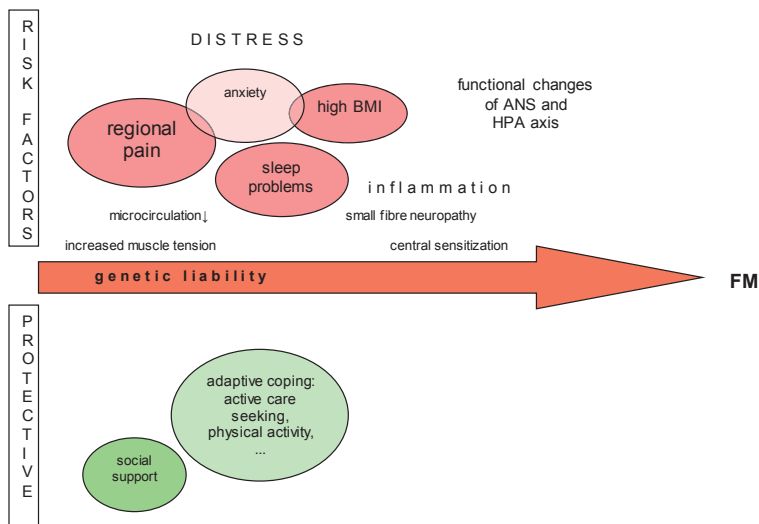
The most problematic issue in the studies of this thesis is the screening and identification of FM by means of an epidemiologic survey. All the questionnaires were designed before the ACR 1990 classification criteria for FM were published, and therefore not even the survey in 1990 included any pain-drawing or any items assessing WSP. However, it included items designed to assess FM based on the preliminary criteria by Yunus (1989). Criteria for WSP in the ACR 1990 report are not straightforward, either (Wolfe *et al.*, 1990). The prevalence of individuals classified into LC3 with a high number of FM-associated symptoms is comparable with findings in the various epidemiologic surveys assessing WSP (Croft *et al.*, 1993; Wolfe *et al.*, 1995; Macfarlane *et al.*, 1999; White *et al.*, 1999a; Buskila *et al.*, 2000; Cho *et al.*, 2012). The classification method also accurately identified the clinical FM patients. Validation succeeded in one direction, but unfortunately we lacked the resources to validate the method in the other direction. Our screening method can, however, be considered reasonably reliable; both our method and the various WSP assessments target subjects who have symptoms of FM, some of whom may also have clinical FM.

Strengths of the studies are in the large twin sample and the long time-perspective of the data collection. The Older Finnish Twin Cohort is large, which gives the statistical evaluation power. It is population-based, which minimizes selection bias, even though bias always occurs in studies with voluntary participation. Participation of the cohort subjects was generally high, which improves reliability. The time-perspective of the two baseline questionnaires and the follow-up assessment after 9 to 14 years makes it possible to evaluate temporal associations and the persistence of phenomena. An important strength is also the comprehensive and accurate Finnish registries, which provides us with reliable individual data about major diseases, work disability, vital status, and emigration.

6.4. GENERAL CONSIDERATIONS

Based on the literature and the results of this study we could make a hypothesis as to the development of FM:

Figure 3. Hypothesis of development of fibromyalgia



ANS = autonomic nervous system
 HPA axis = hypothalamic-pituitary-adrenal axis

One risk factor for FM is underlying genetic liability. Other independent risk factors are regional pain problems such as headache, back pain, and neck pain. Headache may be connected with actual pronounced psychological distress (Figure 3). In addition, underlying enhanced sensitivity to distress or anxiety evoked

by environmental factors may lead to generally increased muscle tension and a slow spreading of pain. At the same time, it may lead to sleep problems: night-time awakenings and difficulties in falling asleep. This, in turn, may contribute to maintenance of the increased muscle tension. Regional pain as such has a tendency, in the surrounding muscles, to create increased tension. The continuing pain may cause changes in top-down pain regulation, leading even to enlarged pain areas (Arendt-Nielsen and Graven-Nielsen, 2011).

Increased muscle tension may cause changes in the local microcirculation (Gerdle *et al.*, 2010). When chronic, this may result in neuropathic changes in the small nerve fibres, aggravating the pain. Disturbed microcirculation, high BMI, and poor sleep may all promote an imbalance between the body's proinflammatory and anti-inflammatory reactions, particularly reflected in increased levels of proinflammatory cytokines. These cytokines may activate trigger points and cause peripheral sensitisation (Bazzichi *et al.*, 2007; Wang *et al.*, 2009; Hernandez *et al.*, 2010; Sarzi-Puttini *et al.*, 2011). Inflammatory mechanisms have also been indicated in neuropathic pain.

Poor sleep, prolonged regional back or neck pain, frequent headache, and high BMI can all be both intra-personally and inter-personally extremely distressing. On the other hand, symptoms like poor sleep and frequent headache can also be consequences of distress. Increased psychological distress as such may augment a development towards widespread pain and clinical fibromyalgia. Psychosocial distress has emerged as a fact predicting multi-site pain -- and vice versa (Haukka *et al.*, 2011).

The association of high BMI and poor sleep with fibromyalgia seemed confounded here by familial factors, in other words, they may share some degree of genetic aetiology or environmental factors appearing by the family. The latter may be due to behavioural patterns learned from within the family culture, related, for instance, to care-seeking or means of coping.

Social support may help to prevent the development of WSP (Bergman *et al.*, 2002) and FM, probably through many mechanisms. Support may relieve distress, supply care and inspire seeking of care, and aid in adaptive coping with problems that may in other circumstances lead to FM. An active method of coping would include physical activity, distraction (from attention to pain), active distress-management, relaxation, and weight control. These may help to reduce back pain, neck pain, poor sleep, and also general muscle tension. In other words, social support may prevent WSP and FM before any functional changes in central pain modulation become established. These changes are, however, reversible (Yarnitsky *et al.*, 2014), and active management can be successful also in a chronic conditions. Education may help in active coping. On the other hand, favourable inherited psychological traits and learned behavioural skills and patterns may also "expose" to higher education and active coping.

7. CONCLUSIONS

We have calculated the prevalence of FM-associated symptomatology as a substitute for FM or WSP among a population-based large Finnish twin cohort and found it to be approximately 13% with no significant gender difference. Our study revealed that heritability is considerable: genetic factors explained 50% of the variance in symptom classification. Prospective analysis of putative risk factors for FM symptoms confirmed headache, back and neck pain, high BMI, and poor sleep to be significant predictors. High frequency of headache and persistence of back and neck pain amplified the risk.

Clustering of FM-associated symptoms predicted disability retirement, which was manifold that in other symptom classes with fewer FM-associated symptoms. After careful exclusions in a 19-year follow-up, the burden of FM-related symptoms was associated with higher risk of death. This finding was fully accounted for by smoking, alcohol consumption, and depressive mode, however.

FM symptoms and associated lifestyle factors and co-morbidities require attention and active management in health-care system. This is important not only in order to alleviate individual suffering but also to prevent disability. Further research is essential to clarify whether early active management of known risk factors such as headache, back or neck pain, obesity or overweight, depressive mode, and sleep problems would prevent development of FM symptoms.

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