Tampere University

ALEKSI VARINEN

Background, Comorbidities, and Experiences of Care among Finnish Patients with Fibromyalgia, with a Special Focus on Depression and Hypothyroidism

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PunaMusta Oy – Yliopistopaino
Joensuu 2023

To my family

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Tampere, July 2023
Aleksi Varinen

ABSTRACT

Fibromyalgia is a somatic syndrome that is characterized by chronic widespread pain and other somatic symptoms. The majority of patients with a fibromyalgia diagnosis are female. A growing number of studies have shed light on the factors behind this syndrome, but its exact aetiopathogenesis and long-term course of symptoms are still somewhat unclear. However, it has become evident that several external factors such as psychological stress can trigger fibromyalgia.

Previous studies have shown that various adverse life events are linked to chronic widespread pain and might also be linked to the onset of fibromyalgia, but the association has not been confirmed by larger studies. Furthermore, there are only a few studies addressing the long-term effects of childhood peer bullying victimization and none of them focus on fibromyalgia.

There are also several difficulties relating to the diagnostic process of fibromyalgia, and many patients find this time confusing and burdensome. Furthermore, a fibromyalgia diagnosis does not always provide an adequate explanation for the patient's experiences, and this uncertainty together with repetitive rule-out tests for other diseases might also lead to the overdiagnosis of the subclinical manifestations of these diseases, such as hypothyroidism. However, there is a lack of studies on over- and underdiagnosis relating to fibromyalgia especially from the patient's point of view.

This thesis consists of two sets of data: the Health and Social Support (HeSSup) postal questionnaire study and the Patients with Fibromyalgia in Finnish Primary Health Care study conducted at Nokia Health Centre. We had four research questions: 1. Is there an association between fibromyalgia and childhood adversities in the general population (HeSSup)? 2. Is there an association between self-reported bullying victimization in childhood and self-reported fibromyalgia in adulthood (HeSSup)? 3. What are the experiences of patients with fibromyalgia during the

diagnostic process, and how do patients with fibromyalgia wish their treatment to be improved (Nokia data)? 4. What was the occurrence of thyroid hormone treatment among patients with fibromyalgia, and were care guidelines followed (Nokia data)? Furthermore, we had the unpublished results of the one-year follow-up from the Nokia Health Centre data.

In the HeSSup study, we used answers to postal questionnaires from 1998, 2003, and 2012 to allocate respondents to a group that had self-reported fibromyalgia (n=515) or else to a group not reporting fibromyalgia (n=11,409). We used these data to analyse associations between six childhood adversities and fibromyalgia, as well as associations between peer bullying victimization in childhood and fibromyalgia. In the Patients with Fibromyalgia in Finnish Primary Health Care study initiated in 2015, we identified 208 patients with fibromyalgia from the patient records at Nokia Health Centre (population 33,000). We sent an information letter with five questionnaires to patients, and an appointment with a GP was scheduled for those responding to the questionnaires (n=103). Altogether 96 patients had fibromyalgia and were included in the study after the GP's appointment. Information on the use of levothyroxine and the patient's thyroid function was obtained from the patient records. For the qualitative part of the study, four focus groups including 18 patients in total were formed using purposive sampling. The interviews were recorded and an interview guide was followed. The experiences of patients with fibromyalgia were coded according to a thematic analysis process resulting in seven themes.

The main findings of these studies show that all six childhood adversities had a significant association with fibromyalgia. Furthermore, peer bullying victimization was also associated with fibromyalgia, but if depression was added as a covariate, this association was no longer statistically significant. Thus, depression seems to have a role in the development of later-life fibromyalgia, but this is a subject for further studies. In the qualitative study, patients appreciated continuity of care as well as a good patient-doctor relationship. Uncertainty was present on several occasions during the diagnostic process and treatment. We also found that there was a considerable overdiagnosis of subclinical hypothyroidism in our study population, suggesting that patients with fibromyalgia might be prescribed unnecessary levothyroxine. In our follow-up, depressed patients seemed to slightly benefit from treatment for depression.

The findings of adverse childhood experiences and peer bullying are in line with the previous literature. In our qualitative study, a new finding was the contradiction that patients had experienced at several levels in health care and in society. Some patients were even advised to hide their diagnosis from other health care professionals in order to retain their credibility. In our study, levothyroxine use for subclinical hypothyroidism was more common than in some other studies, but on the other hand similar numbers have been suggested in the recent literature. As a result, we suggest that further studies seek to confirm the potential association between fibromyalgia and inappropriate thyroid hormone treatment, which might be an example of a situation in which a patient with a functional syndrome is being overtreated for a subclinical condition. We also suggest further studies on the role of depression in patients with fibromyalgia in the development of symptoms. In addition, the effectiveness of treatment of depression for patients with fibromyalgia is a subject for further studies.

TIIVISTELMÄ

Fibromyalgia on toiminnallinen oireyhtymä, joka ilmenee laaja-alaisena kipuna ja muina somaattisina oireina. Suurin osa diagnoosin saaneista on naisia. Oireyhtymästä kertyy jatkuvasti lisää tutkimustietoa, mutta tarkka etiopatogeneesi sekä oireiden pitkäaikaisennuste ovat silti edelleen jonkin verran epäselviä. On kuitenkin selvää, että lukuisat ulkoiset tekijät, kuten psyykkinen kuormitus, voivat laukaista oireilun.

Aiempien tutkimusten pohjalta tiedetään, että monenlaiset kuormittavat elämäntapahtumat sekä lapsuusaja negatiiviset kokemukset ovat kytköksissä laaja-alaiseen kipuun ja niillä voi myös olla tekemistä fibromyalgia-oireilun puhkeamisen kanssa. Tätä yhteyttä ei kuitenkaan olla varmistettu laajoilla tutkimuksilla. Lisäksi vain harvoissa tutkimuksissa on selvitetty lapsuusiän koulukiusatuksi tulemisen pitkäaikaisvaikutuksia ja yksikään näistä tutkimuksista ei ole keskittynyt fibromyalgiaan.

Fibromyalgian toteamiseen liittyy monia hankaluuksia ja useat potilaat kokevat tämän ajanjakson hämmentävänä ja kuormittavana. Lisäksi diagnoosi ei aina tuo riittävää selitystä potilaan kokemille oireille ja tämä epävarmuus yhdistettynä toistuviin poissulkututkimuksiin saattaa johtaa joidenkin sairauksien subkliinisten ilmenemismuotojen ylidiagnostiikkaan. Yhtenä esimerkkinä tällaisesta voi olla kilpirauhasen vajaatoiminta. Kattavaa tutkimustietoa fibromyalgiaan mahdollisesti liittyvästä yli- ja alidiagnostiikasta ei kuitenkaan kirjallisuushaun perusteella ole löydettävissä, etenkään potilaan näkökulmasta

Tämä väitöskirja pohjautuu kahteen erilliseen aineistoon: Health and Social Support (HeSSup) sekä Patients with Fibromyalgia in Finnish Primary Health Care (Fibromyalgia potilaat suomalaisessa perusterveydenhuollossa). HeSSup oli postitse toteutettu kyselytutkimus. Patients with Fibromylgia in Finnish Primary Health Care oli Nokian kaupungin terveyskeskuksessa tehty tutkimus Tutkimuskysymyksiä oli neljä: 1. Onko fibromyalgian ja lapsuuden negatiivisten kokemusten välillä yhteyttä

väestöotoksessa (HeSSup) 2. Onko itseilmoitetun lapsuudessa tapahtuneen koulukiusatuksi tulemisen välillä yhteys aikuisiällä raportoituun fibromyalgiaan (HeSSup) 3. Fibromyalgia potilaiden kokemukset oireyhtymän diagnostiikkaan liittyen sekä miten potilaat itse toivovat hoitoa kehitettävän (Nokian aineisto) 4. Tyroksiinihormonikorvaushoidon esiintyvyys fibromyalgiapotilailla sekä oliko hoidon aloituksessa noudatettu hoitosuosituksia (Nokian aineisto). Lisäksi mukana on aiemmin julkaisemattomia tuloksia fibromyalgiapotilaiden vuoden seurannasta Nokian terveyskeskuksen aineistosta.

HeSSup-tutkimuksessa käytettiin osallistujien vastauksia postin välityksellä toteutettuihin kyselyihin vuosina 1998, 2003 sekä 2012. Vastaajat jaettiin kahteen ryhmään: niihin, jotka raportoivat heillä todetun fibromyalgian (n=515) sekä niihin, jotka eivät raportoineet fibromyalgiaa heillä todetun (n= 11 409). Tätä aineistoa käytettiin sen analysoimiseen, oliko kuudella kysytyllä lapsuuden negatiivisella elämäntapahtumalla yhteyttä fibromyalgiaan, sekä oliko lapsuudessa tapahtuneella koulukiusatuksi tulemisella yhteyttä fibromyalgiaan. Nokian terveyskeskuksessa vuonna 2015 aloitetussa tutkimuksessa terveyskeskuksen potilaskertomuksesta löytyi 208 fibromyalgiapotilasta (Nokian kaupungin väkiluku oli 33 000). Heille lähetettiin kirje, joka sisälsi tietoa tutkimuksesta sekä viisi kyselyä. Tämän jälkeen vastanneille (n=103) varattiin yleislääkärin vastaanottokäynti. Yhteensä 96:lla vastaanotolle saapuneella potilaalla todettiin fibromyalgia ja he muodostivat tutkimusjoukon. Tiedot tyroksiinihoidosta sekä kilpirauhasarvot saatiin potilaskertomuksesta. Tutkimuksen laadullinen osio sisälsi neljä fokusryhmää, joihin osallistui yhteensä 18 potilasta. Ryhmät muodostettiin käyttäen harkintavalintaa. Haastattelut nauhoitettiin ja niissä käytettiin tukena haastattelurunkoa. Potilaiden kokemukset ryhmiteltiin koodeiksi temaattista analyysia noudattaen ja näistä muodostui seitsemän teemaa.

Tutkimusten päätulokset olivat, että kaikilla kuudella tutkitulla lapsuuden negatiivisella elämäntapahtumalla oli yhteys fibromyalgiaan. Lisäksi myös koulukiusatuksi tuleminen oli yhteydessä fibromyalgiaan, mutta kun masennus lisättiin muuttujaksi tilastolliseen malliin tämä yhteys ei ollut enää tilastollisesti merkitsevä. Masennuksella näyttäisikin olevan merkitystä fibromyalgian kehittymisessä, mutta tämän yhteyden selvittäminen vaatii lisää tutkimuksia. Laadullisessa tutkimuksessa tuli esiin, että potilaat ilmaisivat arvostavansa niin hoidon jatkuvuutta kuin myös hyvää potilas-lääkärisuhdetta. Toisaalta epävarmuus oli läsnä useaan otteeseen niin diagnostisen prosessin kuin hoidonkin aikana. Tämän

lisäksi tutkimuksessa selvisi, että subliinisen hypotyreoosin suhteen vaikuttaisi fibromyalgiapotilailla olevan ylidiagnostiikka ja tyroksiinin tarpeetonta käyttöä. Seurantatutkimuksen osalta vaikuttaisi siltä, että masentuneet fibromyalgiapotilaat hyötyvät jonkin verran masennuksen hoidosta.

Löydökset koskien lapsuuden negatiivisia elämäntapahtumia sekä koulukiusaamista ovat linjassa aiemmin kirjallisuuden kanssa. Laadullisessa tutkimuksessa uutena löydöksenä esiin nousivat ristiriidat, joita potilaat olivat kokeneet monella tasolla terveydenhuollossa sekä yhteiskunnassa. Joitain potilaita oli jopa neuvottu salaamaan diagnoosinsa muilta terveydenhuollon työntekijöiltä oman uskottavuutensa säilyttämiseksi. Aineistomme perusteella tyroksiinin käyttö subliiniseen kilpirauhasen vajaatoimintaan oli yleisempää kuin joissain muissa tutkimuksissa, mutta toisaalta osassa tutkimuksia on esitetty samankaltaisia lukuja. Lisää tutkimuksia mahdollisesta fibromyalgiaan liittävästä epätarkoituksenmukaisesta kilpirauhashormonin määräämisestä kuitenkin tarvitaan. Toisaalta tämä saattaa olla vain yksi esimerkki tilanteesta, jossa toiminnallista oireyhtymää sairastavan potilaan oireita epäasianmukaisesti hoidetaan jonain muuna subkliinisenä sairautena. Masennuksen roolista niin fibromyalgian puhkeamisen suhteen kuin myös masennusoireiden hoidon tehosta tarvitaan lisää tutkimuksia.

CONTENTS

List of Figures

List of Tables

Table 14. Thyroid function of patients (n=16) with levothyroxine treatment whose initial TSH and T4-V level information was available from the patient records in the Patients with Fibromyalgia in Finnish Primary Health Care study.

Table 15. Development of symptoms reported by patients with fibromyalgia in a follow-up questionnaire in the Patients with Fibromyalgia in Finnish Primary Health Care study.

ABBREVIATIONS

AAPT	The Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks - the U.S. Food and Drug Administration and the American Pain Society Pain Taxonomy
ACR	American College of Rheumatology
BBCS	British Birth Cohort Study
BDI	Beck's Depression Inventory
BDS	Bodily Distress Syndrome
CD	Cluster of Differentiation
CI	Confidence Interval
COREQ	Consolidated Criteria for Reporting Qualitative Research
EQ	EuroQol
FIQ	Fibromyalgia Impact Questionnaire
fMRI	Functional Magnetic Resonance Imaging
GABA	Gamma-Aminobutyric Acid
GP	General Practitioner
HeSSup	Health and Social Support
HILMO	Finnish Hospital Discharge Register
HPA	Hypothalamic Pituitary Adrenal
ICD	International Classification of Diseases
IL	Interleukin
MUS	Medically Unexplained Symptoms
NSAID	Nonsteroidal Anti-Inflammatory Drugs
ÖMPSQ	Örebro Musculoskeletal Pain Screening Questionnaire
OR	Odds Ratio
PET	Positron Emission Topography
PHQ	Patient Health Questionnaire
PSD	Polysymptomatic Distress
RR	Risk Ratio

SD	Standard Deviation
SNRI	Serotonin and Noradrenaline Reuptake Inhibitors
SPECT	Single-Photon-Emission Computed Tomography
SPSS	Statistical Package for the Social Sciences
SRQR	Standards for Reporting Qualitative Research
SS	Symptom Severity
SSRI	Selective Serotonin Reuptake Inhibitors
T4-V	Thyroxine
TSH	Thyroid Stimulating Hormone
US	United States
WHO	World Health Organization
WPI	Widespread Pain Index

ORIGINAL PUBLICATIONS

Publication I Varinen, A, Kosunen E, Mattila K, Koskela T, Sumanen M. The relationship between childhood adversities and fibromyalgia in the general population: Journal of Psychosomatic Research; 2017:137–142.

Publication II Varinen A, Kosunen E, Mattila K, Suominen S, Sillanmäki L, Sumanen M. The association between bullying victimization in childhood and fibromyalgia. Data from the nationwide Finnish health and social support (HeSSup) study based on a sample of 64,797 individuals. Journal of Psychosomatic Research 2019:48–53.

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Publication IV Varinen A, Vuorio T, Kosunen E & Koskela TH. Experiences of patients with fibromyalgia at a Finnish Health Centre: A qualitative study. European Journal of General Practice, 2022:157–164.

This thesis also includes unpublished material.

1 INTRODUCTION

For decades, fibromyalgia has remained something of a mystery to medicine. Some physicians viewed it as a psychogenic condition, but this outdated view has been overturned by recent research (1). Although the exact aetiopathogenesis is still slightly unclear, the disturbance in pain regulation and central sensitization play a significant role in its pathogenesis (1,2). Central sensitization and fibromyalgia can be long-term disorders and many external or internal factors may trigger them (3).

There are challenges relating both to the diagnosis and treatment of fibromyalgia. Due to the functional character of fibromyalgia syndrome, laboratory tests as well as other clinical markers are normal for patients with fibromyalgia, and various classifications and diagnostic criteria have been developed, which may cause confusion for both the patients and clinicians (4,5). Patients also find the diagnostic process of fibromyalgia confusing, as they often have long searched for a diagnosis and have overlapping symptoms with other diseases or somatic syndromes, causing uncertainty and confusion (6,7).

Numerous traumatic incidents and stressful life events are connected to the onset of fibromyalgia and chronic widespread pain (8–13). The relationship between chronic widespread pain and childhood adversities was confirmed by a British cohort study (14). Depression is a common comorbidity with fibromyalgia, and the neurotransmitters connected to pain also have an effect on mood (3). Furthermore, it has been suggested that those who have genetic risk factors for fibromyalgia and depression are particularly vulnerable to triggering incidents (15). Interactions between genetic and various environmental factors together with physiological, psychological, behavioural, and cognitive factors lead to the manifestation of symptoms of fibromyalgia (16). Previous studies have shown that peer bullying has several long-term adverse effects, such as suicidal behaviour, depression, fewer social relationships, and worse health-related quality of life (17–19). In addition, workplace bullying is associated with newly diagnosed fibromyalgia, and being the target of bullying is associated with chronic pain in adolescence (20,21).

Despite this considerable evidence, the relationship between fibromyalgia and childhood adversities has not been clearly established (22). Furthermore, there

are no previous studies addressing the association between bullying victimization in childhood and fibromyalgia in adulthood.

There are also diagnostic inaccuracies with fibromyalgia syndrome. Rheumatic diseases can be falsely labelled as fibromyalgia, leading to the overdiagnosis of fibromyalgia (23). It also appears that some physicians do not accept the diagnosis of fibromyalgia and are not willing to diagnose it even if the patient has the typical symptoms, which may result in underdiagnosis (24). Despite this, there are no previous studies addressing the under- and overdiagnosis of fibromyalgia from the patients' perspective.

The use of rule-out tests in the diagnostic process of fibromyalgia might lead to the overdiagnosis of subclinical manifestations of other conditions, such as hypothyroidism (25–27). Accordingly, the use of levothyroxine for subclinical hypothyroidism has increased in recent years in Finland (28). Consequently, it has been suggested that the overdiagnosis of subclinical hypothyroidisms might exist. However, there is also an association between overt hypothyroidism and fibromyalgia, even though the aetiology is unclear (29). Nevertheless, there are no previous studies on the use of levothyroxine for subclinical hypothyroidism among patients with fibromyalgia syndrome.

This thesis was conducted to define the possible association between fibromyalgia and childhood adversities in a large population sample. In addition, our aim was to produce new scientific evidence about the association between peer bullying victimization and fibromyalgia. Furthermore, one of our aims was to find out what kind of problems patients with fibromyalgia had encountered relating to over- and underdiagnosis at a Finnish health centre from the patients' perspective. Finally, we studied the use of levothyroxine for hypothyroidism in health centre patients and evaluated whether the care guidelines were followed.

2 REVIEW OF LITERATURE

'So I have been allotted months of futility,

and nights of misery have been assigned to me.

When I lie down I think, "How long before I get up?"

The night drags on, and I toss and turn until dawn.'

Job 7:3-4

2.1 Overview of fibromyalgia

The main symptom of fibromyalgia is chronic widespread musculoskeletal pain (1). Other symptoms include fatigue, unrefreshing sleep, memory problems, and other cognitive and somatic symptoms (1,3,5). Fibromyalgia is the second most common rheumatic condition after osteoarthritis and one of its main symptoms – chronic pain – is a very common complaint in medical practice (3). Fibromyalgia causes a severe personal and social burden, particularly to the most vulnerable subgroups (30). Furthermore, fibromyalgia causes substantial costs to society due to lost productivity and impairment (1).

2.1.1. The development of fibromyalgia as a clinical concept

One of the earliest biomedical models of pain originates from ancient Greece. Hippocrates believed that health, illness, and pain originate from the imbalance of the four bodily humors (31). The Greek physician Galen introduced the term rheumatismos, in which the term 'rheuma' refered to phlegm, as respiratory diseases causing the production of phlegm could result in patients developing painful

conditions, such as inflammation of the joints (32). In the late 16th century, the French physician Guillaume de Baillout reintroduced the term rheumatism to describe muscular pain and acute rheumatic fever (33). In 1666, the British physician Thomas Sydenham differentiated the primary lesion of rheumatic fever and chronic rheumatism, which he mentioned to be 'either the remains of a rheumatic fever, or a continuation of pains that proceeded at first from lesser but neglected colds' (32). In the 19th and 20th centuries, physicians started to make the distinction between deforming arthritis and nondeforming musculoskeletal orders using terms such as neuralgia, chronic rheumatic myositis, neurasthenia, myofascitis, myofibrositis, and phychogenic rheumatism to describe different generalized or regionalized types of muscular rheumatism (34).

'They could see she was a real Princess and no question about it, now that she had felt one pea all the way through twenty mattresses and twenty more feather beds. Nobody but a Princess could be so delicate.'

Hans Christian Andersen - The Princess and the Pea

During the 19th century, various hypotheses on the aetiology of muscular rheumatism were introduced. At the beginning of the 1800s, British physicians formed a hypothesis from inflammatory causes. On the contrary, the French physician Valleix described tender points in various parts of the body and reasoned that the symptoms of muscular rheumatism originated from the nervous system. In Germany and Scandinavia, the assumption was that the symptoms originated from proliferative process of the muscle. Hyperactive nerve endings prone to external influences such as climatic, emotional, or physical exertion were also suggested (34). In the late 19th and 20th centuries, it was believed that pain that did not respond to the narcotics and analgesics that were used to treat acute pain or lasted longer than or exceeded observable tissue damage was caused by psychiatric disease (35). This also had an effect on the concept of fibromyalgia (16).

In 1880, neurologist George Miller Beard from the United States introduced the clinical and diagnostic concept of neurasthenia. He thought that the symptoms were caused by the daily stress of modern life, resulting in nervous exhaustion. The hypothesis of the inflation of the fibrous tissues of the muscles or adhesion of muscular fibrils gained popularity at the beginning of the 1900s. In 1904, the term fibrositis became established and remained in use for the next 72 years. Researchers hypothesized that the sensory nerves were involved in the pathophysiology of

fibrositis and that central nervous system was also involved. Several charts of tender points and their referral patterns were also published (34).

'He suffered much from a morbid acuteness of the senses; the most insipid food was alone endurable; he could wear only garments of certain texture; the odours of all flowers were oppressive; his eyes were tortured by even a faint light; and there were but peculiar sounds, and these from stringed instruments, which did not inspire him with horror.'

Edgar Allan Poe - The Fall of the House of Usher

After the Second World War, a large number of soldiers from the British and US military suffered from muscle pain syndromes. Because of the absence of inflammation and the nondegenerative nature of symptoms and their relation to stress and depression, psychogenic explanations once again gained popularity (34). In 1968, Traut published the first near-modern description of fibromyalgia syndrome (36). He recognized the mind-body interaction, described the various other symptoms besides muscle pain, and demonstrated the common sites of tender points. In 1972, Smythe specified the concept, emphasized the importance of the role of sleep, and provided a working set of criteria for diagnosis (37).

The term 'fibromyalgia' was introduced in 1976 by Hench, replacing the term 'fibrosis' that misleadingly pointed to inflammation (38). Yunus et al. published the first controlled study in 1981 and provided the first data-based criteria for fibromyalgia. In addition, this study showed that fibromyalgia was a poorly recognized condition and patients had seen many physicians and undergone several unnecessary investigations (39). Moreover, the study revealed that patients with fibromyalgia had several other previously undescribed symptoms, such as migraine, tension headache, and irritable bowel syndrome, and it led to the idea that these 'functional' or 'somatic functional' syndromes overlap (34,40). However, central sensitization was not recognized at that time and muscle spasm was thought to be the underlying connection between these conditions (34). Previously, the term 'functional syndrome' referred to the psychological or psychosocial origin of the symptoms, and in 1989 Hudson and Pope suggested that these syndromes as well as several psychiatric disorders, such as depression and panic disorder, are connected via 'affective spectrum disorder' (41). Yunus later utilized this model of overlapping functional syndromes and psychiatric conditions and developed it with the accumulated research evidence from the mechanisms of central sensitization. As a result, a concept of central sensitivity syndromes that include, e.g. fibromyalgia,

chronic fatigue syndrome, irritable bowel syndrome, and multiple chemical sensitivity syndrome, was formed (42).

In 1990, Wolfe et al. published the American College of Rheumatology (ARC) criteria for fibromyalgia (4). These criteria formed a classification of fibromyalgia for research all over the world and in clinical practice; they suggested abandoning the distinction between primary and secondary fibromyalgia (34). Furthermore, researchers suggested no exclusion criteria and posited that fibromyalgia could occur at the same time as inflammatory rheumatic disorders (4). The 2011 ACR criteria introduced a patient self-report survey and conceptualized the main symptoms as a continuum of pain centralization (3). Slight modifications of these criteria were made in 2016 in order to reduce the misclassification of regional pain disorders and to clarify that the diagnosis of fibromyalgia is valid despite other diagnoses. In 2018, other slight modifications for the criteria (AAPT criteria) were made in order to develop a diagnostic system across chronic pain disorders (43).

2.1.2. The current concept of pain

'Gentlemen, I have a confession to make. Half of what we have taught you is an error, and furthermore we cannot tell you which half it is.'

Sir William Osler

There are several challenges regarding the definition of pain. Even though the pain caused by an acute tissue injury is probably universal among humans, problems emerge when the same term is used to describe situations in which tissue damage is not observable or in which the term is used metaphorically (44). In 1979, the International Association for the Study of Pain introduced the following definition of pain: 'An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage' (45). In 2020, six key points were added:

> 1. Pain is always a personal experience that is influenced to varying degrees by biological, psychological, and social factors. 2. Pain and nociception are different phenomena. Pain cannot be inferred solely from activity in sensory neurons. 3. Through their life experiences, individuals learn the concept of pain. 4. A person's report of an experience as pain should be respected. 5. Although pain usually serves an adaptive role, it may have adverse effects on function and social and psychological well-being. 6. Verbal description is

only one of several behaviours to express pain; inability to communicate does not negate the possibility that a human or a nonhuman animal experiences pain. (46)

Pain can be classified by location, time course, underlying pathology, or intensity (47). It can also be classified as nociceptive, neuropathic, or central sensitization (48). The Merriam-Webster medical dictionary defines nociception as: 'the perception of a painful or injurious stimulus' (49). Nociceptive pain is initiated by the activation of primary afferent neurons that are sensitive to a noxious stimulus or a stimulus that becomes noxious if prolonged, and it continues as long as the stimulus is maintained (50). It has an important role, as it activates protective withdrawal reflexes and acts as an alarm system. The current definition of neuropathic pain by the International Association for the Study of Pain stating 'pain caused by a lesion or disease of the somatosensory system' leaves out the word 'dysfunction' from the possible cause and excludes conditions with neuronal hyperexcitability, such as fibromyalgia (51). In central sensitization, the increased membrane excitability and synaptic efficacy together with reduced inhibition leads to the increased function of neurons in nociceptive pathways. Due to the role of the central nervous system, pain no longer correlates with peripheral stimuli and produces pain hypersensitivity by changing sensory inputs, including those that normally do not cause conscious sensations. Pain is no longer protective, and it is exaggerated and prolonged (52). In addition, the term 'nociplastic pain' has been suggested by the international community of pain researchers to describe pain that is mechanistically different from nociceptive or neuropathic pain. The mechanisms behind this type of pain are not fully understood, but central nervous system pain and sensory processing and altered pain modulation play a role (53). Furthermore, pain can be local, or it can be present in several locations when the term 'widespread pain' is used. Widespread pain is also the main symptom of fibromyalgia syndrome (1).

2.1.3. The current concept of fibromyalgia

Fibromyalgia differs from chronic widespread pain because it includes non-pain symptoms like fatigue, unrefreshed sleep, cognitive problems, and other somatic symptoms (54). The current diagnostic criteria for fibromyalgia (AAPT diagnostic criteria) require moderate-to-severe sleep problems or fatigue in addition to multisite pain for diagnosis (43). Unlike chronic widespread pain, fibromyalgia is

also included in the 10th edition of the World Health Organization's (WHO) International Classification of Diseases (ICD) (55). Nevertheless, some physicians still deny the existence of fibromyalgia and believe that the symptoms are caused by other somatic or psychiatric diseases (56).

Although research has revealed that fibromyalgia symptoms result from a dysfunction of pain regulation and central sensitization, the cause of fibromyalgia is still unclear (1). Fibromyalgia has often been regarded as a functional somatic syndrome (57,58). It refers to a clinical picture of a group of somatic symptoms that cannot be explained by structural or functional abnormality (57). It is known that functional somatic syndromes – such as fibromyalgia, irritable bowel syndrome, bodily distress syndrome, and chronic fatigue syndrome – are prevalent in the adult population and are connected to decreased self-reported health, the limitation of daily activities, and psychiatric comorbidities, particularly if they affect multiple organs (59).

Medically unexplained symptoms

Fibromyalgia has also been labelled as a medically unexplained symptom (60). The term 'medically unexplained symptoms' (MUS) is used by health care professionals and researchers to describe persistent bodily complaints for which a sufficient examination of the patient does not reveal an explanatory underlying pathology (61). In addition, medically unexplained symptoms are common complaints in healthcare (62,63). They are particularly common in general practice and internal medicine and represent the most common diagnosis in some medical specialties (63). It is estimated that approximately 25–50% of all symptoms presented in primary health care are medically unexplained (64). The treatment of medically unexplained symptoms requires a multiple methods approach in which primary health care physicians are essential (65). Furthermore, general practitioners also think that medically unexplained symptoms should be treated mainly in primary health care (66). However, it has been suggested that the distinction between medically explained and unexplained symptoms might not be practical. In a population-based study, impairments caused by symptoms did not depend on whether they were medically explained, and in many cases symptoms that were originally labelled as medically explained persisted longer than expected and became medically unexplained (67).

Functional syndromes

Functional syndromes are persistent and burdensome physical symptoms that fit a specific symptom pattern. Syndromes can present themselves as a single symptom within one body system (e.g. the musculoskeletal system) or they can be multi-systemic (68). The concepts of functional somatic syndrome and medically unexplained symptom have been criticized for not recognizing two important factors: the overlapping of central sensitization in different syndromes and the appropriate pathophysiological mechanism (42). In addition, despite the overlapping of symptoms and pathophysiological findings, the approach to diagnosis and treatment has been specialty-specific, as almost every specialty has its own functional syndromes (69). Furthermore, there are two major clinical classification systems: the World Health Organization's International Classification of Diseases (ICD) and the American Psychiatric Association's Diagnostic and Statistical Manual (DSM). In the ICD-10, single-system functional disorders (e.g fibromyalgia) are placed in the organ-specific chapters and medically unexplained or multi-system disorders in the mental disorders chapter. The DSM is restricted to psychiatric manifestations of symptoms and has no section for organ systems (68).

Bodily distress syndrome

To address these issues, a new unifying diagnostic construct of bodily distress syndrome (BDS) has been suggested (70). It consists of four symptom clusters: cardiopulmonary, gastrointestinal, musculoskeletal, and general symptoms or fatigue, and the concept has been confirmed in the general population. It can be used instead of several specialty-specific functional syndrome diagnoses, and by using it, it is possible to distinguish the multi-organ type of patients that have a severe need for treatment (69). Furthermore, the model for BDS is empirically derived from clinical descriptive and epidemiological studies, while the ICD and DMS criteria are based on theories of emotional and psychological factors in illness (68).

To conclude, in recent reviews fibromyalgia is described either as a chronic widespread pain disorder associated with other symptoms or a group of symptoms characterized by central sensitization (1,3). The term 'functional neurologic disorder' has also been proposed to cover cognitive dysfunction in the absence of an organic cause as seen in fibromyalgia, chronic fatigue syndrome, and functional neurological syndromes (58). Furthermore, the role of primary health care in the treatment of these conditions is highlighted both in recent international and national treatment

recommendations (71,72). It is also acknowledged that the concept of fibromyalgia is strongly influenced by culture, context, and social forces (73).

2.2. Pathophysiology of fibromyalgia and predisposing factors

Since the 19th century, the term 'pathophysiology' has meant the study of alterations of the biological processes that are related to medical disorders (74,75). The pathophysiological cause of fibromyalgia is still unknown (1). During the era of modern medicine, there have been several hypotheses considering the cause of fibromyalgia, including the inflammation of soft tissues, malfunction of the peripheral nerves, and psychogenic factors (34). However, there is long-standing evidence of central sensitization in patients with fibromyalgia (3). The current main hypotheses regarding the pathological causes of the manifestations of symptoms of fibromyalgia syndrome are presented in Table 1.

Table 1. Factors behind fibromyalgia symptoms.

Predisposing factor	**Manifestation**
Autonomic nervous system	exercise intolerance, sweating abnormalities, dizziness
Central sensitization	allodynia, hyperalgesia
Cognitive factors	increased self-monitoring, pain catastrophizing, fear-avoidance
HPA axis malfunction	flawed stress-response
Reduced gut bacterial diversity	digestion problems
Sensory augementation	intensified or longer pain sensation
Small nerve dysfunction	unpleasant sensation or burning pain in skin
Social factors	presenting symptoms in culturally accepted ways, transformation of identity into long-term patient

Central sensitization involves hyperexcitement of the central neurons through several synapses and neurotransmitters in the central nervous system (42). It does not mean that peripheral nociceptive input, such as tissue damage, does not contribute to pain sensitization, but that pain sensitization is more severe than would normally be expected (3). Findings from recent functional magnetic resonance imaging also support that central pain sensitization and altered endogenous pain modulation are present in patients with fibromyalgia (76). In addition, it is now understood that also the hypothalamic pituitary adrenal (HPA) axis and autonomic nervous system are involved in the pathophysiological process of fibromyalgia (16).

The fact that patients with fibromyalgia also have a high occurrence of somatic symptoms, other functional syndromes, and mood disorders has led to a theory that the abnormality of neurotransmitters in the central nervous system that causes pain also causes the other symptoms of fibromyalgia, such as poor sleep and mood disorders (77). There is a considerable lifetime overlap of symptoms of various functional syndromes especially between irritable bowel syndrome and fibromyalgia or chronic fatigue syndrome (78). Furthermore, it is quite normal that patients with fibromyalgia have had some regional chronic pain symptoms (e.g. trigeminal neuralgia) before the diagnosis (79). On the other hand, in his recent editorial, Wolfe warns of the possible caveats of fibromyalgia research: When comparing healthy individuals with those who have been classified as patients with fibromyalgia (meaning that they scored enough points according to the diagnostic polysymptomatic distress score criteria), there almost always is a statistically significant difference in symptoms, physical findings, and neuroscience measures. However, this does not necessarily tell us much about fibromyalgia and its mechanisms (80).

2.2.1. Sensory augmentation

Sensitivity to blunt pressure is a well-established element in fibromyalgia syndrome (3). In addition to pressure, patients are also sensitive to thermal stimuli (81). Wind-up is a mechanism in which a pain signal coming to the central nervous system becomes stronger and longer lasting. Patients with fibromyalgia have shown increased wind-up and decreased descending analgesia, which means top-down modulation of pain in which a pain signal from the ascending pathway reaches the somatosensory cortex and triggers the descending pain modulatory system (77). There is evidence that central mechanisms make the pain signal stronger or longer

lasting or decrease the activity of decreasing antinociceptive pathways in fibromyalgia (16). Accordingly, it seems that the nociceptive system is a sensory system of its own and the pain experience is strongly modulated by interactions between ascending and descending pathways (82).

Humans have two different descending inhibitory pain pathways: one involves norepinephrine and serotonin and other opioids (83). It seems that particularly the weakened descending analgesic activity of these pathways identifies patients as those who have a central predominance of pain. Additionally, individuals with psychiatric problems such as depression do not demonstrate this dysfunctional descending nociceptive activity (77). Even so, in psychophysical studies, it is not possible to distinguish whether the norepinephrine and serotonin or opioid pathway is affected (83). However, patients with fibromyalgia have shown low levels of biogenic amines in the central nervous system, implying a descending norepinephrine and serotonin antinociceptive pathway dysfunction (84).

2.2.2. Centralized pain and central sensitization

In acute nociceptive pain, the detection of noxious stimuli helps to prevent injury, and this protective function is further enhanced by the nociceptive system's falling activation threshold and amplification of subsequent inputs. Normally in the absence of further tissue damage, this heightened sensitivity returns to the normal baseline but various forms of functional, chemical, and structural plasticity can lead to sensitization of the central nociceptive system and result in long-term pain hypersensitivity (52). There is a huge variation between individuals in the central nervous system factors that influence pain perception, and there is no chronic pain condition in which the severity of pain can be predicted according to measured tissue damage or inflammation (77).

The enhancement of neurons and circuits in nociceptive pathways, which is caused by increased membrane excitability, synaptic efficacy, or reduced inhibitions, leads to central sensitization (52). Altered levels of various pain-related neuropeptides and neurotransmitters, such as substance P, glutamate, bradykinin, and dopamine, are linked to the altered processing of sensory inputs (3,52). In general, low levels of serotonin, norepinephrine, dopamine, and gamma-Aminobutyric acid (GABA) metabolites can lead to sensory augmentation as well as increased levels of substance P, glutamate, nerve growth factor, and brain-derived neurotrophic factor in the central nervous system (77). Researchers recently hypothesized that thalamic mast cells contribute to pain-releasing neuro-sensitizing

molecules and these molecules could stimulate thalamic nociceptive neurons directly or via stimulation of the microglia in the diencephalon (85).

Recent evidence also suggests that the division of inflammatory and non-inflammatory pain may not be as clear, as immunological cascades have a role in the maintenance of central sensitivity by the increased release of pro-inflammatory cytokines by the central nervous system glia cells (77). In a systematic review, researchers found that patients with fibromyalgia had higher levels of several interleukin (IL) receptor antagonists and higher plasma IL-6 levels compared to the controls (86). Moreover, skin biopsies of patients with fibromyalgia show an increased number of mast cells and neurons producing substance P and corticotropins that in turn activate mast cells to produce proinflammatory substances, which can cause sensitization of the nerves and low-grade inflammation (87). In a Finnish study, some patients with fibromyalgia had elevated levels of high-sensitivity CRP, which also correlated with more severe symptoms (88). However, these elevated levels were more likely explained by overweight and lower physical activity.

The role of the opioid system is slightly unclear: there are reports of central nervous opioid dysfunction relating to higher cerebrospinal levels of opioid peptides or reduced μ-opioid receptor binding potential in several brain regions that have a role in pain modulation (83,89). On the other hand, it has been suggested that the opioid system is the only neurotransmitter system that works normally in patients with fibromyalgia (77). On the contrary, findings from an endogenous opioidergic dysregulation study support the previous findings that opioids might not be effective for fibromyalgia due to the already reduced number of μ-opioid receptors or receptor affinity. Furthermore, the findings support the plausible mechanism that long-term opioid use could worsen the pain by disturbing the already vulnerable endogenous opioid system of patients with fibromyalgia. Further studies are still needed to confirm this hypothesis (90).

To summarize centralized pain, existing data support the hypothesis of the dysfunction in the descending analgesic activity of the norepinephrine and serotonin pathway and possibly vulnerable endogenous opioid system pathway (83).

2.2.3. Heredity and genetic factors

Sensitivity to pain is polygenic and may result from imbalances or the altered activity of neurotransmitters (3). Several genetic polymorphisms involving the

metabolism or transport of monoamines, which play a critical role in stress response, pain sensitivity, and affective vulnerability, have been found to be associated with a high risk of fibromyalgia (16). Studies investigating genome-wide associations between genetic factors and fibromyalgia indicate that the genetic factor might be responsible for 50% of susceptibility (91). Similarly, in a large twin-based population sample, genetic differences accounted for approximately 50% of fibromyalgia symptoms (92).

Resilience has also a genetic base: some genetic characteristics predispose individuals to the effects of chronic stress (93).

2.2.4. Social and environmental stressors

Most disorders have both a molecular pathobiology and a socially constructed experience of illness. Historical context and the intellectual and economic interests of groups of people affect the experience and determine also what is seen as abnormal. Chronic widespread pain is quite common in the community, but only some persons find the psychosocial distress so overwhelming that they seek care. When the suffering is labelled as fibromyalgia, the patient's identity is often transformed to that of a long-term patient whose life is limited by the disease. Patients with fibromyalgia also learn idioms of distress that modify the illness experience (94).

Like in many other disorders, the pathophysiological mechanisms in fibromyalgia include interactions between genetic and environmental factors that together with physiological, psychological, behavioural, and cognitive factors lead to the manifestation of symptoms (16). There is evidence that certain infectious diseases such as hepatitis C, Epstein-Barr virus, parvovirus, and Lyme disease are associated with the onset of chronic pain and fibromyalgia (77). In the Finnish Twin Cohort study, the strongest non-genetic predictors for fibromyalgia symptoms were frequent headache, persistent back pain, and neck pain (95). Various traumatic incidents can also trigger fibromyalgia. Amongst survivors of a major train crash in Israel, there was a high prevalence of fibromyalgia three years after the incident (96). In addition, workplace bullying has been associated with newly diagnosed fibromyalgia (20). In a Finnish study, repeated cognitive stress also increased pain intensity in patients with fibromyalgia (97).

It has been suggested in a number of studies that individual response to long-term stress takes place via epigenetic mechanisms (98). Furthermore, in some

life periods, such as childhood, the epigenome shows more plasticity to stress-induced epigenetic changes, and these changes can also accumulate (99). Gene-environmental interaction through epigenetic alterations, in particular with the hypomethylated DNA pattern, genes implicated in stress response, DNA repair, autonomic system response, and subcortical neuronal abnormalities, have been suggested as the triggering methods of fibromyalgia (91). Resilience can also influence symptoms caused by stressful life events: individuals with a high resilience score do not get more psychiatric symptoms if they encounter stressors whereas individuals with a low resilience develop additional symptoms (93).

2.2.5. Childhood adverse events

There is evidence of an association between chronic widespread pain and childhood adversities, although these findings have been contested on the basis of memory bias (14,100,101). Moreover, depression is quite a common comorbidity with fibromyalgia, and it can contribute to false memories (42). On the other hand, Hardt et al. have suggested that false positive reports of major and easily defined childhood adversities are rare and findings from retrospective case-control studies should not be invalidated because of recall bias (102).

However, a large-scale prospective cohort study in the United Kingdom reported a connection between chronic widespread pain and several adverse childhood events, such as familial financial hardships, maternal death, or residence in institutional care (14). In their systematic review and meta-analysis, Häuser et al. assessed the potential association between fibromyalgia and emotional, physical, and sexual abuse (22). Altogether, 18 studies were included in the analysis and all of them were case control studies. In their analysis, researchers found an association between fibromyalgia and self-reported physical and sexual abuse in childhood and adulthood, but not with emotional abuse. However, a meta-regression of study quality found a correlation between low study quality and the magnitude of the association between childhood sexual abuse and fibromyalgia. In addition, in a cross-sectional study with a representative sample of the German adult population, there was no statistically significant association between noncancerous pain and adverse childhood adversities, and resilience did not protect against disabling chronic pain (103). As a consequence, in their systematic review, Häuser et al. concluded that the association of fibromyalgia and physical and sexual abuse is unclear because of the low study quality (22).

Furthermore, only two studies on this topic recruited patients from the general population: Ciccone et al. recruited 52 patients with fibromyalgia with random digit dialing and randomly from a purchased list of households having an adult female member in Manhattan, of which 72% had major depression and 53 controls of which 60% had major depression (104). No evidence of increased childhood abuse was found. The other study included 10,424 randomly sampled Seventh-Day Adventists from North America; it found a significant association between physical and sexual abuse and fibromyalgia (105).

To summarize, there is only one prospective cohort study confirming the relationship between chronic widespread pain and childhood adversities prior to the age of 7 years (14). On the other hand, the relationship between childhood adversities and fibromyalgia in the general population is not similarly apparent and in most studies the sample has been too small to detect weak associations (106).

2.2.6. Peer bullying

Peer bullying is one of the most common childhood adversities. However, the prevalence depends greatly on the definition and also on the country in which the study is conducted (107). The Olweus definition of peer bullying is: 'A student is being bullied or victimized when he or she is exposed, repeatedly and over time, to negative actions on the part of one or more other students' (108). In addition, Lereya et al. define it as physical or verbal abuse and systematic social exclusion committed by children (109).

The prevalence of occasional peer bullying has varied from 28% in a British cohort study from the 1950s to 47.8% in boys and 36.2% in girls in a Finnish survey (18,19). Regular (once a week or more) peer bullying was reported by 6–9.4% of boys and 3.7–5% of girls in Finnish surveys (18,110). Similar rates have been reported in a world-wide study, and in that study the Northern European countries reported the lowest ratings of peer bullying exposure. In Finland, the prevalence of peer bulling (defined by being bullied at least 2 times a month) was 13.3% among boys and 8.8% among girls (111).

Most studies on the effects of peer bullying are cross-sectional. Peer-bullied children have more sleep disturbances, bed wetting, sadness, headaches, and abdominal pain (112). On the contrary, it has been suggested that this association is rather weak (113). Only a few studies have addressed the long-term impact of peer bullying. In an Australian cross-sectional study, adults who had been the target of childhood peer bullying had a decreased health-related quality of life (17). In a

Finnish birth cohort study, frequent bullying victimization was a risk factor for suicidal behaviour (18). Moreover, in a cohort study conducted in two countries, peer bullying had similar or in some cases worse long-term adverse effects on mental health compared to being a victim of maltreatment (109). Similarly, in a British cohort study peer-bullied children had a poorer perceived quality of life and fewer social relationships at the age of 50 in addition to higher rates of depression, anxiety disorder, and suicidality (19). In a Dutch study, a cross-sectional association between several childhood adversities, such as physical and sexual abuse, family conflicts, and peer bullying, were observed (21).

It is unclear how peer bullying leads to worse health in adulthood, but it is possible that excess stress leads to the development of different health problems (19,20,107). Also, it is known that psychosocial stress initiates many behavioural, neural, hormonal, and molecular responses (99). In a British twin cohort study, bullied children showed a lower cortisol response after a psychosocial stress test. As the HPA axis underlies both adaptive and maladaptive responses to stress, this could explain the association with stress-related diseases and peer bullying (114).

In short, there are several studies addressing the negative long-term effects of peer bullying on the general level and also from a psychological point of view. However, there is only one study concerning the association of widespread pain and peer bullying and none about fibromyalgia and peer bullying.

2.2.7. Behavioural and cognitive factors

It has been suggested that cognitive symptoms of fibromyalgia and some other functional syndromes are caused by the decreasing of externally directed attention and increased distraction and slow information processing interfering with cognitive function (58). Patients may also overemphasize these symptoms because of heightened self-monitoring. Patients with fibromyalgia more often than healthy individuals or even patients with other chronic pain conditions think that their personal input does not influence outcomes and patients with fibromyalgia are also prone to catastrophize the pain they experience (16). Furthermore, cognitive-affective factors like pain catastrophizing and fear-avoidance correlate with functional status and quality of life even more than the intensity of pain (115,116). Resilience may also play an important role in the development of chronic pain. Furthermore, people who are less aware of internal body changes might be less capable of coping with stressful situations like chronic pain (93).

2.2.8. The overlap of depression and fibromyalgia

Fibromyalgia and major depressive disorder often co-occur (117). They share similar pathophysiological mechanisms and the same genetic and environmental factors predispose individuals to them. The independence of treatment effects suggest that they are mediated by independent mechanisms but certain symptoms have an association (15). Furthermore, patients with fibromyalgia have shown significantly reduced resilience, which can lead to the development of psychiatric disorders such as depression (93). In a recent study, domestic violence was linked to the presence of a psychiatric disorder in patients with fibromyalgia, and almost half of patients with fibromyalgia who had encountered severe domestic violence had a mood or anxiety disorder (118).

2.2.9 The role of the hypothalamic-pituitary-adrenal axis

The HPA axis is involved in stress response. In acute stress, resilience is favoured by releasing glucocorticoids, but in chronic stress an elevated level of cortisol and glucocorticoids can be harmful (93). Studies have demonstrated both the hypo- and hyperactivity of the HPA axis and sympathetic nervous system in patients with fibromyalgia (16). The function of the HPA axis is also related to the individual's socio-demographic and psychological characteristics, and people with a low social status and a reduced sense of purpose in life are prone to the maladaptive function of the HPA axis (93).

Furthermore, a maladaptive HPA axis response involves epigenetic changes in genes regulating homeostatic levels of glucocorticoid and also genes that are important for neuronal function (119). Glucocorticoids also activate glucocorticoid receptors affecting transcriptional programs and also induce long-lasting epigenetic changes in many tissues (99). There are also some previous studies on patients with fibromyalgia that support this altered HPA axis response hypothesis (20,120). Corticotropin-releasing factor can also be considered as an important biological element of resilience involving the HPA axis, norepinephrine system, and mesolimbic reward system and fear circuit (93).

The evident suppression of cortisol levels – but not adrenocorticotropic hormone – in the dexamethasone intake test that patients with fibromyalgia have demonstrated suggest that increased sensitivity of glucocorticoid feedback originates

at the adrenal level (120). There is also evidence suggesting two different patterns in corticoid levels with functional somatic syndrome (such as fibromyalgia) symptoms: gastrointestinal and headache are associated with low levels of cortisol levels during stress and fatigue, and dizziness and musculoskeletal pain are associated with low levels of cortisol after awakening (121).

2.2.10. The role of autonomic nervous system

Disturbances in autonomic nervous system functions have been proposed to explain the poorer aerobic capacity of patients with fibromyalgia in some studies (122). Furthermore, orthostatic intolerance is often present and it may suggest abnormalities of cardiovascular neural regulation. In their study, Furlan et al. demonstrated increased cardiovascular sympathetic activity among patients with fibromyalgia when resting and a lack of decreased cardiac vagal activity and increased sympathetic discharge to the vessels during a tilt test (123).

Heart rate variability has also been studied as a surrogate measure for autonomic nervous system dysfunctions, and patients with fibromyalgia demonstrate reduced heart-rate variability compared to healthy individuals (16). Furthermore, some patients with fibromyalgia have demonstrated delayed heart rate recovery and chronotropic incompetence – meaning that they failed to achieve a heart rate over 80% of their age-modified peak heart rate despite reaching a peak exercise respiratory exchange ratio, suggesting adequate effort during a treadmill test – indicating cardiac autonomic impairment (122).

In conclusion, it appears that at rest, autonomic dysfunction is associated with fibromyalgia. However, data regarding exercise is limited (124). Furthermore, patients with fibromyalgia often report autonomic symptoms but objective assessments show only modest autonomic dysfunction (125). Self-reported orthostatic intolerance might also be closely linked to patient-reported brain fog symptoms (126).

2.2.11. Findings of neuroimaging in fibromyalgia

The focus of pain imaging has been to separate the factors that influence nociceptive inputs that alter pain perception in healthy individuals and patients suffering from chronic pain (127). A meta-analysis based on neuroelectric studies has shown that the brain network for acute pain perception in healthy individuals is somewhat different when compared to chronic pain sufferers, and chronic pain

engages brain regions that are involved in cognitive and emotional assessment (82). Furthermore, studies using Single-Photon-Emission Computed Tomography (SPECT) have provided evidence of enhanced sensory processing and reduced attentional and affect regulation in fibromyalgia (16). Several meta-analyses of functional magnetic resonance imaging (fMRI) studies generally agree with the findings from SPECT studies as well as from positron emission topography (PET) studies (77). The findings from fMRI support central nervous system hyperalgesia in which the noxious threshold of sensory stimuli is reduced in patients with fibromyalgia (16). The main areas of the pain processing matrix involve somatosensory, limbic, and associative brain structures: the primary and secondary somatosensory cortex, the insular cortex, the anterior and midcingulate cortex, the posterior cingulate gyrus, and the thalamus (77).

2.2.12. Other aspects of pathophysiology

In their recent work, Clos-Garcia et al. found that patients with fibromyalgia showed a reduction in gut bacterial diversity. In addition, they found increased levels of serum glutamate, and the number of bacteria species that transform glutamate into GABA was reduced. This might explain the quite common co-morbidity of irritable bowel syndrome with fibromyalgia. The altered interchange of serum metabolites with the brain might also be linked to lower serotonin precursor levels (128).

Small nerve fibre dysfunction has also been described among patients with fibromyalgia, and in a recent study, the extent of small fibre pathology was related to the severity of fibromyalgia symptoms (129). Furthermore, C nociceptor dysfunction may contribute to the symptoms. In a study by Serra et al., the majority of patients with fibromyalgia had abnormal C nociceptors, resembling the function of nociceptors of those patients with small-fibre neuropathy (130). In addition, in a study including 46 patients with fibromyalgia, a significant reduction of intraepidermal nerve fibre density in skin biopsies was discovered, indicating that in a subset of patients, their pain might be of neuropathic origin (131).

2.3. Epidemiology of fibromyalgia

The prevalence of fibromyalgia depends on the population and the diagnostic criteria applied (132,133). The international prevalence rate (excluding Oceania, as there are no studies from there, while there is only one from Africa)

varies from 0.4% to 9.3% according to a review article from 2013 (56). In the 2013 review, the worldwide arithmetic mean prevalence rate of fibromyalgia was 2.7% (56). In a representative population sample from Germany using current modified ACR 2010 diagnostic criteria, the prevalence of fibromyalgia was 2.1% (54). The only prevalence study from Finland is based on data from the mini-Finland health survey in 1977–80 (134). The former diagnostic criteria were used in this study and the prevalence in Finland was only 0.75% (126).

In certain populations, a higher prevalence has been reported. In Norway in the city of Arendal, the self-reported prevalence was 10.5% among female participants (135). Furthermore, in clinical or hospitalized samples of patients, the prevalence has been as high as 65% of patients with systemic lupus erythematosus (136). In a recent study, 4.6% of primary health care patients in St. Louis (Missouri) had a fibromyalgia diagnosis (137). The female-male ratio of patients with fibromyalgia also depends on the diagnostic criteria (3). The ACR 1990 criteria emphasized the number of tender points, which leads to a situation where the majority of patients with fibromyalgia are women. With the current criteria, women are two or three times more likely to be diagnosed than men, which is in line with other pain conditions (3,54). In the recent primary health care sample in the US, 76.1% of patients with fibromyalgia were female (137). The prevalence of fibromyalgia also rises with age (54,138). In a Turkish study, the prevalence was 3.6% for the whole sample including females aged 20–64 years old, but 10.1% for females aged 50–59 years old (139).

On the other hand, some studies have reported a low prevalence. In a Venezuelan study conducted in an urban community using a simple diagnostic questionnaire for rheumatic diseases validated and used in Latin American countries, the prevalence of fibromyalgia was only 0.2% (140). Similarly, the authors of a Brazilian review article reported a tendency that in rural areas, the prevalence of fibromyalgia is higher than in urban areas (141).

Other differences between special populations have also been reported. In a Turkish study, the prevalence of fibromyalgia was the highest among uneducated, widowed, and low-income female participants (139). A high prevalence (15%) of fibromyalgia was found among the survivors of a major train crash in Israel three years after the event (96). Furthermore, higher incidences have been reported among Turkish textile workers, elderly Brazilian residents, and low-income users of Brazilian health units (141).

There are two studies reporting the incidence of fibromyalgia. In the US, the incidence of fibromyalgia was reported to be 6.88 cases per 1000 person-years for

males and 11.28 cases per 1000 person-years for females between 1997 and 2002 based on a health insurance claims database (142). In a Norwegian study involving only females and using the former diagnostic criteria for fibromyalgia, the annual incidence for fibromyalgia was 5.83 per 1000 person-years between 1990 and 1995 (143).

To conclude, the international prevalence of fibromyalgia is around 2–3%, and most patients with a fibromyalgia diagnosis are female (56). In certain selected populations, the prevalence is higher, and the highest prevalence is reported among hospitalized patients with rheumatic diseases (136). Furthermore, the prevalence rises with age (54).

2.4. Fibromyalgia diagnosis

In clinical practice, fibromyalgia should be considered if the patient has multifocal pain that is not sufficiently explained by injury or inflammation (3). Diagnosis should be based on the patient's description of symptoms, medical history, and a physical examination of the patient (8,72,144). Often the physical examination of the patient is normal besides the diffuse tenderness that many patients experience (3).

Laboratory tests are not necessary to make the fibromyalgia diagnosis, but they can be ordered to detect other disorders causing fibromyalgia-like symptoms (3,8). Laboratory tests can include a complete blood count, routine serum chemistries, thyrotrophin, erythrocyte sedimentation rate, and C-reactive protein, especially if these measures have not been recently checked (3,8,144). Serologic studies and a specific rheumatic test should be avoided unless the patient has findings (e.g. swollen joints or an elevated level of C-reactive protein or erythrocyte sedimentation rate) suggesting a rheumatoid aetiology (3,8).

In Finland, a fibromyalgia diagnosis can usually be set in primary health care (72). There are also specific diagnostic criteria sets for fibromyalgia. The differences between different ACR criteria are presented in Table 2.

2.4.1. ACR 1990 diagnostic criteria

In 1990, the American College of Rheumatology (ACR) criteria were published; they were based on multicentre research and originally intended for research purposes (4). However, the criteria were soon applied also for diagnostic purposes (145). According to these criteria, the pain should last at least 3 months and be widespread, meaning that it is present on both the left and right side of the body and also above and below the waist and in the midline. Furthermore, pain should be present in at least 11 of 18 predetermined tender points across the body when 4 kg of pressure is applied to these tender points. However, tenderness alone is not a sufficient finding for a fibromyalgia diagnosis, as patients should report the stimulus to be painful for a positive finding in the pressure test (4).

Furthermore, several difficulties with the ACR 1990 criteria have been reported: in primary health care, the role of tender points has been perceived as confusing, and tender point examination was seldom performed either due to a lack of knowledge or the unwillingness of GPs to do it, and even when it was done, it was performed incorrectly (23,146). In a Swedish primary health care setting, physicians had trouble distinguishing between patient-reported pain and tenderness (147). In general, women are more sensitive to blunt pressure than men are, and as a result men who have chronic pain seldom meet the ACR 1990 criteria for fibromyalgia (148). Furthermore, it has been unclear how to classify patients that do not meet the ACR 1990 criteria when their symptoms have relieved: are they cured or asymptomatic (5)?

2.4.2. ACR 2010 and 2011 diagnostic criteria

Deriving from the criticism of the ACR 1990 criteria, there was a need to develop a wider scale to evaluate the severeness of fibromyalgia symptoms. The aim was not to replace the ACR 1990 criteria but to develop a set of criteria without the need to examine tender points and to include symptom severity in the diagnostic criteria that would be also applicable in primary health care. Furthermore, it was also important that the criteria are suitable for the long-term follow-up of patients, and the Symptom Severity (SS) score was introduced (5). As a result, physicians started to interpret fibromyalgia as a continuum disorder, and the polysymptomatic distress score recognizes this continuum (80).

Developed in a multi-centre study, the ACR 2010 diagnostic criteria consist of three criteria: 1) in the widespread pain index (WPI), the patient must have pain at least in 7 different locations and the SS score must be at least 5 (or, if the WPI is between 3 and 6, then the SS score must be at least 9 points), 2) pain must have been present for at least 3 months, and the original version of ACR 2010 included also 3) the symptoms cannot be explained by any other disorder (5).

This last criterion received criticism and it was removed from the revised version of these criteria (54,149). In principle, the ACR 2010 criteria can be applicable for patients to self-fill, but the first version (2010) of the ACR criteria requires at least an interviewer (150). The criteria also paid attention to other symptoms besides pain; the SS scale could divide patients into three categories according to their symptoms, and it also gave a tool to assess the symptoms of patients who at some point met the ACR 1990 diagnostic criteria but no longer do so (5).

Later, the ACR 2010 criteria were modified so that complete self-administration would be possible and the physician's estimate of the SS score was replaced by three specific self-reported symptoms (150). This self-report modification version of the criteria was later named the ACR 2011 diagnostic criteria (149). Differences between the diagnostic criteria are presented in Table 2.

There is also the possibility to combine the WPI and SS scores for the Polysymptomatic Distress scale (PSD), where the patient can score from 0 to 31 points. Patients meeting the ACR 2010 criteria for fibromyalgia will always score at least 12 points on this combined scale (54). However, ACR 2010 and ACR 2011 could have led to the misclassification of regional pain syndromes, and the WPI was modified so that pain must be present in at least 4 of 5 regions (149). In a review of 14 validation studies, the 2010 and 2011 criteria have a mean unweighted sensitivity of 83% and 86% specificity (149).

Table 2. Diagnostic criteria for fibromyalgia syndrome (ACR 1990–2011).

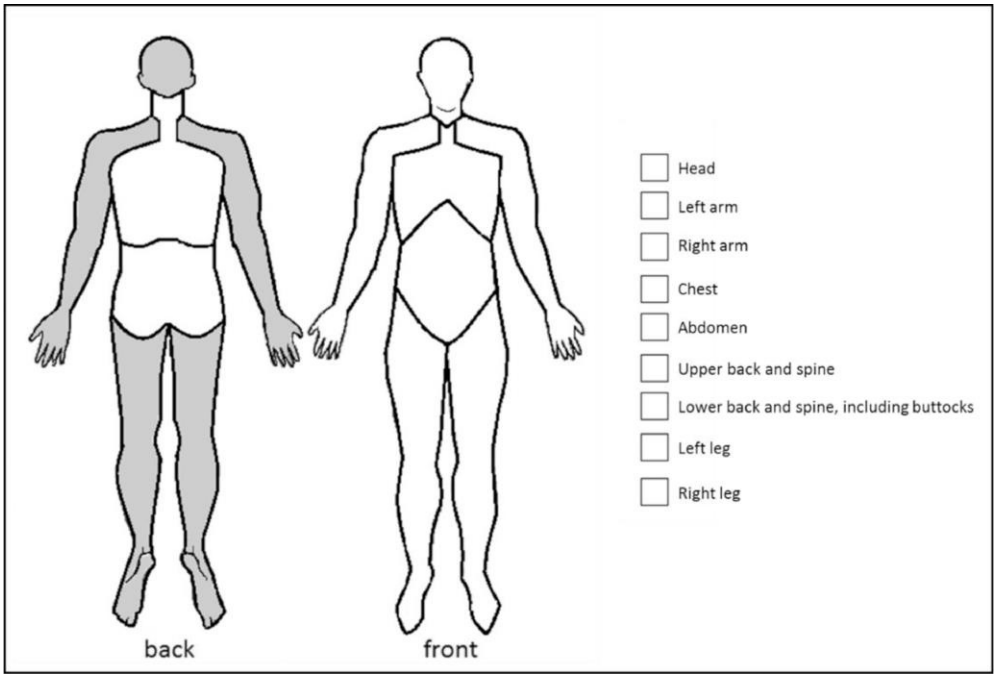
Criteria	**ACR 1990**	**ACR 2010**	**ACR 2011 revised**
Pain duration	Over 3 months	Over 3 months	Over 3 months
Location	Both sides of the body and above and below the waist; widespread	In 7 different locations or in 3 if the patient has several other symptoms; multisite	At least 4 of 5 regions; multisite
Tender points	18 tender points, of which 11 is required for diagnosis	19 self-reported pain areas	19 self-reported pain areas
Tender points examination	Physician performs	Self-reported	Self-reported
Other symptoms	Not required for diagnosis	At least 5 points on the Symptom severity (SS) scale	At least 5 points on the SS scale
Symptom severity (SS) scale	Not included	3 main symptoms and 43 additional symptoms	3 main symptoms and 3 additional symptoms
Symptom severity reporting	Not included	Physician or other interviewer	Self-reported
Scaling	Yes/No	Continuum	Continuum
Exclusion of other diseases	Not needed	In original version needed for diagnosis	Not needed

2.4.3 AAPT Criteria

In 2013, the Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks – a public-private partnership with the US Food and Drug Administration and the American Pain Society – initiated the AAPT (ACTTION-APS Pain Taxonomy) in order to develop a diagnostic system that

would be clinically useful and consistent across chronic pain disorders. Members of the workgroup agreed that fibromyalgia should be predominantly a chronic pain disorder. However, a question was raised whether the pain should be widespread as in the ACR 1990 criteria or multisite as in the ACR 2010/2016 criteria. Based on studies and statistical analyses, the self-reported number of pain sites was considered sufficient when defining pain in fibromyalgia. Regarding non-pain symptoms, fatigue and sleep problems were considered to be two key symptoms. This was confirmed by a a population-based study. The number of pain-sites was reduced to nine: the head, left arm, right arm, chest, abdomen, upper back and spine, lower back and spine (including buttocks), left leg, and right leg. For a fibromyalgia diagnosis, pain must be present in at least 6 of these 9 sites (see Figure 1). The patient must also have moderate or severe fatigue or sleep problems, and these symptoms and pain must have been present for at least 3 months (43).

Figure 1. Number of painful pain sites in fibromyalgia according to the AAPT criteria (16,43,77,82,127).



2.4.4. Fibromyalgia and misdiagnosis, overdiagnosis, and underdiagnosis

In a recent study, there was considerable disagreement between the ICD clinical diagnosis of fibromyalgia and the ACR 2011 criteria-based diagnosis, as university rheumatology physicians failed to identify 49.6% of criteria-positive patients and incorrectly identified 11.4% of criteria-negative patients (151). In the US, three quarters of clinically diagnosed fibromyalgia cases are not severe enough to meet the diagnostic criteria based on the polysymptomatic distress score, and the clinical diagnosis of fibromyalgia is more dependent on demographic and social factors, which are expanding the diagnosis of fibromyalgia (152). Furthermore, in an observational study including physicians who diagnose chronic pain, only 51% used the set of criteria in their daily practice and 49% relied on their clinical judgement (153). The researchers concluded that this may increase diagnostic delays and lead to misdiagnosis. In a survey conducted in six European countries including both primary health care physicians as well as secondary care physicians, 53% of physicians reported difficulty in diagnosing fibromyalgia and 54% considered their training for diagnosis inadequate (154).

Additionally, it has been suggested that financial ties between pharmaceutical companies and guideline panel members may lead to widening disease definitions without the assessment of the negative impacts of potential overdiagnosis for the number of individuals potentially falsely labelled to have the disease (155). There is also evidence from the US that the observed prevalence and health care use of fibromyalgia compared to irritable bowel or chronic fatigue syndrome increased at the same time as when federally approved drugs for fibromyalgia promoted by pharmaceutical companies appeared (156). The pharmacological industry may even have a role in validating and legitimating disputed diagnoses such as fibromyalgia when an officially approved prescription medication supports the biomedical role of the condition itself (157).

The diagnostic inaccuracy of rheumatic diseases might also lead to the overdiagnosis of fibromyalgia (23). On the contrary, it has also been suggested that fibromyalgia is underdiagnosed, as even 3 out of 4 persons with fibromyalgia

symptoms might be without the diagnosis, and the average time to diagnosis is 5 years, which can lead to delays is treatment (8).

Furthermore, some physicians still appear to decline to diagnose fibromyalgia even if the patient has typical symptoms (24). These physicians might be reluctant to set the diagnosis because some believe that by not setting the diagnosis they will avoid the overdiagnosis and medicalization of fibromyalgia symptoms (158). In conclusion, there seems to be a significant mis-, under-, and overdiagnosis of fibromyalgia (25–27,137,159,160).

2.4.5. Patients' perceptions of diagnosis

In his recent editorial, Wolfe aptly states that fibromyalgia is a constructed disorder, and its acceptance depends on things largely external to patients (80). Thus, a fibromyalgia diagnosis often fails to provide a valid explanation of symptoms to patients (159). In a meta-ethnography on the diagnostic experiences of patients with fibromyalgia, a researcher noted that patients had often searched for a long time for the correct diagnosis (7). In line with this, a meta-synthesis of qualitative studies on the illness experience of fibromyalgia reported that this search for a diagnosis is burdensome for patients (160).

On the other hand, when the diagnosis was made, it validated the symptoms, but unfortunately this relief did not last long as patients began to question the validity of the fibromyalgia diagnosis (7,160). Patients also found the overlapping symptoms of different disorders confusing and this also caused uncertainty and doubts about the accuracy of the fibromyalgia diagnosis (6).

Similar themes arose in a Norwegian qualitative focus-group study: many participants had had symptoms for years, and when they received the diagnosis, the first response was relief. After that, sadness and despair emerged when they found out that the treatment options were limited and there was a lack of respect and understanding. Furthermore, some people kept the diagnosis to themselves. Patients also told about experiences of how some physicians associated fibromyalgia with hysterical women and some called it a fashion disorder. Furthermore, in some cases patients realized that due to the fibromyalgia diagnosis, they were seen as difficult

patients, and sometimes specialists – from whom they hoped to get a second opinion – did not even examine them because of the fibromyalgia diagnosis (161).

2.4.6. Doctors' perceptions of diagnosis

In a Spanish qualitative study involving both patients and health professionals, both groups were dissatisfied with the management process of fibromyalgia as a whole: there was a delay in getting the diagnosis and a lack of effective treatment as well as uncertainty surrounding the aetiology of fibromyalgia. Furthermore, health professionals considered themselves as being of little help to the patients (162). Interestingly, in a recent Colombian cross-sectional survey, 25.2% of rheumatologists considered that there was not enough evidence to recognize fibromyalgia as a disease, and 81.3% of the rheumatologists thought that patients with fibromyalgia should be treated by another physician than a rheumatologist (163).

2.5. Comorbidities with fibromyalgia

Fibromyalgia can occur with other chronic pain conditions, such as osteoarthritis and rheumatoid arthritis (3). Approximately 10–30% of patients with a rheumatoid condition that causes chronic pain meet the diagnostic criteria for fibromyalgia (77). Furthermore, there is a considerable overlap between fibromyalgia and other functional somatic syndromes. For instance, the mean prevalence of chronic fatigue syndrome is 39% among patients with fibromyalgia. The mean prevalence of irritable bowel syndrome is even higher at 45%. Patients with fibromyalgia often also have tension-type headache (42%), tempomandibular disorder (50%), and multiple chemical sensitivity (36%). In addition, migraine (38%), post-traumatic stress disorder (57%), and restless legs syndrome (31%) are common comorbidities with fibromyalgia (164).

It is also known that patients with fibromyalgia commonly have psychiatric and pain-related comorbidities, but most of the studies are conducted in specialized care and may not present the characteristics of patients with fibromyalgia in primary health care (137). However, Wan et al. obtained the medical records of nearly forty thousand primary health care patients. As a result, they found out that fibromyalgia

comorbidities in primary health care are the same as in specialized health care. Furthermore, depression and arthritis were more strongly related to fibromyalgia among females than males. In a study that used a health-insurance database from the United States, patients with fibromyalgia had more circulatory system diseases, diabetes, anxiety, depression, irritable bowel syndrome, reflux diseases, and sleep disorders than randomly selected age- and sex-matched controls (165). However, in a Finnish study, impaired glucose regulation observed in patients with fibromyalgia was more likely related to lifestyle factors such as smoking and a higher body mass index (166).

Furthermore, researchers discussed the possibility that some of the comorbidities overlap with fibromyalgia symptoms and physicians may add additional diagnoses when uncertain whether the fibromyalgia explains all the symptoms; several appointments may lead to the incidental finding of other diseases. The use of rule-out tests in the diagnostic process can also lead to the overdiagnosis of subclinical manifestations of different medical conditions (25–27).

2.5.1 Depression, anxiety, and fibromyalgia

In a recent systematic review, the point prevalence of a major depressive disorder in patients with fibromyalgia was around 25%; the life-time prevalence was 50% according to clinician-administered instruments and almost twice as high with self-reported instruments (117). In addition to depression, patients with fibromyalgia also have anxiety disorder as a common comorbidity: the life-time prevalence of anxiety disorder has been reported to be around 35–62% in patients with fibromyalgia (71,167). The life-time prevalence of bipolar disorder was 11% (168). According to one study, there is even some evidence that fibromyalgia might be a risk factor for suicidal behaviour (169).

2.5.2. Subclinical hypothyroidism and fibromyalgia

Persons with normal thyroid function often present one or two classical signs of hypothyroidism, such as constipation, fatigue, muscle weakness, dry skin, memory difficulties, and feeling cold (170). Many of these symptoms also overlap with fibromyalgia, and it has been recommended that when the diagnosis of

fibromyalgia is set, these disorders presenting with fatigue – such as anaemia and hypothyroidism – be ruled out (25). However, it is known that patients with such symptoms may think that the symptoms are caused by thyroid dysfunction, and this might lead to the overdiagnosis and overtreatment of hypothyroidism (27).

The incidence of overt hypothyroidism is reported to be stable, and it concerns around 0.2% to 2% of the population (171). However, the use of levothyroxine – a drug that is used to treat both overt and subclinical hypothyroidism – is increasing, as is the incidence of subclinical hypothyroidism affecting up to 12% of the population (172). It has been suggested that even every third levothyroxine treatment in Finland might be unnecessary, as the number of patients undergoing levothyroxine treatment has doubled in ten years, but the incidence of overt hypothyroidism has not changed (28). There are also reports suggesting the same kind of increased use of levothyroxine in the United Kingdom, United States, and Sweden (173).

The evidence of the benefits of levothyroxine treatment for subclinical hypothyroidism is scant, as the treatment does not result in improved survival, decreased cardiovascular morbidity, or a significant change in health-related quality of life or symptoms in randomized controlled studies (172). Furthermore, there is evidence that subclinical hypothyroidism is not associated with cognitive impairment (174). None of the symptoms or clinical signs of hypothyroidism are sensitive or specific enough for the diagnosis, and it should be based on laboratory tests (175).

On the other hand, there is some evidence that fibromyalgia is associated with some autoimmune diseases, even though fibromyalgia is not an autoimmune disease itself (29). In a Japanese study, 7.7% of patients with fibromyalgia had hypothyroidism, but there was no association between anti-thyroid peroxidase antibodies – autoantibodies targeting the thyroid and indicating the autoimmune background of hypothyroidism – and fibromyalgia symptom severity (176). In one study, patients with fibromyalgia had a 19% prevalence of anti-thyroid peroxidase antibodies compared to 7% of controls (29).

To conclude, the symptoms of hypothyroidism and fibromyalgia overlap, and the incidence of subclinical hypothyroidism is rising. This may be a result of the

overdiagnosis of subclinical hypothyroidism, and due to the similarity of the symptoms, it is possible that patients with fibromyalgia more readily receive this diagnosis.

2.6. Treatment of fibromyalgia

The treatment plan for patients with fibromyalgia should be individual (144). In a systematic review from 2010, evidence-based guidelines for the treatment of fibromyalgia recommended aerobic exercise, cognitive-behavioural therapy, multicomponent treatment, and amitriptyline or pharmacological treatment in general (177).

2.6.1. Exercise

Mixed exercise training seems to have a small-to-moderate effect on health-related quality of life, physical function, and fatigue, but for some patients the size of the effects might be clinically unimportant (178). Studies using electro-acupuncture suggest that there is moderate-level evidence of positive effects lasting for up to one month for stiffness, unrefreshing sleep, and fatigue, and it can be combined with exercise and medication (179). There is only a low certainty of evidence that flexibility training improves stiffness in fibromyalgia (180). In one small study, belly dance reduced pain and improved the quality of life and self-image of patients with fibromyalgia (181).

2.6.2. Psychological and cognitive interventions

Psychological therapies may improve physical function, pain, and mood directly after the therapy, but the effect does not seem to be long-lasting and the quality of evidence is low according to a systematic review from 2015 (182). Findings from another systematic review support the evidence of the small incremental effect of traditional cognitive behavioural therapy and operant therapy reducing key fibromyalgia symptoms after six months, but due the limited data of the telephone- or internet-based therapies, the researchers were not able to assess the effect of these

types of therapies (183). In a recent systematic review, there were no high-quality randomized controlled trials on the effectiveness of health education for patients with fibromyalgia, but despite the heterogeneity of the included studies, a significant reduction in catastrophizing, pain intensity, anxiety, and perception of disease was observed (184). Due to the very low quality of evidence, there is no information on the effects of biofeedback, mindfulness, movement therapies, and relaxation-based therapies (182).

2.6.3. Multidisciplinary rehabilitation

The scientific evidence concerning the effectiveness of multidisciplinary rehabilitation is also limited, but patients and professionals in the field of rehabilitation consider it beneficial (185). Nevertheless, fibromyalgia is a risk factor for disability and the risk increases especially if the patient has some other chronic disease (186).

2.6.4. Pharmacological treatments

There are currently no pharmacological treatment options that have sufficient efficacy for all fibromyalgia symptoms without the risk of side-effects (187). Amitriptyline has been a first-choice drug for fibromyalgia for many years. Surprisingly, a recent systematic review found no unbiased evidence for its effect, but on the other hand there is also no evidence about a lack of effect, and years of clinical experience of patients with fibromyalgia support the conclusion that amitriptyline is still a treatment option, but its effect might be smaller than previously supposed (188).

In a recent systematic review, the serotonin and noradrenaline reuptake inhibitors (SNRI) duloxetine and milnacipran showed some low-quality evidence of benefits compared to placebo in reducing pain and increasing patient-perceived overall improvement, but they also demonstrated side-effects like nausea; in conclusion, the researchers stated that some patients with fibromyalgia may benefit from them without side-effects (189). Even though mirtazapine has no official indication for fibromyalgia, its side-effect profile may suggest that it can be considered if the patient experiences gastrointestinal side-effects from other SNRIs

(duloxetine or milnacipran). However, only a minority of patients will benefit from it without the relevant side-effects, and it should be started with a low dose of 15 mg and stopped and switched to another treatment if the patient does not respond to it within a certain time (190). In a recent open-label randomized controlled trial, duloxetine was more effective than pregabalin for the treatment of pain associated with fibromyalgia (191). However, drop-out from the study and nausea were also more common with duloxetine. There is no evidence of the effectiveness of other SNRIs, such as venlafaxine, for fibromyalgia (189). Furthermore, there is some evidence that switching from duloxetine to milnacipran may be useful if the patient has had an inadequate response to duloxetine (192).

Selective serotonin reuptake inhibitors (SSRI) have not shown unbiased evidence of being superior to placebo in treating the key symptoms of fibromyalgia but can still be considered as a treatment option when treating depression in patients with fibromyalgia (193).

Pregabalin at a dose of 300–600 mg can provide a major reduction in pain intensity with tolerable side-effects for a small portion of patients with fibromyalgia, but it will not work for most patients (194). Benzodiazepines are not recommended for the treatment of fibromyalgia (177). The quality of evidence on the use of cannabinoids to treat fibromyalgia symptoms is very weak and their tolerability is low (195). Only in the Canadian fibromyalgia guidelines is there a weak recommendation for cannabinoids for important sleep disturbances in fibromyalgia (196). In fibromyalgia, quetiapine may be considered for a time-limited trial to reduce sleep problems and depression if antidepressants have failed (197).

It has been suggested that the endogenous opioid system is the only neurotransmitter system that seems to be working properly in patients with fibromyalgia, and this may explain why opioid drugs do not work well in fibromyalgia and other conditions with central sensitization (77). On the contrary, specific regional alterations of opioid receptors by dysfunction or concentration are also suggested to explain the lack of the effect of opioid drugs in fibromyalgia (83). In a systematic review from 2016, there were no studies that met the inclusion criteria, and the researchers stated that there is no randomized trial-based evidence to

support the argument that the opioid drug oxycodone alone or in combination with naloxone reduces pain in fibromyalgia (198).

Oral nonsteroidal anti-inflammatory drugs (NSAID) are not useful in the treatment of fibromyalgia (199). There are not enough good-quality studies to evaluate the effects of combination pharmacotherapy in patients with fibromyalgia (187).

2.6.5. Other treatment options

Recent studies suggest that hyperbaric oxygen therapy may benefit patients with fibromyalgia, and the effect is probably due to changes in proinflammatory cytokines produced by CD4 T cells or due to neuroplasticity (200–202).

In a recent systematic review and meta-analysis, noninvasive repetitive transcranial brain stimulation therapy relieved pain and enhanced the quality of life of patients with fibromyalgia compared to placebo treatment. However, it had no effect on depression, anxiety, fatigue, pain catastrophizing, or mood (203).

Patients with fibromyalgia have often also tried complementary or alternative treatments. There is some evidence that gentle forms of physical exercise can help in relieving the symptoms, and although Western forms such as Nordic walking and water aerobics are best-studied, traditional Eastern practices such as tai chi, qigong, and gentle yoga styles can also help (204). It seems that aerobic exercise reduces autonomic dysfunction and resistance training helps with psychological symptoms like anxiety and depression (205).

2.6.6. Physicians' perceptions of treatment

There have been suspicions that a fibromyalgia diagnosis might be harmful for the patient, as it might increase the use of health care resources. However, a cohort study conducted in Canada did not support this hypothesis, as a fibromyalgia diagnosis did not increase health care use and the symptoms did not get worse in the three-year follow-up after the diagnosis (145). On the other hand, in a study from the United States, patients with fibromyalgia used health care services four times more than the control population (165). In a questionnaire survey, 37% of

respondents including primary and secondary care physicians were not confident in developing a fibromyalgia treatment plan or managing patients with fibromyalgia long-term (154). In a Japanese cross-sectional postal study, only 44.2% of physicians with previous experience of patients with fibromyalgia were willing to accept additional patients with a fibromyalgia diagnosis to their consultations. Physicians were frustrated with the difficulty of controlling the symptoms and the patients' emotional responses (206).

2.6.7. Patients' perceptions of treatment

It is known from the previous qualitative studies that five themes emerge from the illness experiences of patients with fibromyalgia: feelings of loss, uncertainty, stress, stigmatization, and coping with the symptoms (207). The lack of understanding of the complexity of symptoms by friends and family members is also common among patients with fibromyalgia (208). Patients also think that the invisibility of their symptoms raises questions about their creditability (160). Patients have developed different ways to cope with the symptoms. Pacing everyday pursuits with symptom severity is one way to cope (160). Patients also want help and advice from health care on how to cope with symptoms as well as continuity of care and correct information on the aetiopathogenesis of fibromyalgia (209). Furthermore, patients hoped for longer consultation times in primary health care (210).

2.7. Summary of literature

Fibromyalgia is still somewhat a mystery to medicine. Despite the accumulating scientific evidence, the exact aetiopathogenesis remains unclear. However, there is sound evidence that central sensitization plays an important part in the pathogenesis of fibromyalgia and that environmental factors like psychological stress can trigger fibromyalgia. The main symptoms of fibromyalgia are widespread pain and various somatic symptoms. The international prevalence of fibromyalgia is around 2–3% of the population, and the majority of persons who have received a fibromyalgia diagnosis are female. The current prevalence of fibromyalgia in Finland is unclear.

Various adverse life events have been linked to the onset of fibromyalgia, and the relationship between chronic widespread pain and childhood adversities has been shown by a British prospective cohort study. However, most studies on the association between childhood adversities and fibromyalgia have been too small to detect weak associations and such relationships have not been similarly established. Furthermore, even though peer bullying is one of the most common childhood adversities, there are only a few studies addressing the long-term effects of peer bullying and there are no studies on the association between peer bullying victimization in childhood and fibromyalgia in adulthood.

There are also several challenges relating to the diagnostic process of fibromyalgia. Various diagnostic criteria have been developed mainly for research purposes, but these criteria are also used for diagnostic purposes. There is a variation of symptoms required for the diagnosis, and the self-reporting of symptoms or else a physical examination performed by a physician create differences between the different criteria sets. Laboratory tests are not required for the diagnosis, but clinical guidelines recommend them to rule-out diseases causing fibromyalgia-like symptoms. From the patients' perspective, the time before diagnosis is often confusing, as laboratory tests are used sometimes repetitively and different diagnostic alternatives are suggested.

Furthermore, there is under- and overdiagnosis concerning fibromyalgia, and the diagnosis does not always provide an adequate explanation of the experience of the illness. Many symptoms of fibromyalgia also overlap with other diseases and the use of rule-out tests might lead to the overdiagnosis of subclinical manifestations of these diseases. There are no previous studies addressing the association between functional syndromes, such as fibromyalgia, and subclinical hypothyroidism and inappropriate levothyroxine use.

From the patients' perspective, findings from qualitative studies report that patients have often had to search for a long time for a diagnosis, and the multiplicity of symptoms has caused uncertainty and doubts about the correctness of the diagnosis. Some physicians are also reluctant to make a fibromyalgia diagnosis even though the patient has the typical symptoms, and this might partially originate from the belief that by not setting the diagnosis, they will protect the patient from

overmedicalization. Furthermore, the patient's credibility is questioned by the invisibleness of the symptoms and in addition to this, patients experience insufficient understanding from their close ones.

There are no previous qualitative studies on the diagnostic experiences of patients with fibromyalgia in terms of the under- and overdiagnosis of fibromyalgia, or on the comorbidities of fibromyalgia from the patients' viewpoint.

3 RESEARCH QUESTIONS

The aim of this thesis is to provide more information on the causes of fibromyalgia syndrome and a perspective on the experiences of the patients during the diagnostic process. Furthermore, we wanted to evaluate whether the care guidelines of hypothyroidism, a common comorbidity of fibromyalgia, are followed. Additionally, we had the data from a one-year follow-up questionnaire. This thesis consists of two sets of data. This means that this thesis brings out evidence both at the population level and oncerning primary health care. One dataset is derived from the on-going Health and Social Support (HeSSup) postal questionnaire study and the other is from a study, Patients with Fibromyalgia in Finnish Primary Health Care, conducted at Nokia Health Centre.

The first two research questions concern the HeSSup data:

1. Is there an association between fibromyalgia and childhood adversities in the general population with a large population sample?

2. Is there an association between self-reported bullying victimization in childhood and self-reported fibromyalgia in adulthood?

The other two research questions concern the Nokia Health Centre data and address the problems in the diagnostic process of fibromyalgia:

3. What are the experiences of patients with fibromyalgia during the diagnostic process, especially in terms of possible diagnostic inaccuracies, and how do patients with fibromyalgia wish their treatment to be improved in primary health care?

4. What is the occurrence of thyroid hormone treatment among patients with fibromyalgia and and what are their thyroid hormone levels at the beginning of their treatment? Are the guidelines of care followed?

4 MATERIAL AND METHODS

This thesis consists of two sets of data: the first from the Health and Social Support (HeSSup) postal questionnaire study and the second from the Patients with Fibromyalgia in a Finnish Primary Health Care study conducted at Nokia Health Centre.

4.1 Health and Social Support (HeSSup (I and II))

The on-going Health and Social Support (HeSSup) postal questionnaire study was initiated in 1998. The aim of the study is to explore psychosocial risk and protecting factors of subsequent health in the Finnish working-age population. Our research questions from these data were: 1) Is there an association between fibromyalgia and childhood adversities? and 2) Is there an association between self-reported bullying victimization in childhood and self-reported fibromyalgia in adulthood?

4.1.1. The study design

Initially, questionnaires were sent to a representative sample of 64,797 individuals in the Finnish population in 1998. The sample comprised four age groups: 20–24, 30–34, 40–44, and 50–54 years at baseline. Initially 25,898 questionnaires were returned, leading to a response rate of 40%. Two follow-up questionnaires were sent to the respondents of the initial survey in 2003 and 2012. The response rate was 80% (N=19,629) in the first follow-up and 57% (N=13,050) in the second follow-up. Later, with the respondents' written consent, the survey data were linked to several national health registries, among them the Finnish Hospital Discharge Register (HILMO).

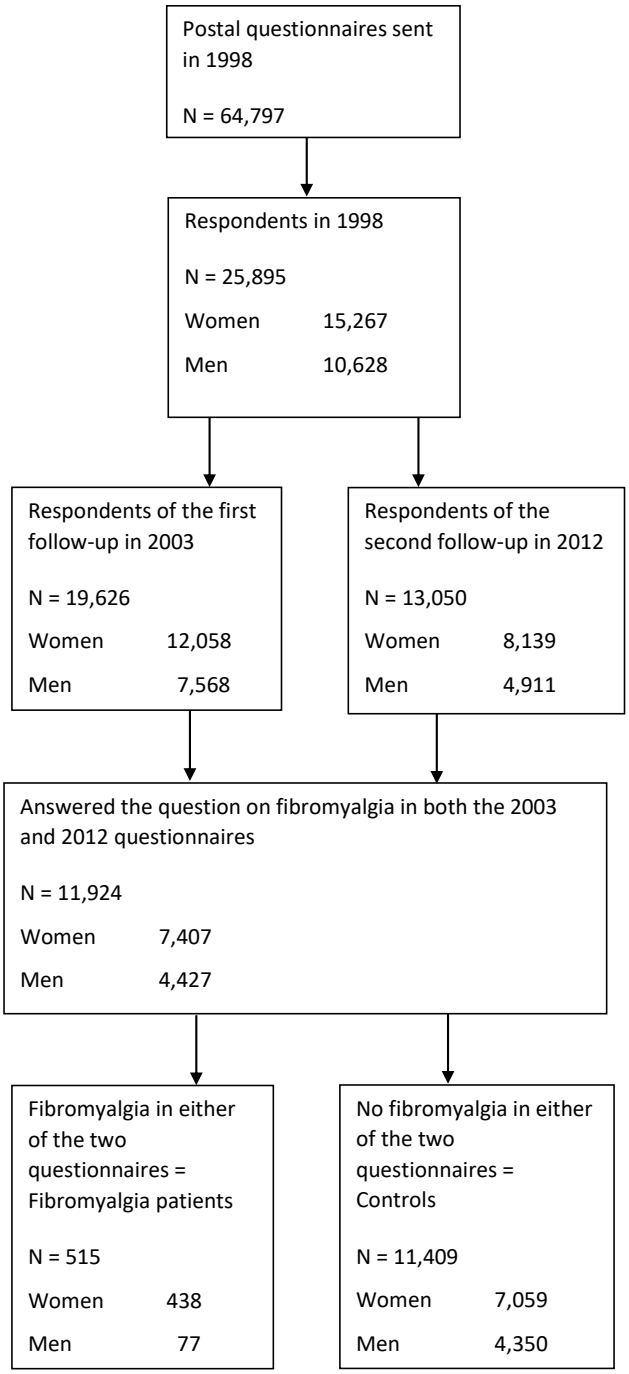


Figure 2: Flow chart of the HeSSup study population.

In the non-response analysis of the HeSSup Study, there were only slight differences in physical health between the respondents and the general population (211). Furthermore, in a study of the mortality of the respondents and non-respondents, male non-respondents showed a small but significant increase of mortality due to external causes compared to the respondents, while female non-respondents again showed a small but significant elevation of disease mortality compared to the respondents (212).

4.1.2. Fibromyalgia and childhood adversities

The setting of this study is retrospective. Information on childhood adversities is from the first HeSSup questionnaire (1998) and the information concerning fibromyalgia diagnoses is from two follow-up questionnaires (2003 and 2012).

In the first questionnaire, participants were asked to think about their childhood adversities in terms of the following six questions: 'When you think about your childhood…' The six question alternatives are presented in Table 3.

Table 3. Questions on childhood adversities presented to the respondents of the HeSSup survey.

Did your parents separate (divorce or similar)?
Did your family have long-lasting financial difficulties?
Did serious conflicts arise in your family?
Were you often afraid of a member of your family?
Was someone in the family seriously or chronically ill?
Did someone in the family have problems with alcohol?

The alternatives were 'Yes', 'No', or 'I do not know'. The length of the adversity and the time when the adversity occurred was not asked in the questionnaire. In order to minimize the recall bias, information from childhood adversities was obtained from the first HeSSup survey in 1998.

In the follow-up questionnaires (2003 and 2012), there was a question on whether a medical doctor had told them that they have or have had various medical

diagnoses including fibromyalgia. The answer alternatives were 'Yes' or 'No'. Thus, the fibromyalgia diagnosis was self-reported. It was not asked when the patient received the diagnosis.

Participants responding with fibromyalgia in either survey were classified as patients with fibromyalgia. Only those who had responded to both follow-up questionnaires were included in the study population. Data from national registers of hospital care (known as HILMO) between 2000 and 2012 were also utilized to ascertain if any participant had ICD-10 codes (M79.7 or M79.0) corresponding to fibromyalgia. As a result, one person was transferred from the control group to the fibromyalgia group. Thirty-seven patients had both self-reported fibromyalgia and the ICD-10 code for fibromyalgia in the registers. The vast majority of patients with fibromyalgia (n=477) had no register information, because fibromyalgia is often treated in primary health care or in outpatient clinics.

Covariates were derived from the 1998 questionnaire. Patients were divided into four age groups corresponding to those used in the 1998 questionnaire. Educational level was divided into two groups: those who had taken the matriculation exam and those who had not. The matriculation exam is a Finnish version of the upper secondary school graduation exam. Passing the exam entitles the pupil to continue studies at university. Marital status was divided into two groups: Single/divorced/widowed or married/cohabiting. Information on symptoms of depression was gained from Beck's Depression Inventory (BDI). The responses were divided into two groups and those scoring more than 18 points were considered to have clinically significant symptoms of depression (213).

4.1.3. Fibromyalgia and peer bullying

As with the previous study (fibromyalgia and childhood adversities), we used two follow-up questionnaires from the HeSSup study (2003 and 2012) to identify patients with fibromyalgia. These studies included a question about the presence of various medical diagnoses with the phrase: 'Has a doctor ever told you that you have or have had…?' followed by a number of names of diseases or conditions. Fibromyalgia was one of the conditions included here. The response alternatives were 'no' and 'yes'. Only those who responded to this question in both follow-ups

were included in the final study population (N=11,924). Those having reported the condition affirmatively in either of the questionnaires were considered as having fibromyalgia (n=515). Participants not reporting fibromyalgia were classified as not having fibromyalgia (n=11,409). We also carried out additional analyses with patients that did not report fibromyalgia in the 2003 survey but reported it in the 2012 questionnaire. We identified 185 newly diagnosed patients with fibromyalgia.

Information from childhood bullying victimization was gathered from the 2012 questionnaire with two questions and four-item Likert scale answer alternatives (from mild to severe).

Table 4. Childhood bullying victimization questions in the 2012 HeSSup survey:

When you think about your school years, were you being bullied at school or in the neighbourhood? Was the bullying heavy for you?

The age of the respondents was grouped into four categories. Marital status was asked in the 2012 questionnaire and divided into two groups with those reporting to be single, divorced, or widowed combined into one group and the married, re-married, or cohabiting into the other group. Education was also asked in the 2012 questionnaire and dichotomized. Those reporting having completed vocational college, polytechnic, or university education were classified as having higher education. Those without vocational education or training or lacking completed apprenticeship training, trade school, or a vocational course were classified as having lower education. Information on the symptoms of depression was gained from Beck's Depression Inventory (BDI). The responses were divided into two groups and a BDI score of more than 18 was considered to mark a clinically significant depression symptom (213).

4.1.4. Statistical analyses

In order to explore associations between fibromyalgia and childhood adversities, analyses of the data were conducted using SAS release 9.4 (2012, SAS Institute Inc., Cary, NC, US). From the cross tabulation, *p*-values were calculated using the Chi-squared test, and values of 0.05 or lower were considered statistically

significant. The results from standard, unconditional logistic regression analysis are presented as odds ratios (OR) with 95% confidence intervals (CI). These were calculated for each childhood adversity and fibromyalgia, with fibromyalgia as a dependent variable (Model 1). In Model 2, adjustment for gender, age, marital status, and educational level (matriculation examination) was performed. Model 3 added adjustment for gender, age, educational level, marital status, and symptoms of depression (BDI>18).

With peer bullying, the severity of bullying victimization was divided into three groups: 1) No bullying: those reporting not being bullied; 2) Minor bullying: those reporting being bullied seldom, sometimes, or often and reporting it not having been heavy at all or only a little bit disturbing; and 3) Severe bullying: those reporting bullying victimization seldom, sometimes, or often and it having been quite hard or very heavy. Answers with missing data or the option 'I do not know' were considered as missing values in the statistical analyses. First, the association between self-reported bullying in childhood and other potentially significant explanatory variables and self-reported fibromyalgia in adulthood was explored with cross tabulation using Pearson's Chi-squared test. The associations were further analysed with logistic regression models including all explanatory variables with a statistically significant association with self-reported fibromyalgia. The models yielded odds ratios (OR) with 95% confidence intervals (CI). The association between fibromyalgia, bullying, and symptoms of depression was also explored in log-linear models. An alpha level of 0.05 was used to indicate statistical significance. The data were analysed using SAS software version 9.4 for Windows (2012, SAS Institute Inc., Cary, NC, US).

4.1.5. Ethical issues

The Ethics Committee of the University of Turku and Turku University Central Hospital did not consider approval necessary for a customary cohort study. All participants were requested to sign a consent form to permit the combination of the data with the national health registries.

4.2 Patients with Fibromyalgia in Finnish Primary Health Care (Study III, Study IV, and unpublished material)

The Patients with Fibromyalgia in Finnish Primary Health Care study was conducted at the city of Nokia Health Centre. The study was initiated in 2015.

4.2.1. The study design

Patients with fibromyalgia were sourced from the electronic medical records of Nokia Health Centre. The inclusion criteria were the ICD-10 code corresponding to fibromyalgia (M79.7) or a diagnosis of fibromyalgia in the patient records with some other code (M79.0, M25.5, R52.9, and M79.1). Altogether, 208 patients with fibromyalgia were identified. An information letter containing five questionnaires was sent to the patients. The questionnaires included the Fibromyalgia Impact Questionnaire (FIQ), Örebro Musculoskeletal Pain Screening Questionnaire (ÖMPSQ), the 2010 version of the American College of Rheumatology Diagnostic Criteria for Fibromyalgia (ACR 2010), EuroQol (EQ-5D-3L), and Patient Health Questionnaire (PHQ-9). A GP's appointment was scheduled for the 103 patients who responded to the letter. In this first stage of the study, a physical examination was performed on the patients. Altogether, 96 patients had fibromyalgia according to the ACR 2010 criteria and seven patients did not meet the ACR 2010 criteria for fibromyalgia at the time of the study. During the appointment, patients who met the criteria had the chance to ask questions about the syndrome. The appointments took place between 2015 and 2016. Furthermore, patients whose symptoms and clinical findings needed laboratory tests to exclude other diseases or who needed some other treatment or follow-up (e.g. referral to a psychiatric nurse or physiotherapist) were given the referrals that they needed and they were defined to have had their care plan modified.

The patients meeting the ACR 2010 criteria for fibromyalgia (n=96) received another letter one year later containing the same questionnaires, excluding the ÖMPSQ. In addition, the patients received a question that aimed to discover the patient's own perception of the development of fibromyalgia. The patients were asked whether the symptoms had got worse, stayed the same, or got better. Finally, the patients were asked whether they had received any additional treatment for fibromyalgia during the study.

4.2.2. Qualitative study on the experiences of patients with fibromyalgia

The methodological orientation of this study is thematic analysis based on the phenomenological theory of the description of the participants' personal subjective experiences (214).

Two members of the research team, Aleksi Varinen (AV, male, GP) and Tiina Vuorio (TV, female, GP), conducted the focus-group interviews. The other members of the team, Tuomas Koskela (TK, male, GP, professor of general practice) and Elise Kosunen (EK, female, professor of general practice), participated with AV and TV in designing the study and interpreting the data. AV worked as a clinical lecturer at Tampere University, and at the time of the interviews, TV worked as a clinical lecturer at the University of Turku. AV had established prior contact with all the patients at one research appointment during the previous phase of the fibromyalgia study. Three of the patients were formerly patients of AV at Nokia Health Centre. However, they were not AV's patients during or after the study, and their fibromyalgia diagnosis was set before they became AV's patients. Therefore, the researchers were not involved in the diagnostic process of the study patients. The interviews were recorded (by audio).

The participants were selected using purposive sampling. The study is based on data from patients with fibromyalgia participating in the Finnish Primary Health

Care study conducted at Nokia Health Centre. AV selected the patients based on the information gathered from the first stage of the fibromyalgia study (GP's appointment) in order to create a maximum variation sample. The criteria used for this were age, gender, educational level, and years since the original diagnosis of fibromyalgia. All patients were originally approached by mail in order to obtain written consent for the fibromyalgia study. The patients selected for the focus groups were contacted by telephone by AV. Originally, the four focus-group sessions were planned based on the estimate that four groups would be sufficient to achieve data saturation (215). Each group was planned to contain five patients because of the complexity and possibly controversial content of the topic (215). Four patients declined the invitation to participate in the focus-group interviews due to timetable constraints. Altogether, 20 patients were selected for the study at this point, but two patients cancelled their appointment at the last minute.

As a result, the study sample consisted of 18 patients divided into four focus groups (two groups with five participants and two with four participants). The participants were referred to the different groups according to their age in order to keep the pace of the conversation comfortable for all participants (216). The interviews took place in the Nokia Health Centre auditorium on 19–20 March 2018. No-one else was present besides the participants and researchers. The characteristics of the participants are shown in Table 5.

The interview guide was available to the interviewers during the interviews. A preliminary interview guide was developed based on the previous literature. All the researchers participated in formulating the interview guide. The three main questions considered patients' wishes for their treatment in primary health care, the way the diagnostic process of fibromyalgia started, and patients' thoughts about the diagnostic tests used. The first session was also a pilot for the interview guide (Figure 3). However, no modifications to the guide were considered necessary based on that session.

Figure 3. Interview guide used in the qualitative study of the experiences of patients with fibromyalgia at Nokia Health Centre.

Beginning of session:

(The interviewer introduces himself/herself and another interviewer) 'Today we are going to discuss fibromyalgia. Our aim is to find out how you wish fibromyalgia to be treated in the future and what kind of thoughts you have on the diagnostic process of the syndrome. Do you have any questions about the interview?'

The rules of the interview are reviewed. Cellphones are turned off. In order to follow who is saying what, the participants are asked to speak only one at the time. The participants are asked to raise their hand to indicate that they want to speak. It is explained that if the interviewer interrupts someone, it is only to ensure that everyone has a chance to participate and the conversation stays on topic.

The participants are informed that everything that is discussed is going to be confidential and after the conversations the interviewers and other two members of research group are going to summarize the discussion so that the individual participants cannot be recognized and to compare themes that arise with themes that have come up in other focus groups.

'First I will ask everybody to tell their name and age' (participants are picked up in random order so that they do not think that they should say something based on their sitting order).

Main theme 1: How do you wish that fibromyalgia would be treated in the future (in primary health care)?

-What kind of health care services do you wish there would be for patients with fibromyalgia?
-What treatment or advice that you have received from health care has been most helpful?
-What has been the most useful thing to help you to cope with fibromyalgia?

Main theme 2: What do you think about internet-based therapy for fibromyalgia?

-In what situation do you think it might be helpful?

-How should it be put into practice?

Main theme 3: (Overdiagnosis)

What happened after the first time you went to see a physician because of fibromyalgia symptoms?

-What do you think about it now?

-Did the symptoms worry you before the appointment?

What do you think now about the diagnosis of fibromyalgia and its diagnostic process?

-Was something in the treatment particularly useful?

-Did you think that something was unhelpful?

-Would you have preferred something in the diagnostic process to have been left out? (Can you give an example?)

-Did the treatment reduce the burden that fibromyalgia caused to you?

-Did you receive contradictory information about the cause of fibromyalgia? How did this feel?

-Did you get a different/contradictory diagnosis or treatment plan based on your symptoms?

-Were previous diagnoses overruled in the diagnostic process? How did this feel?

Table 5. The characteristics of the participating fibromyalgia patients in the Finnish Primary Health Care study.

Demographic features Characteristic	Participants (N=18)
Age (mean & standard deviation, SD)	54.7 ± 15.5
Gender (n)	
Female	15
Male	3
Educational level (n)	
Primary school	6
Upper secondary school or vocational school	11
University or polytechnic	1
Employment status (n)	
Engaged in working life (full- or part-time)	5
Unemployed	2
Unable to work (absence due to illness or disability pension)	9
Old-age pension	2
FM severity: PSD[a] score (mean & SD)	22.5 ± 4.0
Years with FM[b] (mean & SD)	13.8 ± 9.9
FM diagnosis set in (n)	
Primary health care	6
Secondary health care	12

Number of other diagnoses (mean & SD)	1.8 ± 1.2
Regular medication (n)	
Yes	9
No	9
Number of GP visits last year (mean & SD)	3.5 ± 2.0

[a] The PSD score is derived from the American College of Rheumatology (ACR) 2010 diagnostic criteria as the widespread pain index and symptom severity scale are combined into one index ranging from 0 to 31. A patient who meets the ACR2010 criteria for FM will always have at least 12 points from the PSD score. The PSD score is strongly related to somatic symptom severity (54).

[b] The time since the FM diagnosis ranged from 2 to 32 years.

Field notes were also made during the sessions. The interview guide was followed in the same way during every focus-group interview. The four sessions were carried out and after that the researchers agreed that data saturation had been reached based on the field notes, hence no more focus-group interviews were needed. All participants participated equally, with the exception of one patient who had suffered a stroke earlier; this had slightly affected her ability to speak as fluently as the other patients. The duration of the interviews ranged from 61 to 95 minutes.

4.2.3. Excess use of thyroid hormone treatment among patients with fibromyalgia

In this study, the design was cross-sectional. It was based on data from the Patients with Fibromyalgia in Finnish Primary Health Care study conducted at the City of Nokia Health Centre. By the time of the study, the population of the city of Nokia was 33,210 and 19 doctors worked at the health centre. Patients who met the American College of Rheumatology (ACR) 2010 diagnostic criteria for fibromyalgia in the study appointment were included in this study.

Information on thyroid hormone treatment and TSH and free thyroxine (T4-V) levels were obtained from the electronic patient record. Reference values for TSH and T4-V were provided by Fimlab Laboratories, which provided laboratory services to the Tampere University Hospital district at the time of the study. We used the Finnish guidelines for hypothyroidism (217): a TSH level over 4.2 mU/l was defined as subclinical hypothyroidism if the T4-V level was normal. A T4-V level under 11.0 pmol/l was defined as central hypothyroidism if the TSH level was normal or low. A TSH level over 4.2 mU/l and a T4-V level under 11.0 pmol/l was defined as overt hypothyroidism. TSH levels of 0.27–4.2 mU/l and T4-V levels of 11.0–22.0 pmol/l were defined as normal thyroid function.

There was no statistically significant difference between those not answering the study invitation and those participating in the study with regard to age, gender, number of regularly taken medicines, GP's visits before the study, and number of other diseases. The features of the study population are presented in Table 6.

4.2.4. Analyses of the data

In the qualitative study exploring the experiences of patients with fibromyalgia, the data were coded according to the thematic analysis process (215). We identified subordinate codes within group interviews and arranged them into larger themes across interviews. Initially 61 codes were generated. Due to overlaps, some codes were unified, resulting in 55 codes altogether. Finally, seven themes were formulated. Researchers used back-and-forth translation to verify that the citations were properly translated. COREQ and SRQR checklists were used in reporting this study. The researchers coded the data first independently and after that they discussed their findings. A description of the coding tree was provided after that. Initially 61 codes were generated from the data. Due to overlap, some codes were unified, ultimately resulting in 55 codes.

Table 6. Demographic features of the patients with fibromyalgia in the Finnish Primary Health Care Study.

	Participants		Not participating		
	N=103		N=105		
	%	n	%	n	*p*-value
Gender					0.19
Male	10.7	11	5.7	6	
Female	89.3	92	94.3	99	
	Mean and 95% CI for mean				
Age	55.1 (52.1–58.1)		57.4 (54.4–60.5)		0.3
Number of regular medicines	3.3 (2.7–3.4)		4.0 (3.3–4.7)		0.15
GP's visit in last 12 months	5.3 (4.0–6.5)		5.0 (4.0–6.0)		0.52
Number of chronic illnesses excluding FM	2.5 (2.2–2.9)		2.8 (2.4–3.2)		0.39

The researchers used Microsoft Excel to organize the codes and after that identified the themes together from the data. Initially nine themes emerged, but two themes were combined during the analysis. Feedback was not asked from the participants. Researchers used back-and-forth translation to verify that the citations were properly translated.

In the quantitative study for the excess use of thyroid hormone treatment among patients with fibromyalgia, the data were analyzed using SPSS version 23. Cross-tabulation and Chi-squared tests were used when categorical variables were present and the two-sample t-test was performed with variables following a normal distribution. The Kolmogorov-Smirnov test was used to confirm the normal distribution of the variables.

Furthermore, we explored the perception of symptoms after a one-year follow-up by using the FIQ score as an outcome variable. The FIQ score in the follow-up letter was compared to the FIQ score in the initial letter. In addition, the change in FIQ score was categorized into patients with and without symptoms of depression. The paired sample t-test was used for analyzing the relation between the main variables. Logistic regression was used to analyze the relationship between additional treatment, symptoms of depression, and the perception of improvement of symptoms. Crosstabulations were analyzed with the Chi-squared test. Confidence intervals (95% CI) and *p*-values were calculated for all results.

4.2.5. Ethical issues

The study protocol was approved by the Regional Ethics Committee of Tampere University Hospital (R15041). Furthermore, all participants gave their written consent to participate in the study and for the publication of the results.

5 RESULTS

5.1 The relationship between childhood adversities and fibromyalgia (Study I)

The occurrence of self-reported fibromyalgia was 4.3% in the final study population, which consisted of 11,924 respondents. Some 515 of them had replied affirmatively to the fibromyalgia question or had the corresponding diagnosis in the health care registers.

The demographic features of the respondents are presented in Table 7. Patients with fibromyalgia were older than the controls (those answering negatively to the question about fibromyalgia) and most of them were female. Furthermore, the controls were more often single compared to patients with fibromyalgia. The educational level was lower in the fibromyalgia group than in the control group.

Patients with fibromyalgia reported statistically significantly higher numbers of all childhood adversities besides parental divorce, although the difference was not statistically significant. Long-lasting financial difficulties in the family was the most often reported adversity both in the fibromyalgia group and the control group. The proportions of patients with fibromyalgia and controls reporting childhood adversities are presented in Table 8.

Table 7. Features of those assigned to the fibromyalgia group and the controls in the HeSSup survey in 1998.

	Patients with fibromyalgia		Controls		
	%	n	%	n	*p*-value
Gender					<0.001
Female	85.0	438	61.9	7059	
Male	15.0	77	38.1	435	
Age in 1998					<0.001
20−24	10.7	55	21.2	2415	
30−34	13.1	69	20.8	2371	
40−44	33.1	160	26.5	3025	
50−54	44.8	231	31.5	3598	
Marital status					0.021
Single/divorced/ widowed	24.7	127	29.4	3354	
Married/re-married/ cohabiting	73.3	388	70.6	8044	
Education					<0.001
Taken the matriculation exam	32.6	168	45.6	5194	
Not taken the matriculation exam	67.4	347	54.4	6203	
Symptoms of depression					<0.001
Beck's Depression Inventory >18	8.8	45	4.0	454	
Beck's Depression Inventory ≤18	91.2	469	96.0	10899	

All six childhood adversities were associated with fibromyalgia after adjustment for gender and age. Adjustment for at least moderate depression symptoms, marital status, or educational level had no statistically significant effect on this association. Furthermore, the correlation between being afraid of a family member and being diagnosed with fibromyalgia was the strongest both with adjustment and without adjustments. The weakest correlations with adjustments were seen in serious or chronic illnesses in the family and alcohol problems. The results from the multivariate logistic regression analysis for childhood adversities and fibromyalgia with adjustments for covariates are shown in Table 9.

Table 8. Proportion (%) of the fibromyalgia (FM) patients and the controls reporting childhood adversities in the HeSSup survey.

	FM patients N=439−495*	Controls N=10,182−11,118*	
	%	%	*p*-value
Parental divorce	17.4	14.5	0.076
Long-lasting financial difficulties in the family	41.0	27.8	<0.001
Serious conflicts in the family	35.0	26.4	<0.001
Being afraid of a family member	22.4	12.9	<0.001
Serious or chronic illnesses in the family	36.0	26.5	<0.001
Alcohol problems in the family	29.4	23.9	0.005

*Individuals answering 'I do not know' to any question or leaving a question unanswered were excluded from the data (to enable cross tabulation), which is the cause for the different numbers of patients with fibromyalgia and controls included in the analyses.

Furthermore, patients with fibromyalgia reported more adversities than the controls. The OR (95% CI) for fibromyalgia with 1–2 adversities vs no adversities was 1.54 (1.25–1.91) and the corresponding figure for 3–6 adversities vs no adversities was 2.15 (1.69–2.73).

Table 9. Crude and adjusted odds ratios for childhood adversities associated with fibromyalgia in the multivariate logistic regression analyses in the HeSSup survey.

Adversity in the family	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Parental divorce	1.24 (0.98–1.58)	1.36 (1.06–1.74)	1.34 (1.05–1.72)
Long-lasting difficulties	1.81 (1.49–2.20)	1.49 (1.22–1.82)	1.45 (1.18–1.77)
Serious conflicts	1.50 (1.23–1.83)	1.45 (1.19–1.78)	1.40 (1.14–1.72)
Being afraid of a family member	1.95 (1.56–2.42)	1.66 (1.33–2.08)	1.60 (1.28–2.01)
Serious or chronic illnesses	1.56 (1.30–1.89)	1.30 (1.07–1.57)	1.27 (1.05–1.55)
Alcohol problems	1.33 (1.09–1.62)	1.27 (1.04–1.56)	1.25 (1.02–1.53)

Model 1: Crude
Model 2: Adjusted for gender, age, educational level, and marital status
Model 3: Adjusted for gender, age, educational level, marital status, and depression smyptoms

5.2. The association between bullying victimization in childhood and fibromyalgia (Study II)

The demographic features of the final study population are presented in Table 10. Minor bullying victimization was reported by half of the participants and severe bullying by 20% of all respondents. Males reported minor bullying more often, but severe bullying was more common among females. Altogether, female respondents with fibromyalgia reported bullying more often than those not reporting fibromyalgia, and the difference was statistically significant (*p=0.027*).

When gender and bullying were included in the model as explanatory variables, there was no statistically significant interaction (*p=0.379*) between these variables. Among all participants, minor bullying was reported slightly more often in the fibromyalgia group, but the difference was not statistically significant (*p=0.337*). Likewise, severe bullying was slightly more common in those reporting fibromyalgia,

but the association was not statistically significant (*p=0.075*). The proportions of the study population reporting childhood bullying are presented in Table 10.

We found significant associations between minor and severe bullying victimization in childhood and fibromyalgia after adjustments for gender, age, and educational level in the multiple logistic regression analysis. The observed association was more evident in severe bullying, but statistically significant in minor bullying as well. The results from the crude and the adjusted logistic regression analysis are presented in Table 11.

However, when interactions were added in the logistic regression model to explore the role of depression symptoms with patients with fibromyalgia, the three-way interaction between bullying, gender, and depression symptoms was not statistically significant (*p=0.994*). In further analyses, the two-way interaction between bullying and gender (*p=0.314*), gender and symptoms of depression (*p=0.240*), and bullying and depression symptoms (*p=0.122*) were not statistically significant either. After removing these interaction terms from the model, depression symptoms ($p<0.001$) and gender ($p<0.001$) showed statistically significant associations with fibromyalgia, whereas bullying did not (*p=0.171*).

In a log-linear model, there was no statistically significant four-way association between fibromyalgia, bullying, gender, and depression symptoms (*p=0.994*). No statistical significance was found in three-way models assessing the associations between bullying, fibromyalgia, and gender (*p=0.314*), fibromyalgia, bullying, and depression symptoms (*p=0.142*), fibromyalgia, gender, and symptoms of depression (*p=0.188*), and bullying, gender, and depression symptoms (*p=0.779*). On the contrary, in a two-way model, there were associations between fibromyalgia and gender ($p<0.001$), bullying and gender ($p<0.001$), fibromyalgia and depression symptoms ($p<0.001$), bullying and symptoms of depression ($p<0.001$), and gender and depression symptoms (*p=0.002*), but not with fibromyalgia and bullying (*p=0.173*).

When the 185 newly diagnosed patients with fibromyalgia were analysed, there was no statistically significant association in logistic regression analysis between bullying and fibromyalgia before adjustments either with minor bullying (*p=0.512*) or severe bullying (*p=0.063*). After adjustments for gender, age, and educational

level, there was a weak association between bullying and fibromyalgia (*p=0.043*), but when depression was added to the model, the interaction was no longer statistically significant (*p=0.071*).

Table 10. Frequencies and percentages of participants reporting victimization of childhood bullying in the HeSSup 2012 follow-up survey.

Fibromyalgia	Yes		No		
	n	%	n	%	*p*[a]
Males					0.887
No bullying	20	26.0	1057	24.6	
Minor bullying	44	57.1	2420	56.4	
Severe bullying	13	16.9	815	19.0	
Females					0.027
No bullying	119	27.3	2324	33.2	
Minor bullying	216	49.5	3285	47.0	
Severe bullying	101	23.2	1387	19.8	
All					0.203
No bullying	139	27.1	3381	30.0	
Minor bullying	260	50.7	5705	50.5	
Severe bullying	114	22.2	2202	19.5	
Total	512	100.0	11288	100.0	

[a]: Pearson's Chi-squared test.

Table 11. Odds ratios for childhood bullying adversities associated with fibromyalgia in the crude and adjusted logistic regression models in the HeSSup survey.

	Crude OR (95% CI)	Adjusted OR (95% CI)
No bullying (Ref.)	1	1
Minor bullying	1.11 (.90–1.37)	1.35 (1.09–1.67)
Severe bullying	1.26 (.98–1.62)	1.65 (1.27–2.14)

5.3. Experiences of patients with fibromyalgia in Finnish primary health care (Study III)

In our qualitative thematic analysis, seven themes emerged from the data (Table 12):

Table 12. Themes emerging from the focus-group interviews in the Patients with Fibromyalgia in Finnish Primary Health Care study.

I Prolonged diagnostic process
II Contradictory and suspicious thoughts regarding the diagnosis
III Searching for a reason for their illness
IV Lack of compassion and understanding
V The importance of the patient-doctor relationship
VI Illness and identity
VII Conceptions of the treatment

I Prolonged Diagnostic Process

The patients felt that physicians ordered diagnostic tests for rheumatoid arthritis and other various somatic diseases, but as they were negative, receiving the fibromyalgia diagnosis was a slow process: 'Laboratory tests for rheumatoid arthritis had been taken quite regularly since I was 14 or 15 years old, and nothing had ever been found' (woman, 40 years, 16 years since the diagnosis).

In many cases, the participants mentioned that the rheumatologist had set the final diagnosis of fibromyalgia. In addition, the patients felt that on several occasions physicians considered the symptoms of fibromyalgia (e.g. fatigue) to be a sign of depression, even though the patients did not feel their mood was low: 'When I went to clinical examinations for my pain, the only diagnosis that I got was depression' (woman, 33 years, 4 years since the diagnosis).

Some participants felt that physicians did not set the diagnosis and tried to provide treatment advice instead: 'At some point I was getting frustrated and the doctor just said that there is nothing wrong with me: a person can have pain that comes from an unknown origin' (man, 62 years, 3 years since the diagnosis).

Sometimes patients thought that physicians knew more than they revealed, but they were not allowed to tell everything, especially if there was a lack of sound scientific evidence*:* 'But I think that many doctors know more, but they cannot – is it their ethics or what – but they just can't tell you what to do even if it would ease the symptoms. They have to use that medical jargon.' (Woman, 40 years, 16 years since the diagnosis)

Uncertainty was more evident if the patients were told they had a fibromyalgia-like syndrome or the patients were atypical (e.g. young or male). The role of tender points was also confusing, as many patients had more severe pain

elsewhere. Some participants had a different pain syndrome diagnosis (e.g. fibromyalgia and chronic pain syndrome), and this was also considered confusing.

II Contradictory and Suspicious Thoughts Regarding the Diagnosis

This theme included negative attitudes towards the diagnosis of fibromyalgia from the patient's, physician's, and society's perspective because of the negative stigma: 'But at the moment when the diagnosis was set, the doctor said to me that you have to understand that this is a disease which is not taken seriously. So shall I set this diagnosis or not? And I replied that you have to do it if the symptoms match.' (Woman, 65 years, 9 years since the diagnosis)

Patients often felt it was hard to accept the diagnosis of fibromyalgia, and they would have wanted more tests to find out what was wrong with them. Sometimes the patients received only the diagnosis but no treatment or instructions on how to cope with the situation: 'It was actually the only thing that I did not want – the diagnosis – I wanted instructions for treatment' (woman, 49 years, 13 years since the diagnosis).

Some patients argued that fibromyalgia did not explain all of their symptoms. On the other hand, some patients reported that they were diagnosed quickly, as the GP seemed to be familiar with the syndrome and a few patients already suspected they had fibromyalgia.

In some cases, the participants felt that the physician had kept the diagnosis secret from them or made them decide whether they wanted the fibromyalgia diagnosis to be written in the medical record: 'I felt so embarrassed about that disease, because the occupational health doctor said to me, that do you want… are you really sure that you want me to put this diagnosis in your medical records' (woman, 65 years, 9 years since the diagnosis).

Furthermore, many patients felt that they did not go to see their GP because of the fibromyalgia symptoms, but due to other symptoms or because they did not know if the symptoms were the result of fibromyalgia. They thought it was very hard to tell which condition was causing the symptoms, especially when they had many comorbidities: 'I have gout and other diseases. And osteoarthritis. I have several diseases that cause pain. Fibromyalgia is not the only one. You don't always know which the pain is from.' (Woman, 50 years, 10 years since the diagnosis)

III Searching for a Reason for the Illness

This theme included the patients' thoughts about heritability and psychological factors (e.g. adverse life events) that could trigger fibromyalgia, as well as thoughts about defects in their body (e.g. the hypermobility of joints) predisposing them to fibromyalgia: 'I am the third generation of women with this disease' (woman, 49 years, 13 years since the diagnosis); 'I guessed that I have it, because we have that in my family and the symptoms are the same' (man, 59 years, 3 years since the diagnosis); 'I also have too straight a spine' (woman, 49 years, 13 years since the diagnosis).

IV Lack of Compassion and Understanding

A lack of empathy and understanding of the effects of fibromyalgia were the main features of this theme. The participants felt that close relatives and health care professionals did not understand them. Furthermore, they felt that physicians questioned their credibility because they did not look sick: 'Even strangers tell you that you look so lively and happy that how can you not go to work' (woman, 49 years, 13 years since the diagnosis).

In addition, the patients reported that they often found physical examinations painful, and the physicians did not seem to understand this: 'When

doctors say that checking blood pressure can't hurt, and it hurt so much that I almost fainted' (woman, 47 years, 14 years since the diagnosis).

Moreover, patients felt that there was a lack of understanding also from society, as the diagnosis of fibromyalgia does not entitle one to a disability pension. On the other hand, one patient described how she regained her credibility when she was granted a disability pension: 'When I got my disability pension it did not make me healthy, but I felt that my dignity was restored' (Woman, 69 years, 27 years since the diagnosis).

Furthermore, some patients felt that fibromyalgia was not taken into consideration in the care planning for other medical conditions: 'After the fibromyalgia diagnosis, when I have visited doctors for other symptoms, no one has considered that they may be from fibromyalgia' (woman, 65 years, 9 years since the diagnosis).

On the contrary, some felt that physicians thought that every symptom they had derived from the fibromyalgia syndrome. Participants also considered that the multiplicity of symptoms complicated the diagnostic process. Furthermore, patients were aware that fibromyalgia might not cause all of their symptoms: 'It takes time to understand what the symptoms are and how they present. It takes time to know yourself and your symptoms.' (Woman 65 years, 9 years since the diagnosis)

V The Importance of the Patient-Doctor Relationship

The patient-doctor relationship was important for the patients. Additionally, patients appreciated if the physician was familiar with the treatment of fibromyalgia: 'If you have a good doctor, he understands what is the correct treatment for you' (woman, 40 years, 16 years since the diagnosis).

Listening and understanding the condition were key elements for a good relationship. Still, many physicians seemed to lose interest after making the diagnosis, and they did not give any instructions for self-treatment. Patients also reported that the physician they saw changed constantly and the consultations were too short: 'The consultation time is short. Or if you get an on-call appointment then it is even shorter.' (Woman, 33 years, 4 years since the diagnosis)

Furthermore, the patients desired consultations where specialists and their own GP would plan the treatment together: 'Sometimes you hope that there would be some kind of joint consultation with your GP and the rheumatologist or some other specialist' (man, 62 years, 3 years since the diagnosis).

Some patients also recognised the limitations of the effective treatment methods for fibromyalgia.

VI Illness and Identity

The patients stated that when they realized that there was no curative treatment for fibromyalgia, they were forced to adopt a new identity. GPs often tried to provide reassurance by pointing out that the condition is not malignant. This, however, did not always work: 'Doctors often try to comfort you that this does not kill you. But I think that it is not comforting when you have forty or fifty years left to live and you know that the pain is not going anywhere.' (Woman, 49 years, 13 years since the diagnosis)

Some patients felt that the illness burden of fibromyalgia was very high and experienced desperation due to the fact there is no cure for the syndrome: 'I have noticed that some older patients would rather have cancer, which can either be cured or it kills you. With fibromyalgia you have constant pain and no-one can help you.' (Woman, 49 years, 13 years since the diagnosis)

The younger patients in particular described difficulties accepting the restrictions in their functional ability. On the other hand, older patients tended to accept fibromyalgia better as a part of their burden of illness. Some patients mentioned that for a while they had even forgotten they had fibromyalgia when they got some more severe diseases: 'I had breast cancer a few years ago, and I have not visited the doctor because of fibromyalgia for about 20 years' (woman, 72 years, 25 years since the diagnosis).

After accepting the diagnosis, it was easier to find coping strategies. Most patients said that the best advice for coping with the symptoms was to listen to one's body. As a result, they felt their life had to be organized according to the disease: 'On a holiday trip I have to schedule my life. Today I go walking and tomorrow I will lie by the pool. Makes you laugh (ironically), but that's how it is.' (Woman, 40 years, 16 years since the diagnosis)

VII Conceptions of the Treatment

The patients had different perceptions of the effectiveness of different medications, nutritional guidance, physiotherapy, psychological interventions, cold therapy, peer support, and acupuncture: 'I was in a rheumatology clinic, and when they examined my tender points I yelled like a dying swan, and there was no question about the diagnosis, and then they started trying different medications: oral corticosteroids, etc., and nothing helped' (woman, 69 years, 32 years since the diagnosis).

In general, some patients had experienced short-term benefits from corticosteroids and long-term benefits from exercise: 'Exercise helps, even if it is only ten minutes of walking' (woman, 65 years, 9 years since the diagnosis).

More information on fibromyalgia and meaningful pursuits in daily life were also seen as beneficial: 'Maybe the best thing to do is to exercise – but not too much – and try to clear your mind of issues related to pain with meaningful daily life pursuits' (man, 62 years, 3 years since the diagnosis).

Furthermore, the patients recognized the importance of sleep: 'You are more sensitive to pain if you do not sleep well' (man, 62 years, 3 years since the diagnosis).

5.4. Excess use of thyroid hormone treatment among patients with fibromyalgia (Study IV)

In the Patients with Fibromyalgia in Finnish Primary Health Care study conducted at the city of Nokia Health Centre, the data included 96 patients with fibromyalgia according to the ACR 2010 criteria. Seven patients identified from the patient records did not meet the criteria for fibromyalgia at the time of the study. From that group of 96 patients, 33 (34%) had thyroid hormone treatment and 63 (66%) had not. No statistical significant difference was found between those taking thyroid hormone replacement and those not taking it in functional ability (FIQ) (p=0.36) or symptoms of depression (PHQ-9) (p=0.71). Information regarding regular medication was present in their electronic patient record. The characteristics of the study population are shown in Table 13.

Table 13. Characteristics of the study population in the Patients with Fibromyalgia in Finnish Primary Health Care study.

	No levothyroxine	Levothyroxine	
	N=64	N=33	
	Mean and 95% CI for mean		*p*-value
Number of other chronic diseases			
	2.4 (1.91–2.90)	2.79 (2.32 –3.25)	0.32
Number of regularly taken medicines			
	3.05 (2.15–3.95)	3.45 (2.63–4.28)	0.65
FIQ* Score (Mean)			
	44.42 (39.87–48.97)	41.07 (34.36–47.77)	0.36
PHQ-9** Score			
	10.05 (8.64–11.46)	10.52 (8.39–12.64)	0.71

*FIQ=Fibromyalgia Impact Questionnaire, **PHQ-9=Patient Health Questionnaire for depression. All characteristics were normally distributed.

Of those 33 patients with levothyroxine treatment, 16 had information regarding the initial TSH and T4-V levels before thyroid hormone treatment: Ten (10/16) patients had hypothyroidism based on laboratory tests. Of them, subclinical hypothyroidism was present in six cases (6/16), central hypothyroidism in three cases (3/16), and overt hypothyroidism in one case (1/16). The diagnosis of central hypothyroidism was confirmed in all three cases by a specialist of internal medicine working at the

Nokia Health Centre. Of the 16 patients with thyroid hormone treatment, six patients (37%) had normal thyroid function at the beginning of the treatment. The thyroid function of those patients with fibromyalgia with levothyroxine treatment is presented in Table 14.

Table 14. Thyroid function of patients (n=16) with levothyroxine treatment whose initial TSH and T4-V level information was available from the patient records in the Patients with Fibromyalgia in Finnish Primary Health Care study.

Patient	Daily thyroxine dose (µg)	TSH (mU/l) before threatment	T4-V (pmol/l) before treatment	Current TSH (mU/l)	Current T4-V (pmol/l)	Year of hypothyroidism dg
1 overt hypothyroidism	75	7.3	10.0	2.5	13.6	2012
2 subclinical hypothyroidism	37.5	7.9	11.2	1.4	15.1	2012
3 subclinical hypothyroidism	93	7.1	11.0	0.31	19.1	2008
4 subclinical hypothyroidism	75	6.7	13.8	3.2	15.7	2004
5 subclinical hypothyroidism	50	5.7	13.0	2.5	16.0	2016
6 subclinical hypothyroidism	50	4.9	13.7	2.6	18.6	2011
7 subclinical hypothyroidism	50	4.4	14.1	2.8	14.1	2014
8 central hypothyroidism	75	2.6	10.8	0.78	19.3	2012
9 central hypothyroidism	125	2.6	10.7	1.3	11.6	2012
10 central hypothyroidism	71	0.24	10.9	0.18	14.2	2011

11 normal thyroid function	50	3.5	12.1	1.6	16.2	2013
12 normal thyroid function	100	1.6	16.6	1.2	16.0	2015
13 normal thyroid function	50	1.9	12.6	1.3	13.6	2013
14 normal thyroid function	150	4.2	11.9	0.01	20.2	2012
15 normal thyroid function	100	1.2	13.9	0.87	20.3	2014
16 normal thyroid function	25	1.1	11.0	0.87	13.9	2016
Mean (*p*-value)	73.5	3.9	12.3	1.5 (<0.001)	16.1 (<0.001)	
Median	73	3.83	12	1.3	15.85	

Overt hypothyroidism (TSH>4.2 mU/l and T4-V<11.0 pmol/l), subclinical hypothyroidism (TSH>4.2 mU/l and T4-V=11.0–22.0 pmol/l), central hypothyroidism (TSH=0.27–4.2 mU/l and T4-V<11.0 pmol/l), normal thyroid function (TSH=0.27–4.2 mU/l and T4-V=11.0–22.0 pmol/l). The paired samples t-test was used to determine the statistical significance of a change in TSH values and T4-V values.

5.5 Patients with Fibromyalgia in a Finnish health centre: One-year follow-up (Unpublished material)

Altogether 79 patients returned the letter (82% of the follow-up cohort). In regard to fibromyalgia symptoms, 45% of the patients felt that the symptoms had increased, 50% thought that the symptoms had stayed the same, and 5% thought the symptoms

had improved. The numbers of respondents to the symptom development question in the follow-up questionnaire are presented in Table 15.

Table 15. Development of symptoms reported by patients with fibromyalgia in the follow-up questionnaire in the Patients with Fibromyalgia in Finnish Primary Health Care study.

Variable	Got worse	Stayed the same	Got Better	*p*-value
Modification to care plan*				0.046
Care plan modified	3	4	2	
Care plan not modified	32	35	2	
Depression symptoms**				0.87
Symptoms of depression	20	12	2	
No symptoms of depression	15	26	2	
Gender				0.511
Male	3	3	1	
Female	32	36	3	
Time of diagnosis				0.226
Diagnosis before 2007	20	16	3	
Diagnosis after 2007	15	23	1	

*Modification of care plan during the study for fibromyalgia ** PHQ-9 score >10, PHQ=Patient Health Questionnaire.

Although most participants reported that their symptoms had either got worse or stayed the same, the mean PHQ-9 scores decreased by 1.0 points (95% CI -2.1–0.1). This was not statistically significant overall, but there was a significant decrease in PHQ-9 score by 3.2 points (95% CI -4.8–-1.5) in the subgroup of depressed patients.

In our analyses, holding all other predictor variables constant, the odds of a perception of an improvement in symptoms occurring was 9.6 (95% CI 1.2–78.9) if the patient had had some modification to the care plan after the GP's appointment at the beginning of the follow-up. However, patients with depression symptoms were more likely to think that their symptoms had got worse during the follow-up (OR 2.7 95% CI 1.1–6.7), even though their FIQ and PHQ-9 scores were lower at the end of the follow-up.

6 DISCUSSION

6.1. Main results

The main results of this thesis can be divided into three categories: the results from the association studies in regard to childhood adversities and fibromyalgia, the results from the qualitative study, and the results from the study in regard to fibromyalgia and the thyroid hormone. However, there are some common themes concerning fibromyalgia rising from all four sub-studies: the complex associations with fibromyalgia and depression arose in the retrospective study about childhood peer bullying when it was not possible to separate the role of depression and fibromyalgia behind the observed association. In addition, depression was often offered as an explanation for all of the symptoms in our qualitative study, even though patients did not perceive themselves as depressed. In our follow-up study in Nokia, the treatment of depression seemed to be effective to improve the quality of life of patients with fibromyalgia, even though depressed patients themselves thought that their overall condition had worsened.

According to the first study in regard to the association between fibromyalgia and six different childhood adversities, there were significant associations between all the adversities and fibromyalgia, even after adjustments for age, gender, educational level, marital status, and symptoms of depression.

In the second study exploring the association between fibromyalgia and peer bullying victimization, there was also a significant association between peer bullying in childhood and fibromyalgia in adulthood after adjustments for gender, age, and educational level. However, upon adding symptoms of depression as an explanatory variable, this association no longer remained statistically significant despite several different statistical analyses.

In the qualitative part of our study, the main unifying concepts were the uncertainty and contradictions that patients had faced with fibromyalgia on several occasions. Physicians sometimes offered other diagnoses (e.g. depression) as an

explanation for the symptoms or used repetitive tests to rule out other possible causes for the symptoms. Furthermore, a good patient-doctor relationship, the physician's attitude, and continuity of care were important to the patients.

In the fourth sub-study about hypothyroidism and fibromyalgia, our findings suggest that patients with fibromyalgia and normal thyroid function might be prescribed levothyroxine unnecessarily.

In our follow-up study, patients with symptoms of depression seemed to benefit from the treatment of depression also in terms of their fibromyalgia symptoms.

6.2. The association between fibromyalgia and childhood adversities

The findings of our studies are in line with the findings from previous studies in terms of the association between fibromyalgia and childhood adversities (14,100,101). However, there are some differences: the British Birth Cohort Study (BBCS) focused on widespread pain, while our studies concerned fibromyalgia (14). Still, in the BBCS widespread pain was defined using the ACR 1990 classification criteria for fibromyalgia. These criteria include pain present for at least three months both above and below the waist and on both sides of the body as well as in the axial skeleton. Based on our results, it seems that childhood adversities appear to be associated with fibromyalgia in the same way as chronic widespread pain. In our study, the association between a family history of alcohol problems and fibromyalgia resulted in an OR of 1.3 after all adjustments. In the BBCS, alcoholism resulted in a risk ratio (RR) of 1.3 when adjusted for sex, social class, and psychological distress. Furthermore, in the BBCS the adjusted RR for financial difficulties in the family was 1.6, while in our study the OR was 1.5. In the same way, parental divorce resulted in an adjusted RR of 1.3 in BBCS and an OR of 1.3 in our study.

In their study (Biopsychosocial Religion and Health Study), Haviland et al. reported that physical abuse resulted in an OR of 1.38 (1.07–1.78) for a physician-made fibromyalgia diagnosis and sexual abuse resulted in an OR of 1.41 (1.11–1.80) (105). However, the study sample of Haviland et al. was unique, as it contained only Seventh-day Adventists who rarely smoke or use alcohol, and only 47% eat meat,

and these factors may have an impact on the generalizability of the results. Furthermore, participants were not matched for psychological distress or mental comorbidity. In the Haviland et al. study, the OR was 1.16 (0.90–1.49) for emotional trauma, 1.17 (0.92–1.47) for life-threatening trauma, and 1.15 (0.98–1.61) for major life stressors. In that study, major life stressors were defined as serious illness, abortion, miscarriage, divorce, homelessness, and the death of a child. However, it was not specified at what age these stressors had occurred, and due to the heterogeneity of these stressful events, the results are not entirely comparable with our findings. In their study, Haviland et al. considered insults, swearing, or being ignored by a mother or father as emotional trauma. In our study, we asked about being afraid of a family member, which might capture the emotional effect of the event more effectively.

In the BBCS, the association between widespread pain and a family history of alcohol problems, financial difficulties in the family, and parental divorce was weaker after adjustments for sex, social class, and psychological distress (14). In our study, adjustment for gender and age weakened the associations, but adding educational level did not have a substantial effect on the associations. However, when symptoms of depression was added to the model, the association became weaker. This might be due to the complex connection between fibromyalgia and depression.

6.3. The association between bullying victimization in childhood and fibromyalgia

We found significant associations between bullying victimization and fibromyalgia after adjustments for gender, age, and educational level. However, in spite of further statistical analyses including the addition of depression symptoms as an explanatory variable, the association was no longer statistically significant. It is likely that fibromyalgia and depression have several common risk factors, and their association is so complicated that it is difficult to completely separate their effects.

There have been similar findings concerning the association between bullying and adulthood chronic pain in previous studies. In a Dutch study with 15,220 adolescents, the OR for suffering from chronic pain was 1.23 (95% CI 1.17–

1.29) for those having been bullied after adjustment for gender, age, ethnic origin (Dutch vs non-Dutch), and school level (21). For those who reported severe bullying, the association with fibromyalgia was stronger in our study, and with those who reported minor bullying it was only slightly stronger. However, there was a longer time period between bullying and fibromyalgia in our study, as the Dutch study only included adolescents attending 7th and 8th grade (early adversities such as peer bullying were asked at that point).

To the best of our knowledge, our study was the first reporting the association between peer bullying and fibromyalgia. Although the cross-sectional setting allows only the observation of associations, it may suggest that peer bullying may have long-lasting effects, especially on those who have encountered severe bullying. However, it is also possible that children who later develop fibromyalgia have features that predispose them to bullying. Furthermore, all participants that reported bullying in childhood did not develop fibromyalgia later in life. This leads us to consider why some bullying victims get fibromyalgia while others do not. Based on our findings, depression might have some kind of role in that process. Furthermore, it is probable that fibromyalgia and depression share numerous common risk factors and their association is so complex that it is extremely hard to totally separate their effects.

6.4. Experiences of patients with fibromyalgia in Finnish health care

We had expected that patients would have talked more about diagnostic procedures. However, during the conversations only repeated laboratory tests for ruling out rheumatoid arthritis and for some other somatic diseases were brought up. Instead of diagnostic procedures, patients were willing to discuss the uncertainty and contradictions regarding fibromyalgia that patients had faced on several occasions.

It is known from previous studies that patients face uncertainty. However, the contradictions patients had faced in several sectors of health care was a new finding. One source of uncertainty and also a potential source of overdiagnosis was physicians' repetitive use of rule-out tests for other diseases without setting the fibromyalgia diagnosis. One explanation for this might be that according to the

former diagnostic criteria for fibromyalgia, other similar conditions had to be ruled out before a fibromyalgia diagnosis could be set. However, in the revised diagnostic criteria, a diagnosis of fibromyalgia is valid irrespective of other diagnoses (149).

In our study, patients with fibromyalgia experienced contradictions in many sectors of health care, as well as in personal relationships and society. Even though fibromyalgia is a medical diagnosis, some physicians seemed not to believe in it and were reluctant to make the diagnosis. There is also data from a previous study showing similar results that some physicians are not willing to set the fibromyalgia diagnosis, even though the patient may have typical symptoms (24). Furthermore, some physicians think that a fibromyalgia diagnosis is not helpful, and by not setting the fibromyalgia diagnosis they might avoid medicalization and overdiagnosis (158). On the other hand, various other diagnoses such as depression were offered as an alternative explanation for the symptoms in our material. Patients had also received different chronic pain diagnoses from other medical specialties.

Some patients implied they hid their diagnosis as other healthcare workers might not believe the diagnosis. This reflects the controversial attitudes towards the diagnosis in healthcare.

6.5. Excess use of thyroid hormone treatment among patients with fibromyalgia

The occurrence of thyroid hormone treatment was much higher in our study population (34%) than in a previous study with patients with fibromyalgia in Japan (8%) and the known prevalence of hypothyroidism among the general population in Finland (171,176). In our study, over one third of the patients with fibromyalgia using thyroid hormone treatment – whose initial thyroid hormone levels were available – had normal thyroid function. This shows that the Finnish guidelines of care for hypothyroidism are not followed in one third of the cases when levothyroxine treatment is prescribed to a patient presenting with fibromyalgia symptoms.

Moreover, it is not clear whether patients with fibromyalgia benefit from the diagnosis of subclinical hypothyroidism, which might be an incidental finding from thyroid function screening at the time of the diagnosis of fibromyalgia. There are likely several explanations for the relatively weak adherence to the guidelines of care

fo the treatment of hypothyroidism among patients with fibromyalgia. One reason might be that one of the main symptoms of fibromyalgia is fatigue, which is also common in hypothyroidism. Patients are aware of this and some may want to try out thyroid hormone treatment even though their thyroid function is normal. On the other hand, it might be tempting for a physician to diagnose a somatic disease – instead of a functional syndrome – causing the fatigue and to try if levothyroxine treatment would reduce the patient's symptoms.

6.6. One-year follow-up

We found that modification of the care plan was useful when the GP found that there was an indication for it in the first appointment. This could include referral to a physiotherapist or psychologist or some additional laboratory tests. However, unlike other studies, our follow-up results found patients mostly reported neutral or negative changes in symptoms in the one-year follow-up. In a 10-year prospective follow-up study, the patients' perception of their symptoms improved slightly for most (169). Still, none of the patients reported being free of all the symptoms, and over half of the participants reported having at least moderately severe pain or stiffness as well as sleeping problems and fatigue. In a three-year follow-up study in Canada, patients also reported that their symptoms had eased over time (145). However, it must be taken into account that these two studies had a longer follow-up than our study, and they used different inclusion criteria for fibromyalgia.

Furthermore, based on our findings, the treatment of depression seemed to be effective because the PHQ-9 score decreased significantly in patients with depression. In addition, the FIQ score also decreased among patients who had symptoms of depression at the beginning of the study. This is in line with previous studies, as it has been suggested that treatment should be started for depression if the patient with fibromyalgia has that condition as a comorbidity (167,168).

6.7. Possible explanations for the associations between childhood adversities, peer bullying, and fibromyalgia

One possible explanation for the observed association between fibromyalgia and both childhood adversities and bullying victimization in childhood might be that the same mechanisms that cause the other negative effects of peer bullying or

childhood adversities have an impact on the onset of fibromyalgia. Several studies suggest that the individual response to stress is mediated by both environmental factors and genetics, and this takes place via epigenetic mechanisms (98). Furthermore, some previous studies with patients with fibromyalgia support this altered HPA axis response hypothesis (20,120). Studies have also demonstrated that a maladaptive HPA axis response involves persistent epigenetic changes to the genes that regulate homeostatic levels of glucocorticoid as well as to genes that are important for neuronal function and behaviour (218). In addition, glucocorticoids activate glucocorticoid receptors that affect transcriptional programs and also induce long-lasting epigenetic changes in many tissues, and there are some life periods with more plasticity in the epigenome for stress exposure, such as adolescence (99). Stress-induced epigenetic changes also accumulate throughout life. This could explain why childhood adversities could have life-long effects and increase the later risk of stress-related diseases.

6.8. Strengths and limitations: HeSSup Studies

The main strength of our study is that the HeSSup study includes a representative sample of Finnish working-age population. A non-response analysis showed that no significant selective health-related factor among the respondents was identified (211). The large and non-selected population increases the generalizability of the results. The relatively low response rate could have had an influence on prevalence estimates but should not have had a considerable effect on our analyses of associations (212).

On the other hand, in the HeSSup study, the fibromyalgia diagnosis was self-reported. We used information from the Finnish Hospital Discharge Register (HILMO) to confirm the validity of the data. However, the vast majority of patients with fibromyalgia did not have data on their condition because fibromyalgia is often treated in primary or ambulatory health care. For 477 patients in the sample, the fibromyalgia diagnosis was only self-reported, which could be considered as a weakness of the study. On the other hand, over time the diagnostic criteria for fibromyalgia have varied and according to the recommendations in clinical work, the diagnosis should be based on both clinical findings and patient history. As a result, we considered the patients' self-reported diagnosis applicable to our study. Out of

the 38 patients who had an ICD-10 code corresponding to fibromyalgia in the HILMO, only one failed to report it in the HeSSup questionnaire.

Furthermore, the HeSSup study did not include questions concerning whether the respondent had participated in bullying as a bully. As a result, we do not know how many victims of bullying were also involved as bullies. In addition, the data on bullying and childhood adversities are based on the participant's recollection, so memory bias is possible. However, a study conducted in Britain showed that participants were able to recall important events in their lives, including childhood bullying victimization, and there was great consistency in these memories across a 12–14-month period (219). Still, memory bias may be present. In our study, childhood adversities and peer bullying victimization were enquired from the participants aged between 20 and 54 years. It is possible that the duration of the adversity and the age when the adversity happened could have contributed to the effect. The information concerning six childhood adversities was asked in the first questionnaire in order to decrease memory bias. Information on peer bullying was asked for the first time in the 2012 follow-up questionnaire. It is still possible that patients with fibromyalgia recall these negative events more accurately than the controls. On the other hand, Hardt et al. suggested that false positive reports of major or easily defined childhood adversities are rare, and recall bias is not sufficient to invalidate retrospective case-control studies (102).

In regard to the generalizability of the findings of the HeSSup study, 4.3% of the individuals included in the HeSSup study reported having fibromyalgia, and this is in line with the recently reported prevalence of fibromyalgia in other studies (56). However, the prevalence of fibromyalgia in Finland was reported to be significantly lower in one previous study (134). There might be several explanations for this: the use of different diagnostic criteria, the ageing of the Finnish population, and most likely an increased awareness of fibromyalgia among medical doctors, especially in primary health care (54,220). In addition, the characteristics of the patients with fibromyalgia and controls in our study were similar as in the other studies (54).

6.9. Strengths and limitations: Patients with Fibromyalgia in Finnish Primary Health Care

The strengths of the qualitative study consist of a comprehensive group of patients that included three male participants. The participants represented various age groups and their symptoms varied from mild to severe. The study group also included recently diagnosed patients as well as those who had had fibromyalgia for decades. Furthermore, none of the participants had a patient-doctor relationship with the interviewers and the interviewers were not employees of the health centre at the time of the study. The interview questions were open-ended and the participants started conversations without further encouragement. The interviews were held face-to-face.

The limitation of our Nokia health centre studies is that only one health centre was included. Many study patients had had consultations in occupational health care and specialized health care. Another weakness is that only half of the patients identified from the patient records participated in the main study. On the other hand, there was no statistically significant difference in the demographic features between participants and those not participating. Still, a selection bias might be possible.

Furthermore, in the focus group interviews of our qualitative study, not all the participants participated equally, and some might have left something unsaid. On the other hand, the conversation in the focus groups might have formulated new themes.

The main weakness of our hypothyroidism study is the small sample size. In addition, we do not know for sure what kind of symptoms the patients had at the moment of the diagnosis of thyroid dysfunction, but we know from the fibromyalgia questionnaires that all patients experienced symptoms at the moment of the study that could be also linked to hypothyroidism, such as fatigue. Furthermore, altogether 33 patients had levothyroxine treatment, but we had information on thyroid function only for 16 patients before the treatment. It is likely that patients without this information either had had levothyroxine treatment for a long time or it was prescribed by occupational health care or specialized health care using different electronic patient records.

6.10. Clinical implications

The findings of our study call for improved actions to help prevent adverse childhood experiences and emphasize the importance of actions to prevent childhood bullying. Our results from the HeSSup studies provide important information on the possible aetiological features of fibromyalgia, which will help health care professionals to better understand these patients and their background.

In our interviews, a good patient-doctor relationship and continuity of care were important, as were the physician's attitude and knowledge of fibromyalgia. These core values of general practice should be supported both in teaching and in clinical work (221). Based on our findings and other studies, there is a need to improve the diagnostic process of fibromyalgia in primary health care in order to avoid over- and underdiagnosis. Furthermore, overdiagnosis of subclinical hypothyroidism should be considered carefully by not starting levothyroxine treatment as a trial if the patient's thyroid hormone levels are normal.

The study found that treatment of depression was effective because the PHQ-9 score decreased significantly in patients with depression symptoms. In addition, the FIQ score decreased in depressed patients. However, these patients did not themselves perceive that their condition had improved. This might be because the estimated minimal clinically important difference (MCID) in the FIQ score is 14% (222). In our study, the FIQ score changed by two to four per cent, which probably was not clinically significant. In addition, depression can also cause memory bias, meaning depressed patients might see their condition in a more negative way. Further research is needed on this topic.

6.11 Future research perspectives

There still remains a need for further prospective cohort studies addressing the connections between fibromyalgia and adverse events and peer bullying in childhood, especially in clarifying the role of depression in the process. Furthermore, the role of resilience could be a topic for further studies.

In our qualitative study, patients hoped for development care guidelines for fibromyalgia that are also meaningful to them. Our first aim of this study was to find

out from the patients' perspective how to improve the treatment of fibromyalgia in primary health care and avoid overdiagnosis. These goals were only partially met, even though our other studies gave some new insight into these topics. Still further studies are needed, especially on the subject of how to avoid overdiagnosis related to fibromyalgia and its comorbidities.

Regarding thyroid hormone treatment and fibromyalgia, we suggest further larger studies to confirm the potential association between fibromyalgia and inappropriate thyroid hormone treatment. This association might be only one example of a situation in which a patient with functional syndrome is being overtreated for a subclinical condition that is not supported by clinical findings. There are likely several explanations for the relatively weak adherence to the guidelines of care for the treatment of hypothyroidism amongst patients with fibromyalgia shown in our study. One might be that one of the main symptoms of fibromyalgia is fatigue, which is also common with hypothyroidism. Patients are aware of this, and some of them may wish to try out the thyroid hormone treatment even though their thyroid function is normal. On the other hand, it might be tempting for a physician to diagnose a somatic disease – instead of a functional syndrome – causing the fatigue and to try out if levothyroxine treatment would reduce the patient's symptoms. Altogether, further studies with appropriate study designs are needed to study these hypotheses.

In regard to the follow-up study, we suggest further studies be made on the treatment of depression and its impact on the symptoms of fibromyalgia. A longer follow-up with more patients could also give important information on the long-term prognosis of fibromyalgia syndrome among Finnish primary health care patients.

7 CONCLUSIONS

1. All six enquired childhood adversities were associated with fibromyalgia with and without adjustments.
2. There was a significant association between bullying victimization in childhood and fibromyalgia before adding depression symptoms as a covariate. This association was strongest amongst those reporting more severe bullying.
3. In the qualitative study, our findings suggest that it is necessary to have a diagnostic concept of fibromyalgia that is meaningful both for the patients and for the physicians in order to avoid overdiagnosis.
4. A good patient-doctor relationship and continuity of care were highly valued by the patients, and these core values of general practice should be supported also when treating patients with fibromyalgia.
5. There is a need for further studies on unnecessary treatment for subclinical hypothyroidism in patients with fibromyalgia, and further studies are also needed to find out whether there is overtreatment of other subclinical conditions among patients with functional syndromes.
6. Treatment of depression seems to be effective in reducing FM symptoms. Furthermore, depression seems to have a role in the development of later-life fibromyalgia in bullied children, but this is a subject for further studies.

Author's Contribution

In the first publication, the author of this thesis contributed substantially to the design of the study and to the interpretation of the data, wrote the first draft of the manuscript, and revised it several times critically for important intellectual content. Furthermore, he read and approved the final version of the manuscript.

In the second publication, the author contributed to the design of the study and interpretation of the data, wrote the first draft of the manuscript, and revised it several times critically for important intellectual content. He also read and approved the final version of the manuscript.

In the third publication, the author made substantial contributions to the conception, design, analysis, and interpretation of the data. Furthermore, he examined the patients, performed the statistical analyses, and wrote the first draft of the manuscript. In addition, he was involved in revising it critically for important intellectual content and gave final approval of the version to be published. He also read and approved the final manuscript.

In the fourth publication, the author participated in planning and organizing the study. He examined the patients and was the moderator in the focus-group interview. He also participated in the data analysis and reporting, and he read and approved the final manuscript.

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The relationship between childhood adversities and fibromyalgia in the general population

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ABSTRACT

Background: Fibromyalgia is a syndrome characterized by widespread pain and a variety of somatic symptoms. The international prevalence of fibromyalgia is 2–5%, but its current prevalence in Finland is unclear. Various adversities are linked to the onset of fibromyalgia. However, there is need for more data regarding the association between childhood physical abuse and fibromyalgia. Further, the association of childhood emotional stressors and fibromyalgia is disputed. The aim of the current study is to produce more information about that relationship using data from the Health and Social Support (HeSSup) Study.

Methods: HeSSup is a postal study consisting of a random sample of the Finnish population. The study setting is cross-sectional. Participants in the study were asked if they have been diagnosed with fibromyalgia. Those responding affirmatively were classified as fibromyalgia patients. Six childhood adversities were enquired, and the relationship between fibromyalgia and these events were analysed by cross tabulation and logistic regression.

Results: There were associations between examined adversities and fibromyalgia before and after adjustments for demographic features and depression (being afraid of a family member: odds ratio after adjustment 1.60, 95% CI 1.28–2.01; long-lasting financial difficulties 1.45, 1.18–1.77; serious conflicts in the family 1.40, 1.14–1.72; parental divorce 1.34, 1.05–1.72; serious or chronic illnesses in the family 1.27, 1.05–1.55; alcohol problems in the family 1.25, 1.02–1.53).

Conclusion: All six enquired adversities were associated with fibromyalgia after adjustments. These findings emphasize the importance of preventing adverse childhood experiences.

Introduction

While the exact aetiopathogenesis unclear, fibromyalgia has previously remained something of a mystery to medicine [1]. Nevertheless, recent findings indicate that central sensitization and disturbances in the function of the sympathetic nervous system both play a significant role in its pathogenesis [2,3]. Centralized pain state can be a lifelong disorder and environmental factors, such as psychological stress, may trigger fibromyalgia [4]. Fibromyalgia is included in the 10th edition of the World Health Organization's (WHO) International Classification of Diseases (ICD) [5]. Its specific code has been M79.7 since 2006; prior to that, the code M79.0 included fibromyalgia.

Different classification and diagnostic criteria for fibromyalgia have been developed. The introduction of the American College of Rheumatology's (ACR) 1990 classification criteria led to the increased recognition of fibromyalgia [6]. The criteria require tenderness on pressure of at least 11 of the 18 defined anatomical tender points and the presence of chronic widespread pain for a positive diagnosis [7]. Over time, it became apparent that there was a need for an alternative method of diagnosis. This resulted to the introduction of the ACR 2010 diagnostic criteria [6], which have two components: the widespread pain index (WPI) and the symptom severity scale (SS scale). The WPI correlates with the tender point count and the SS scale emphasizes the importance of cognitive problems and somatic symptoms characteristic for fibromyalgia patients.

Recent studies have documented that the international prevalence of fibromyalgia is 0.4–9.3% with the arithmetic mean rate of 2.7% [8]. In German representative population sample using modified ACR 2010 criteria prevalence was 2.1% [9]. The prevalence depends inter alia on the classification or diagnostic criteria applied [10,11]. The prevalence of fibromyalgia in Finland was reported to be only 0.75% in a former study published in 1991 [12]. In that study, prior diagnostic criteria

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were applied and researchers concluded that the prevalence was sensitive to the minor modification of the definition. Studies also suggest that the rate of fibromyalgia increases with age [13]. Because of these issues, the current prevalence of fibromyalgia in Finland is unclear.

There are several studies focused on the epidemiology of fibromyalgia and widespread pain. Numerous traumatic incidents – for example, falling, motor vehicle accidents, sexual and physical violence, surgical procedures, severe illnesses, and occupational accidents – as well as stressful life events – for example, divorce, death of a family member, or monotonous working conditions – are connected to the onset of fibromyalgia and chronic widespread pain [14–19]. Reports regarding the relationship between childhood adversities and chronic widespread pain have also been published [20–22]. However, some these findings have been contested on the basis of recall bias [20,22]. As depression is a relatively common comorbidity with fibromyalgia, its contribution to false memories is also possible [2].

A large-scale prospective cohort study conducted in the United Kingdom reported a connection between several adverse events in childhood and chronic widespread pain [21]. Häuser et al. systematically assessed the potential association of fibromyalgia with emotional, physical and sexual abuse [23]. Two studies recruited patients from general population. Ciccone et al. recruited 52 female fibromyalgia patients and 53 controls and found no evidence of increased childhood abuse in fibromyalgia group. Haviland et al. recruited 10,424 Seventh-day Adventists to evaluate the relationship between traumatic and major life stressor and fibromyalgia [24]. Fibromyalgia patients reported more adversities. Emotional abuse or stressful life events did not have statistically significant association, whereas physical and sexual abuse were associated with fibromyalgia. In their systematic review Häuser et al. concluded that the association of fibromyalgia and physical and sexual abuse is confounded by study quality [23].

In summary, the relationship between chronic widespread pain and childhood adversities prior to the age of 7 years has been confirmed by one British prospective cohort study [21]. However, the relationship between childhood adversities and fibromyalgia in the general population has not been similarly established and in most studies the sample has been too small to detect weak associations [25]. The aim of this study is to provide information regarding the relationship between fibromyalgia and childhood adversities in the general population with a large population sample.

Methods

Study population, setting, and design.

Launched in 1998, the Health and Social Support (HeSSup) study is a prospective follow-up study. The aim of the study is to collect data on the psychosocial health of the Finnish working-age population. The first postal questionnaire was sent to a random sample of 64,797 individuals drawn from the Finnish Population Register. The questionnaire consisted of four age groups: 20–24, 30–34, 40–44, and 50–54 years old. The response rate was 40%, and 25,898 questionnaire forms were returned by 22 September 1998, when the follow-up began. A detailed demographic description of the respondents was presented earlier by Suominen et al. [26]. Study population was a representative sample of Finnish population. However, the Swedish speaking Finns as well as the Turku region were slightly over-represented by purpose.

A follow-up questionnaire was sent in 2003 to the respondents of the first HeSSup survey. Those who had died, moved abroad, or whose present address was unknown were excluded. In 2003, the response rate for the eligible group was 80% (N = 19,629). A second follow-up was sent in 2012 and this time response rate was 57% (N = 13,050).

Our study setting is cross-sectional, deriving information on childhood adversities from the first questionnaire (1998) and the information concerning fibromyalgia diagnoses from two follow-up questionnaires (2003 and 2012). Flow chart of the study population is presented in Fig. 1.

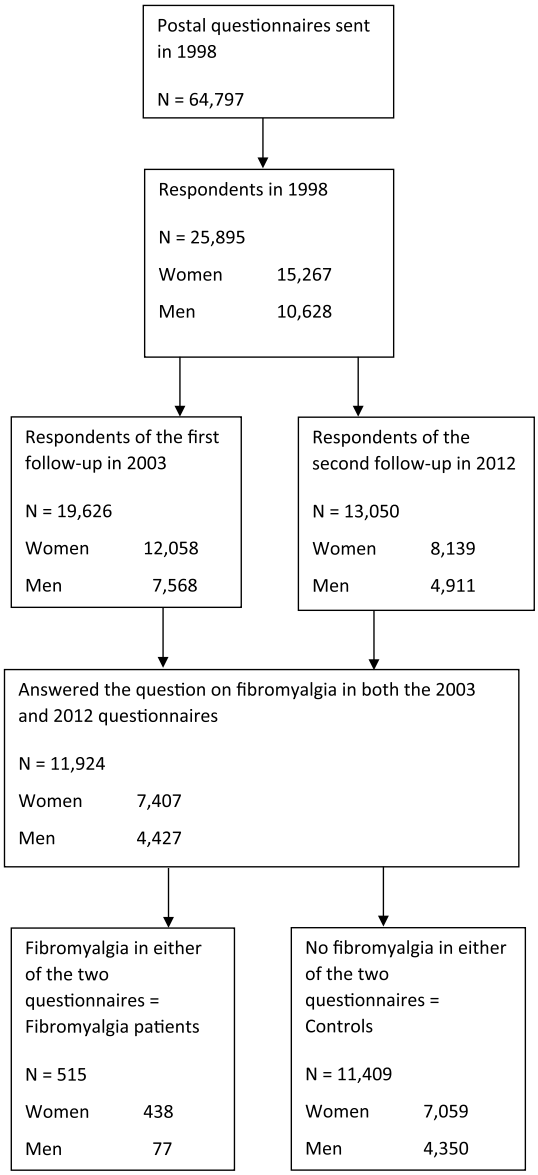

Fig. 1. Flow chart of the study population.

Childhood adversities.

In the first questionnaire mailed in 1998, participants were requested to recollect their childhood adversities in terms of the following six questions: "When you think about your childhood…": "Did your parents separate (divorce or similar)?"; "Did your family have long-lasting financial difficulties?"; "Did serious conflicts arise in your family?"; "Were you often afraid of a member of your family?"; "Was someone in the family seriously or chronically ill?"; and "Did someone in the family have problems with alcohol?". The alternatives were "Yes," "No", or "I do not know." The length of the adversity and time when the adversity occurred was not asked in the questionnaire.

Childhood adversities were drawn from this first survey in order to minimize recall bias.

Fibromyalgia patients.

Follow-up questionnaires sent to the participants in 2003 and 2012 included a question on whether a medical doctor had told them that they have or have had various medical diagnoses including fibromyalgia. The answer alternatives were "Yes" or "No". As a consequence, the fibromyalgia diagnosis was self-reported and it was not specified when the patient received the diagnosis.

Participants responding affirmatively in either survey were classified as fibromyalgia patients. Only those who had responded to both follow-up questionnaires were included in the study population. Data from national registers of hospital care (known as HILMO) between 2000 and 2012 were also utilized to ascertain if any participant had ICD-10 codes (M79.7 or M79.0) corresponding to fibromyalgia. As a result, one person was transferred from the control group to the fibromyalgia group. Thirty-seven patients had both self-reported fibromyalgia and the ICD-10 code for fibromyalgia in the registers. A vast majority of fibromyalgia patients (n = 477) had no register information, because fibromyalgia is treated in primary health care or in ambulatory care.

Covariates.

Covariates were derived from the 1998 questionnaire. Patients were divided into four age groups corresponding to those used in the 1998 questionnaire. Educational level was divided into two groups: those who had taken the matriculation exam and those who had not. The matriculation exam is a Finnish version of the upper secondary school graduation exam. Passing the exam entitles the pupil to continue studies at university [27]. Marital status was divided into two groups: Single/divorced/widowed or married/cohabiting. Information on symptoms of depression was gained from Beck's Depression Inventory (BDI). The responses were divided into two groups and a BDI score of more than 18 was considered depression [28].

Statistical analyses.

Analyses of the data were conducted using SAS release 9.4. From cross tabulation, p-values were calculated using the Chi-squared test, and values of 0.05 or lower were considered statistically significant. The results from standard, unconditional logistic regression analysis are presented as odd ratios (OR) with 95% confidence intervals (CI). These were calculated for each childhood adversity and fibromyalgia with fibromyalgia as a dependent variable (Model 1). In Model 2, adjustment for gender and age was performed. Model 3 added educational level (matriculation examination). Model 4 added marital status and, finally, Model 5 added adjustment for gender, age, educational level, marital status, and depression (BDI > 18).

Ethics approval.

The Ethics Committee of the University of Turku and Turku University Central Hospital did not consider approval necessary for a customary cohort study. All participants were requested to sign a consent form to permit the combination of the data with the national health registries.

Results

The occurrence of self-reported fibromyalgia was 4.3%, as the final study population consisted of 11,924 respondents and 515 of them had replied affirmatively to the fibromyalgia question or had the corresponding diagnosis in the health care registers.

There were differences between fibromyalgia patients and controls. Most respondents were female, but this was even more evident in fibromyalgia group. Fibromyalgia patients also tended to be older than other respondents. With regard to marital status, fibromyalgia patients were more often married, re-married, or cohabiting than the control group respondents. Fibromyalgia patients had a lower educational level than the control cases, as having taken the matriculation examination was more common among the controls than among the fibromyalgia patients. Features of the fibromyalgia patients are presented in Table 1.

Table 1
Features of the fibromyalgia patients and the controls in 1998.

	Fibromyalgia patients		Controls		
	%	n	%	n	p-value
Gender					< 0.001
Female	85.0	438	61.9	7059	
Male	15.0	77	38.1	4350	
Age in 1998					< 0.001
20–24	10.7	55	21.2	2415	
30–34	13.4	69	20.8	2371	
40–44	31.1	160	26.5	3025	
50–54	44.8	231	31.5	3598	
Marital status					0.021
Single/divorced/ widowed	24.7	127	29.4	3354	
Married/re-married/ cohabiting	73.3	388	70.6	8044	
Education					< 0.001
Taken the matriculation exam	32.6	168	45.6	5194	
Not taken the matriculation exam	67.4	347	54.4	6203	
Depression					< 0.001
Beck's Depression Inventory > 18	8.8	45	4.0	454	
Beck's Depression Inventory ≤ 18	91.2	469	96.0	10,899	

Table 2
Proportion (%) of the fibromyalgia (FM) patients and the controls reporting childhood adversities.

	FM patients	Controls	
	N = 439–495*	N = 10,182–11,118*	
	%	%	p-value
Parental divorce	17.4	14.5	0.076
Long-lasting financial difficulties in the family	41.0	27.8	< 0.001
Serious conflicts in the family	35.0	26.4	< 0.001
Being afraid of a family member	22.4	12.9	< 0.001
Serious or chronic illnesses in the family	36.0	26.5	< 0.001
Alcohol problems in the family	29.4	23.9	0.005

* Individuals answering "I do not know" to any question or leaving a question unanswered were excluded from the data (to enable cross tabulation), which is the cause of the different number of fibromyalgia patients and control cases included in the analyses.

Long-lasting financial difficulties in the family was the most often reported adversity both in the fibromyalgia group and the control group (Table 2). All six adversities were associated with fibromyalgia after adjustment for gender and age (Table 3). Adjustment for at least moderate depression, marital status, or educational level had no statistically significant effect on this connection. Furthermore, the correlation between being afraid of a family member and being diagnosed with fibromyalgia was the strongest both before adjustment and after adjustment for gender, age, educational level, marital status, and depression. The weakest correlations after adjustments were seen in serious or chronic illnesses in the family and alcohol problems.

Fibromyalgia patients also reported more adversities than the controls. Fig. 2 presents the amount of adversities reported by the fibromyalgia patients and the control group. The OR (95% CI) for fibromyalgia with 1–2 adversities vs no adversities was 1.54 (1.25–1.91) and the corresponding figure for 3–6 adversities vs no adversities was 2.15 (1.69–2.73).

Table 3
Childhood adversities in multivariate logistic analysis for fibromyalgia with adjustments for gender, age, educational level, marital status and depression.

	OR with 95% CI	
Adversity in the family	Model 1	Model 2
Parental divorce	1.24 (0.98–1.58)	1.34 (1.05–1.72)
Long-lasting financial difficulties	1.81 (1.49–2.20)	1.45 (1.18–1.77)
Serious conflicts	1.50 (1.23–1.83)	1.40 (1.14–1.72)
Being afraid of a family member	1.95 (1.56–2.42)	1.60 (1.28–2.01)
Serious or chronic illnesses	1.56 (1.30–1.89)	1.27 (1.05–1.55)
Alcohol problems	1.33 (1.09–1.62)	1.25 (1.02–1.53)

Model 1: Not adjusted.
Model 2: Adjusted for gender, age, educational level, marital status, and depression (BDI > 18).

Discussion

In brief, we found statistically significant associations between fibromyalgia and all six examined childhood adversities after adjustment for gender and age. Further adjustments for educational level, marital status, and depression did not change this.

Some of our findings are consistent with the data obtained from previous studies [20–22]. Nevertheless, there are differences between the studies. The British Birth Cohort Study (BBCS) concentrated on widespread pain, while our study focused on fibromyalgia. On the other hand, in the BBCS widespread pain was defined according to the ACR 1990 classification criteria for fibromyalgia. However, recent diagnostic criteria emphasize the importance of characteristic symptoms of fibromyalgia in addition to pain in the diagnostic process [29]. For these reasons, patients in our study and BBCS are not identical.

Nevertheless, childhood adversities appear to be associated with fibromyalgia in the same manner as chronic widespread pain. The correlation between a family history of alcohol problems and fibromyalgia was evident in our data with an OR of 1.3 after adjustments for gender and age and after all adjustments. In the BBCS, alcoholism resulted in a risk ratio (RR) of 1.3 when adjusted for sex, social class, and psychological distress, and an RR of 1.7 before adjustment [21]. Furthermore, in BBCS the adjusted RR for financial difficulties in the family was 1.6, while in our study the OR was 1.5. Parental divorce resulted similar risk in both studies (adjusted RR of 1.3 in BBCS and an OR of 1.3 in our study).

In previous studies addressing stressful life events and fibromyalgia the associations have not been similarly congruent. In their meta-analyses Häuser et al. presented no significant association between fibromyalgia and emotional abuse in childhood [23]. However, most studies were carried out in hospital setting and were in risk with a selection bias. Furthermore, Romans and Cohen suggested that often studies in this field are underpowered to detect low or modest associations [25]. Haviland et al. found no statistically significant associations between fibromyalgia and emotional trauma or major life stressors [24]. In our study, OR for fibromyalgia with 1–2 adversities vs no adversities was 1.54 (1.25–1.91). In Haviland et el. study, participants were not matched with psychological distress or mental comorbidity. Major life stressors were defined as serious illness, abortion, miscarriage, divorce, homelessness and death of a child. Further, study sample was unique, as Seventh-day Adventists rarely smoke, use alcohol and only 47% eat meat [24]. Due the heterogeneity of these stressful events, results are not entirely comparable with our study. In their study, insulting, swearing or ignoring from mother or father was considered as an emotional trauma, whereas in our study we inter alia asked about being afraid of family member, which might capture the emotional effect of the event more effectively. The features of fibromyalgia patients relating to the controls in our study corresponds to information from other studies [9,30]. The occurrence of self-reported fibromyalgia in our study population is consistent with the recently reported prevalence of fibromyalgia in other countries [8]. Furthermore, our study population is more representative sample of general population and for that reason we believe our results are more generalizable.

There are obvious weaknesses regarding the self-reporting of fibromyalgia. A fibromyalgia diagnosis does not provide any social security advantages in Finland. Thus, it is improbable that the patients would want to be labelled with fibromyalgia if they did not have the diagnosis. On the other hand, a diagnosis of fibromyalgia is sometimes considered stigmatizing [31]. This may lead to the underreporting of fibromyalgia in surveys. As physicians have not adopted a standard diagnostic algorithm for fibromyalgia and because of the fluctuation of symptoms over time, it is virtually impossible to verify the accuracy of self-reported fibromyalgia diagnoses [6,32]. At the time of these surveys, the national health registers with the ICD-10 diagnosis provided only limited information on fibromyalgia, because they included data only on hospital care, and fibromyalgia patients seldom need that. Apparently, a fibromyalgia diagnosis in the national health register is a true positive, but the absence of the diagnosis in the patient records

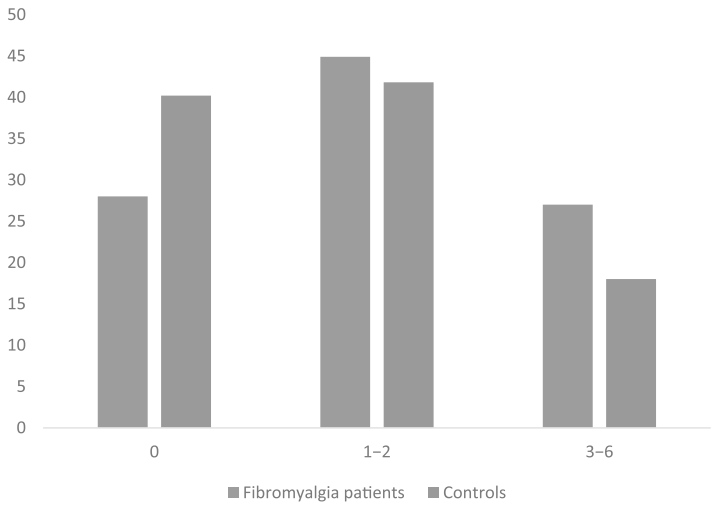

Fig. 2. Proportion (%) of the fibromyalgia patients and the controls reporting various numbers of childhood adversities.

does not mean the absence of fibromyalgia. In our data, only one patient had ICD-10 fibromyalgia diagnosis in HILMO register but did not report it. Altogether 37 patients had fibromyalgia diagnosis in register and also reported it correctly. For these reasons, we considered a self-reported fibromyalgia diagnosis an applicable parameter for this study.

Another weakness of our study is the relatively modest (40%) response rate in the first survey. Recent studies have reported similar numbers with questionnaires that do not pose a question obviously important and current to recipient [33]. In that sense, the response rate to the HeSSup questionnaire was unexceptional. Additionally, participants had to answer all three questionnaires to be included in the study population. Furthermore, analysis of non-respondents in the first postal questionnaire revealed that differences in physical health between the participants and the general population were minor [34]. Response delay analysis suggested that non-respondents were probably more likely to smoke and use psychopharmaceutical drugs. There was also a difference in the educational level of participants and non-participants. Previous studies suggest that there are some associations between these factors and fibromyalgia, as lower socioeconomic status correlates with fibromyalgia symptom severity and functional impairment [35]. Furthermore, fibromyalgia patients are more likely to be smokers than patients with rheumatoid arthritis [36]. These factors may lead to a slight underestimation of fibromyalgia among respondents. On the other hand, women responded to the survey more actively than men, and as women are more likely to be diagnosed with fibromyalgia, this may increase the observed occurrence of fibromyalgia [34,37]. There is also a register-based mortality analysis of respondents and non-respondents of the HeSSup study's first questionnaire [26]. The mortality of non-respondents was higher than the respondents. There were differences between sexes. Women responding to the first survey were healthier than those who did not respond. Non-respondent men had a higher mortality than the respondents due to external causes. The researchers concluded that this could probably be explained by excessive alcohol consumption. However, according to a previous study, results related to the association between the examined variables are not necessarily biased, even in the case of health selection [38]. Suominen et al. concluded that: 'Selection by health, especially mental health in men, can cause bias in health related population surveys. However, this applies to prevalence estimates and does not necessarily jeopardise results from studies on risk and protective factors.' [26] For this reason, response rate should not have affected considerably on our analyses for associations.

Another factor is that recall bias may be present. Despite the fact that HeSSup is a prospective cohort study, childhood adversities were enquired from participants aged between 20 and 54 years. It is possible that the duration of the adversity and the age when the adversity happened could have contributed to the effect, but because this information was not asked; it is beyond the scope of this study. The information concerning adversities was administered from the first (1998) questionnaire in order to decrease recall bias. It is still possible that fibromyalgia patients recalled these events more accurately than the control cases. On the other hand, Hardt et al. suggested that false positive reports of major or easily defined childhood adversities are rare and recall bias is not sufficient to invalidate retrospective case-control studies [39]. Adjustment for depression did not eliminate the association between various adversities and fibromyalgia in our results, even though it did slightly reduce the association. On the other hand, this could also be explained by the fact that depression is quite a common comorbidity with fibromyalgia [2]. It has also been suggested that the emotional reaction concerning a trauma rather than the seriousness of the trauma determines whether or not the trauma results in a chronic pain condition (14). In that sense, self-reported adversities capture the emotional importance of childhood events. Thus, we consider self-reporting a useful tool for this study, but it is possible that increased recall of childhood adversity in fibromyalgia cases could have led to some over-estimation of the odds ratios.

Finally, childhood adversities were inquired using validated questions on living conditions [40]. In our study, adding educational level and depression as explanatory variables in the logistic regression models reduced the association between adversity and fibromyalgia. On the other hand, marital status did not significantly change this association. Additionally, as depression is a relatively common comorbidity with fibromyalgia and shares the same risk factors, adding it in the analysis as a covariate may lead to the underestimation of the association [2]. Other covariates, such as socioeconomic status and employment, would probably provide more information, but we did not have access to that information.

Conclusion

The findings of our study call for improved actions to help prevent adverse childhood experiences. There still remains a need for further prospective cohort studies addressing the connections between fibromyalgia and adverse events in childhood. It is also unknown if childhood adversities increase risk of fibromyalgia more than they increase the risk for other diseases, such as asthma. Further studies on this subject are needed. Our results provide important information on the aetiological features of fibromyalgia, which will help health care professionals to better understand these patients and their background.

Contributorship statement.

Aleksi Varinen contributed substantially to the design of the study and to the interpretation of the data, wrote the first draft of the manuscript, and revised it several times critically for important intellectual content. Elise Kosunen contributed substantially to the design of the study and to the interpretation of the data, and revised the manuscript critically several times for important intellectual content. Kari Mattila contributed substantially to the acquisition of the data, the design of the study, and the interpretation of the data, and revised the manuscript critically several times for important intellectual content. Tuomas Koskela contributed substantially to the interpretation of the data and revised the manuscript critically several times for important intellectual content. Markku Sumanen contributed substantially to the design of the study, carried out the first data analyses, contributed substantially to the interpretation of the data, and revised the manuscript critically several times for important intellectual content. All the authors have read and approved the final version of the manuscript.

Competing Interest Statement.

The authors have no competing interests to report.

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The association between bullying victimization in childhood and fibromyalgia. Data from the nationwide Finnish health and social support (HeSSup) study based on a sample of 64,797 individuals

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ABSTRACT

Background: Fibromyalgia is a functional pain syndrome presenting with various psychological symptoms. Several studies have shown that adverse life events are associated with fibromyalgia. The aim of the current study is to explore the association between self-reported bullying victimization in childhood and self-reported fibromyalgia in adulthood.

Methods: The basic study setting is cross-sectional - with focused use of retrospective data - derived from a large on-going postal follow up survey (sample $N = 64,797$) initiated in Finland in 1998. Only respondents having answered the questions on fibromyalgia in both follow ups in 2003 and 2012 were included ($N = 11,924$). Severity of bullying was divided into three groups starting from no bullying followed by minor and severe bullying. Covariates having shown statistically significant associations with fibromyalgia in cross tabulation using Pearson's chi-squared test were included in the final multiple logistic regression analyses.

Results: In our study, 50.6% of the respondents reported victimization of minor and 19.6% of severe bullying in childhood. Participants reporting fibromyalgia in adulthood reported more bullying, and in females alone this association was statistically significant ($p = .027$). In multiple logistic regression analysis statistically significant associations between bullying victimization in childhood (reference: no bullying) and fibromyalgia were found: adjusted odds ratio (OR) for minor bullying was 1.35 (95% CI 1.09–1.67) and for severe bullying 1.58 (95% CI 1.21–2.06). However, in log-linear and logistic regression interaction models the association between bullying and fibromyalgia was not statistically significant when depression was included in the models.

Conclusions: Our results suggest that peer bullying victimization might be associated with fibromyalgia. However, in logistic log linear and logistic interaction models there was no statistically significant association when depression was included. As a result, there is need for further, preferably prospective cohort studies. The findings also emphasize the importance of actions to prevent childhood bullying.

1. Introduction

Fibromyalgia, classified as a functional syndrome, is characterized by central sensitization [1,2]. Central sensitization refers to altered processing of pain in the central nervous system and can become a lifelong disorder. Various genes and neurotransmitters are associated with pain sensitivity. Failure in breakdown or binding of these transmitters or inflammatory mediators can result in increase of pain sensitivity. [1].

In recent studies, a prevalence of 2–5% has been reported for fibromyalgia [3–5]. In a study published in 1991 using Yunus diagnostic criteria, the prevalence of fibromyalgia was reported to be only 0.75% in Finland [6]. The current prevalence of fibromyalgia in Finland is unknown as no recent studies on this topic are available. Traumatic

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incidents, sexual and physical violence, severe illness, surgical procedures, and stressful life events are associated with fibromyalgia [7–12]. Furthermore, childhood adversities are risk factors for chronic pain and fibromyalgia [13,14]. Neurotransmitters mediating pain also have an effect on mood, and they are linked to psychiatric disorders, including depression, which is a common comorbidity of fibromyalgia [1]. Moreover, individuals with genetic risk factors for the fibromyalgia syndrome and depression are particularly vulnerable to triggering events [15].

Peer bullying is one of the most common childhood adversities, but the prevalence of childhood peer bullying depends on country and definition [16]. Moreover, there are several definitions for peer bullying in childhood. According to the Olweus definition bullying is defined as follows: 'A student is being bullied or victimized when he or she is exposed, repeatedly and over time, to negative actions on the part of one or more other students' [17]. Lereya et al. defined it as a physical or verbal abuse and systematic social exclusion committed by children [18]. In Finland, the term school bullying is more commonly used to describe peer bullying among school-aged children.

In a British cohort study from the 1950s, prevalence of occasional childhood bullying was 28% [19]. In Finnish surveys, 3.7–5% of the girls and 6–9.4% of the boys have reported regular bullying victimization [20,21] and 47.8% of the boys and 36.2% of the girls reported it to have happened sometimes [21]. Similar exposure rates were reported in a study, conducted simultaneously in 40 countries. The prevalence of bullying victimization was 13.3% among boys and 8.8% among girls in Finland in that study. [22].

Effects of childhood bullying have been studied mainly among children and young adults in cross-sectional settings. Children being bullied present with more sleep disturbances, bed wetting, sadness, headaches and abdominal pain [23]. On the other hand, the association has been suggested to be relatively weak [24].

There are only few studies reaching beyond adolescence and addressing the long-term impact of bullying. In a Finnish birth cohort study, frequent bullying was a risk factor for suicidal behaviour [21]. Furthermore, bullying victimization in childhood has similar, and in some cases worse, long-term adverse effects on mental health, than being a target of maltreatment [18]. In a British birth cohort study, victims of bullying had higher rates of depression, anxiety disorder and suicidality. The victims also had fewer social relationships and had poorer perceived quality of life at the age of 50 [19]. In an Australian cross-sectional study, adult victims of childhood peer bullying had significantly poorer health-related quality of life [25]. Additionally, workplace bullying was associated with risk of a newly diagnosed fibromyalgia in a Finnish cohort study [26], and being bullied was associated with chronic pain in adolescence in a Dutch study [27].

To the best of the authors' knowledge, there are no studies addressing the association between bullying victimization in childhood and fibromyalgia in adulthood. The aim of this study is explore this association in a population based sample of the adult population in Finland.

2. Methods

2.1. Study design and setting

The study setting is cross-section based on data from the on-going Health and Social Support (HeSSup) postal questionnaire study initiated in 1998 in order to explore psychosocial risk and protecting factors of subsequent health of the Finnish working-age population. Questionnaires were sent to a representative sample of 64,797 individuals of the Finnish population. The sample comprised of four age groups: 20–24, 30–34, 40–44 and 50–54 years at baseline in 1998. Initially 25,898 questionnaires had been returned leading to a response rate of 40%. A non-response analysis revealed only slight differences between responders and non-responders. Women, more educated, younger women, and older men responded somewhat more actively to the initial survey as compared to the rest. There were only slight differences in physical health between respondents and the general population. [28] In a study of mortality of respondents and non-respondents, male non-respondents showed a small but significant increase of mortality due to external causes as compared to respondents, whereas female non-respondents again showed small but significant elevation of disease mortality as compared to respondents. A detailed demographic description of the respondents was provided as well. The minority of Swedish speaking Finns as well as the Turku region were slightly over-represented on purpose. [29] Two follow-up questionnaires were sent to the respondents of the initial survey in 2003 and 2012. In the first follow-up the response rate was 80% (N = 19,629) and in the second follow-up 57% (N = 13,050). Later, the survey data were - with respondents' written consent - linked to several national health registries, among them the Finnish Hospital Discharge Register (HILMO).

2.2. Participants and study size

Two follow-up questionnaires (2003 and 2012) included a question about presence of various medical diagnoses with the phrase: 'Has a doctor ever told you that you have or have had' followed by a number of names on diseases or conditions'. Fibromyalgia was one of the conditions included here. Response alternatives were "no" and "yes". Only those who responded to this question in both follow-ups were included in the final study population (N = 11,924). Flow chart of the study population is presented in Fig. 1.

2.3. Variables and data sources

As mentioned above, information about fibromyalgia was collected in 2003 and 2012. Those having reported the condition affirmatively in either of the questionnaires were considered as having fibromyalgia (n = 515). Participants not reporting fibromyalgia were classified as not having fibromyalgia (n = 11,409). We also carried out additional analyses with patients that did not report fibromyalgia at the 2003 survey, but reported it in the 2012 questionnaire. We identified 185 newly diagnosed fibromyalgia patients. Childhood bullying victimization was inquired in the 2012 questionnaire with two questions. The first question was: 'When you think about your school age, were you being bullied in school or in the neighbourhood?' with response alternatives 'never', 'seldom', 'sometimes' and 'often'. The second question was: 'Was bullying heavy for you?' with alternatives 'not at all', 'a little bit disturbing', 'quite heavy' or 'very heavy'. The age of respondents was grouped in four categories, i.e. 20–24, 30–34, 40–44 and 50–54 years. Marital status and education were inquired in the 2012 questionnaire and were divided into two groups with those reporting to be single, divorced, widowed combined to one group and married, remarried and cohabiting into another group. Education was also dichotomized with those reporting having completed vocational college, polytechnic or university education classified as having higher education. Those without vocational education or training or lacking completed apprenticeship training, trade school or vocational course were classified as having lower education. Information of depression was obtained from Beck's Depression Inventory (BDI), with scores ranging from 0 to 63 [30]. The responses were divided into two groups and a BDI score of > 18 was considered marking at least moderate depression [31].

2.4. Statistical methods

The severity of bullying victimization was divided into three groups: 1) No bullying: those reporting not being bullied. 2) Minor bullying: those reporting being bullied seldom, sometimes or often but reporting it not having been heavy at all or only a little bit disturbing. 3) Severe bullying: those reporting bullying victimization seldom, sometimes or

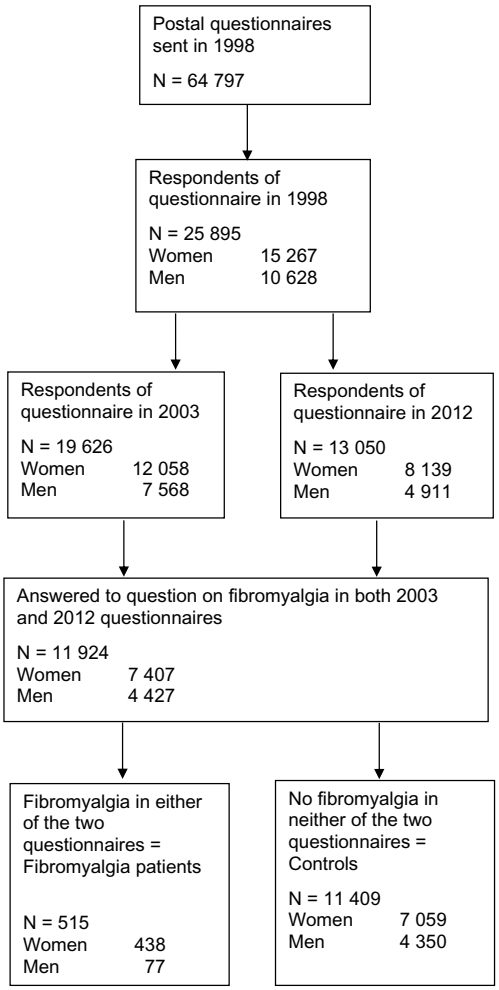

Fig. 1. Flow chart of study population.

often and having perceived it being quite or very heavy. Responses with missing data or the option 'I do not know' were considered as missing values in statistical analyses. First, the association between self-reported bullying in childhood and other potentially significant explanatory variables and self-reported fibromyalgia in adulthood was explored with cross tabulation using Pearson's chi-squared test. The associations were further analysed with multiple logistic regression models including all explanatory variables with a statistically significant association with self-reported fibromyalgia. The models yield odds ratios (OR) with 95% confidence intervals (CI). The associations between fibromyalgia, bullying and depression were also explored with log-linear and logistic regression interaction models. Alpha level of 0.05 was used to indicate statistical significance. Data were analysed using SAS software version 9.4 for Windows (2012, SAS Institute Inc., Cary, NC, USA).

3. Results

Demographic background of the study population (N = 11,924) and results from logistic regression analyses (OR with 95% CI) with demographic background and depression as explanatory variables of fibromyalgia are presented in Table 1. In Pearson's chi-squared test age *($p < .001$)*, gender *($p < .001$),* education *($p < .001$)* and depression *($p < .001$)* were statistically significantly associated with fibromyalgia whereas marital status *($p = .480$)* was not.

Minor bullying victimization was reported by 50.6% and severe bullying by 19.6% of all respondents. Men reported minor bullying more often, but severe bullying was more common among females. Altogether, female respondents with fibromyalgia reported bullying more often than those not reporting fibromyalgia and the difference was statistically significant ($p = .027$). However, when gender and bullying were included in the model as explanatory variables there was no statistically significant interaction *($p = .379$)* between these variables. Among all participants minor bullying was reported slightly more often in the fibromyalgia group, but the difference was not statistically significant ($p = .337$). Likewise, severe bullying was a bit more common in those reporting fibromyalgia, but the association was neither here statistically significant ($p = .075$). Proportions of study population reporting childhood bullying are presented in Table 2.

There were statistically significant associations between minor and severe bullying victimization in childhood and fibromyalgia in adulthood after adjustments for gender, age, educational level and depression in multiple logistic regression analysis (Table 3). The observed association was more evident in severe bullying, but statistically significant in minor bullying as well.

However, when interactions were added into the logistic regression models in order to explore the role of depression with fibromyalgia patients the three-way interaction between bullying, gender and depression was not statistically significant ($p = .994$). In further analyses the two-way interaction between bullying and gender ($p = .314$) or gender and depression ($p = .240$) or bullying and depression ($p = .122$) were neither statistically significant. After removing these interaction terms from the model depression *($p < .001$)* and gender ($p < .001$) showed statistically significant associations with fibromyalgia whereas bullying did not ($p = .171$).

In a log-linear models there was no statistically significant four-way association between fibromyalgia, bullying, gender and depression ($p = .994$). In a three-way model the associations between bullying, fibromyalgia and gender ($p = .314$), fibromyalgia, bullying and depression ($p = .142$), fibromyalgia, gender and depression ($p = .188$) or bullying, gender and depression ($p = .779$) were neither statistically significant. On the contrary, in the two-way model there were associations between fibromyalgia and gender ($p < .001$), bullying and gender ($p < .001$), fibromyalgia and depression ($p < .001$), bullying and depression ($p < .001$) and gender and depression ($p = .002$) but not with fibromyalgia and bullying ($p = .173$).

When the subgroup of 185 newly diagnosed fibromyalgia patients were analysed, there was no statistically significant association in logistic regression analysis between bullying and fibromyalgia before adjustments either with minor bullying *($p = .512$)* or severe bullying *($p = .063$)*. After adjustments for gender, age and educational level there was a borderline statistically significant association between bullying and fibromyalgia *($p = .043$)*, but when depression was added to the model the interaction was no longer significant *($p = .071$)*.

4. Discussion

We found statistically significant associations between bullying victimization and fibromyalgia after adjustments for gender, age, educational level and depression. However, effect size of this association was small according to Cohen's categories and should be interpreted cautiously because of the cross-sectional design of our study [32]. Furthermore, in log-linear and logistic regression interaction models this association was not statistically significant. Gracely et al. hypothesized that there are common predisposing genetic and

Table 1
Basic characteristics and logistic regression analysis results (OR with 95% CI) of demographic features and depression as predictors of fibromyalgia.

	Fibromyalgia					
	Yes		No			
	n = 515		n = 11,409		Simple logistic regression models	Multiple logistic regression model
	%	n	%	n	OR (95% CI)	OR (95% CI)
Age (years of birth)						
1974–1978	10.7	55	21.2	2415	1.00 (Ref.)	1.00 (Ref.)
1964–1968	13.4	69	20.8	2371	1.28 (0.89–1.83)	1.26 (0.87–1.83)
1954–1958	31.1	160	26.5	3025	2.32 (1.70–3.17)	2.20 (1.58–3.05)
1944–1948	44.8	231	31.5	3598	2.82 (2.09–3.80)	2.66 (1.93–3.68)
Gender						
Male	15.0	77	38.1	4350	1.00 (Ref.)	1.00 (Ref.)
Female	85.0	438	61.9	7059	3.51 (2.74–4.48)	3.89 (3.04–4.98)
Education						
Higher education	52.2	268	62.4	7072	1.00 (Ref.)	1.00 (Ref.)
Lower education	47.8	245	37.6	4262	1.73 (1.43–2.09)	1.51 (1.24–1.85)
Marital status						
Married/*Re*-Married/Cohabiting	74.8	382	76.1	8648	1.00 (Ref.)	1.00 (Ref.)
Single/Divorced/Widowed	25.2	129	23.9	2713	1.27 (1.04–1.56)	1.09 (0.88–1.35)
Depression						
No depression (BDI ≤ 18)	91.2	469	96.0	10,898	1.00 (Ref.)	1.00 (Ref.)
Depression (BDI > 18)	8.8	45	4.0	455	2.30 (1.67–3.17)	1.98 (1.43–2.75)

Table 2
Frequencies and percentages of participants reporting victimization of childhood bullying. Results from the Finnish nationwide HeSSup 2012 follow-up study.

Fibromyalgia	Yes		No		
	n	%	n	%	p[a]
Males					0.887
No bullying	20	26.0	1057	24.6	
Minor bullying	44	57.1	2420	56.4	
Severe bullying	13	16.9	815	19.0	
Females					0.027
No bullying	119	27.3	2324	33.2	
Minor bullying	216	49.5	3285	47.0	
Severe bullying	101	23.2	1387	19.8	
All					0.203
No bullying	139	27.1	3381	30.0	
Minor bullying	260	50.7	5705	50.5	
Severe bullying	114	22.2	2202	19.5	
Total	512	100.0	11,288	100.0	

[a] Pearson's chi-squared test.

Table 3
Childhood bullying victimization in logistic regression analyses for fibromyalgia in adulthood. Finnish nationwide HeSSup study.

	Simple logistic regression model	Multiple logistic regression model[a]
	OR (95% CI)	OR (95% CI)
No bullying (Ref.)	1	1
Minor bullying	1.11 (0.90–1.37)	1.35 (1.09–1.67)
Severe bullying	1.26 (0.98–1.62)	1.58 (1.21–2.06)

[a] Adjusted for gender, age, educational level and depression (BDI > 18).

environmental factors that make individuals vulnerable to adversities that can trigger fibromyalgia or depression or both [15]. Hence, it might be possible that the association between childhood peer bullying and fibromyalgia syndrome is attributable to depression and peer bullying victimization in childhood would be associated with adulthood fibromyalgia only when depression is present but our cross-sectional setting allows us only to observe associations. Furthermore, is has been suggested that fibromyalgia and depression might even be part of same affective spectrum disorder, but the evidence is controversial [15,33].

Compared to recent Finnish surveys, bullying was more common in our study, as half of the subjects studied reported minor bullying victimization. This was particularly evident among females. In their study, Klomek et al. suggested that from 20% to 30% children were involved in frequent bullying victimization in 1989 in Finland [21]. The prevalence of 19.6% of severe bullying among the participants in our study is in line with this finding. Furthermore, in our study the question about bullying victimization included both school and neighbourhood. In a British study – aiming at a holistic exploration of victim experiences – adolescent participants experienced on average 2.8 different types of victimization [34]. Furthermore, our aim was to capture the emotional impact, rather than the frequency of bullying. As a result, our definition of minor bullying also included bullying, that occurred only seldom, and was not perceived to be burdensome by the victim. It is unlikely, that all of our study subjects reporting minor bullying would fulfil the Olweus definition of bullying.

There are studies of underreporting childhood adversities. In a German case-control study depression accounted for the group difference in physical abuse and emotional neglect and partially in emotional abuse, but did not account for the group difference in sexual abuse [35]. However, depressed mood can also result in biased recall towards negative information [36]. Fibromyalgia patients with mental disorders report childhood adversities more often than patients without mental disorders [37]. On the other hand, Hardt et al. proposed that false positive memories of easily defined childhood adversities are rare [38]. Nevertheless, it is possible that increased recall of childhood peer bullying victimization in fibromyalgia patients could lead to slight overestimation of the association between bullying and fibromyalgia before adjustment for depression.

In a Dutch study with 15,220 adolescents a similar association between bullying and adulthood chronic pain was reported. OR for suffering from pain was 1.23 (95% CI 1.17–1.29) for those having been bullied after adjustment for gender, age, ethnic origin (Dutch vs. non-Dutch) and school level [27]. In our study, the OR was slightly higher with those reporting severe bullying and similar with those who reported minor bullying. However, in our study there was a longer follow up between bullying and fibromyalgia. Furthermore, we concentrated in fibromyalgia whereas Voerman et al. studied chronic pain, which is

to some extent a different condition [27].

In our study, the fibromyalgia diagnosis was self-reported. We used information from the Finnish Hospital Discharge Register (HILMO) to confirm the validity of the data. However, a vast majority of fibromyalgia patients lack data on their condition because fibromyalgia is often treated in primary or ambulatory health care. For 477 patients the fibromyalgia diagnosis was only self-reported which could be considered a weakness of the study. On the other hand, over time the diagnostic criteria for fibromyalgia have varied and according to recommendations the diagnosis should be based both on clinical findings and patient history in clinical work [39,40]. Thus, we considered patient reported diagnosis applicable to our study. Out of the 38 patients who had ICD-10 code corresponding to fibromyalgia in HILMO only one failed to report it in the HeSSup questionnaire. However, there is possibility of either under- or overestimation of the prevalence of fibromyalgia in our study. Altogether 4.3% of individuals included in the study reported fibromyalgia [41]. The occurrence of fibromyalgia was slightly higher in our study than the arithmetic mean prevalence rate of 2.7% reported by Queiroz in a review article, but it is not exceptional compared to other studies [41]. Furthermore, response rates of our surveys, and the fact that women responded to the survey more actively than men, might have influenced the prevalence estimates, but should not affect the associations between the variables studied [29,42]. We gathered information from fibromyalgia diagnosis from two different sources and time points and as a result we have period prevalence which is expected to be higher than point prevalence. In addition, the characteristics of fibromyalgia patients and controls in our study are consistent with other studies [3].

Unfortunately, the HeSSup study did not include questions about respondent's participation in bullying so we do not know how many were also involved as bullies. In addition, data on bullying are based on participant's recollection. However, a study conducted in Britain showed that participants were able to recall important events in their lives, including childhood bullying victimization, and there was great consistency in these memories across the 12–14 -months period [43].

The total response rate was 40.0%, with women (47.7%) responding more actively than men (32.1%). The youngest age group responded most actively, especially women in this age group (54.6%). Among men, the oldest age group responded most actively (36.8%) [28]. A non-response analysis showed that no significant selective health-related factor among the respondents was identified [28]. This is an important strength of our study, as our large and non-selected population increases the generalizability of the results. Low response rate could have influenced prevalence estimates, but should not have had considerable effect on our analyses of association [14,29]. According to the most likely scenario, with higher dropout for bullying victims and fibromyalgia patients, the observed associations would have been weakened.

It is still unclear how childhood bullying victimization leads to poorer health in adulthood [19]. One possible explanation is that the stress of victimization leads to the development of health problems [16,26]. It is known that psychosocial stress initiates many behavioral, neural, hormonal and molecular responses [44]. Additionally, genetic factors play an important role via epigenetic mechanisms [45]. There are some life periods with more plasticity in the epigenome for stress exposure –for example adolescence and stress-induced epigenetic changes also accumulate through life [44]. This could explain why childhood adversities could have life-lasting effects and increase the later risk of stress-related diseases. You et al. studied mechanisms of widespread pain in young adults. Their findings suggested that depressive symptoms were more common within the group reporting more adversities, but they did not explain the observed relationship between childhood adversities and chronic pain [46]. It is also known that depression is a relatively common comorbidity with fibromyalgia and that may also be a result of common risk factors [1,2]. Moreover, depressed children are more likely to be victims of peer bullying [16]. As a result, we suggest the relationship between peer bullying, depression and fibromyalgia as a subject for further studies.

To the best of the authors' knowledge, our study is the first reporting the association between peer bullying and fibromyalgia. Although our cross-sectional setting allows us only to observe associations, it may suggest that peer bullying has long-lasting effects, especially on those who have encountered severe bullying. However, it is also possible that children who later develop fibromyalgia have features that predispose them to bullying. Furthermore, not all participants reporting bullying in childhood develop fibromyalgia later in life. This leads us to the concept of resilience: why do some bullying victims get fibromyalgia, while others do not. This, however, is beyond the scope of our study, but we suggest it as a topic for further studies.

5. Conclusion

We found a statistically significant association between bullying victimization in childhood and fibromyalgia after adjustments for gender, age, educational level and depression and this association was stronger in those reporting more severe bullying. However, in log-linear and logistic regression interaction models the association between bullying and fibromyalgia was not statistically significant when depression was included in the models. It is unclear whether this is for example due to recall bias or whether fibromyalgia is associated with peer bullying only when depression concomitantly as a comorbidity is present. As a result, there is need for further prospective cohort studies. The findings also emphasize the importance of actions to prevent childhood bullying.

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Competing interests

The authors have no competing interests to report.

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III

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RESEARCH NOTE

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Excess use of thyroid hormone treatment among patients with fibromyalgia: a cross-sectional study in primary health care

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Abstract

Objective: From previous studies, it is known that the association between fibromyalgia and thyroid autoimmunity diseases exists. On the other hand, it was recently suggested that in many cases thyroid hormone treatment might be unnecessary. The aim of our study is to explore the thyroid hormone treatment among primary health care fibromyalgia patients. Our study is cross-sectional and based on fibromyalgia study from the city of Nokia Health Center. Clinical examination was performed to participants, patients filled five questionnaires and information from electronic patient records was gathered. In addition to other parameters, we studied patient's thyroid function levels at the beginning of thyroid hormone treatment.

Results: From those patients participating in the study (n = 103), 34% (n = 33) had thyroid hormone treatment. From those taking thyroid hormone treatment, 48% (n = 16) had information regarding the initial TSH and T4-V levels at the beginning of the treatment. 37% (n = 6) of them had normal thyroid function. Small sample size and data gathered from single health center effects on the generalizability of our findings. However, we suggest further studies to confirm the potential association between fibromyalgia and inappropriate thyroid hormone treatment.

Keywords: Fibromyalgia, Thyroid hormone treatment, Family practice, Drug prescription, Cross-sectional study

Introduction

Fibromyalgia is a functional syndrome characterized by disturbances of sympathetic nervous system and central sensitization [1]. Although fibromyalgia is not regarded as an autoimmune disease, several autoimmune diseases—like thyroid autoimmunity—are associated with it [2]. In a Japanese study, 7.7% of fibromyalgia patients had hypothyroidism, but no association between fibromyalgia symptom severity and anti-thyroid peroxidase (TPO) antibodies was found [3].

The incidence of overt hypothyroidism is reported to be stable around 0.2–2.0% of population. In Finland, the prevalence of hypothyroidism was 3.6% in 2007 based on regularly purchased levothyroxine sodium tablets [4]. However, subclinical hypothyroidism affects up to 12% of population and the use of levothyroxine is increasing. [5] It was recently suggested, that in Finland every third levothyroxine-treatment might be unnecessary, as the number of patients taking levothyroxine has almost doubled during last 10 years, although the prevalence of hypothyroidism has not changed [6]. The levothyroxine treatments have increased also in USA, UK and Sweden, where the prevalence of subclinical hypothyroidism is estimated to be around 12–18% [7].

The symptoms of hypothyroidism are diverse, and the diagnosis of hypothyroidism should be based on laboratory tests, because none of the symptoms or clinical signs

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are sensitive or specific enough [8]. Around 20–25% of patients with normal thyroid function present with one or two classic hypothyroidism symptoms such as constipation, fatigue, muscle weakness, dry skin, memory difficulties and feeling cold [9].

In clinical practice, the diagnosis of fibromyalgia should be based on multifocal pain not explained by injury or inflammation. Other symptoms include fatigue, memory difficulties, sleep disturbances, irritable bowel symptoms and mood problems [1]. Many of these symptoms overlap with hypothyroidism. Consequently, it is suggested that other disorders that commonly present with fatigue, such as anemia and thyroid disease, are ruled out when the diagnosis of fibromyalgia is set [10]. On the other hand, it is known that patients with neuropsychiatric symptoms may attribute unrelated symptoms to thyroid dysfunction and this can lead to overtreatment [11].

In conclusion, it is known that thyroid autoimmunity associated to fibromyalgia and the symptoms of these two conditions overlap considerably. The number of levothyroxine treatments is increasing even though the incidence of overt hypothyroidism is reported to be stable. According to guidelines, the diagnosis of hypothyroidism should be based on the findings from laboratory tests. To the best of the author's knowledge, there are no previous studies addressing the association between functional syndromes, such as fibromyalgia, and inappropriate levothyroxine use.

This study is based on data from patients with fibromyalgia participating in the Finnish Primary Health Care study conducted at Nokia Health Centre and the objective of that study is to describe the demographic features of patients with fibromyalgia in a Finnish health center.

Our aim is also to explore the occurrence of thyroid hormone treatment among fibromyalgia patients and thyroid hormone levels at the beginning of their treatment and to evaluate were the guidelines of care followed.

Main text

Materials and methods

Population of the city of Nokia was 33,210 in 2016 and 19 doctors were working in the Nokia Health Center at the time of the study.

Fibromyalgia patients were searched from the electronic patient records of the health center. Inclusion criteria were ICD-10 code corresponding to fibromyalgia (M79.7) or diagnosis of fibromyalgia with some other codes (M79.0, M25.5, R52.9 and M79.1). Altogether 208 fibromyalgia patients were identified. Information letter containing five questionnaires, including Fibromyalgia Impact Questionnaire (FIQ) and Patient Health Questionnaire-9 (PHQ-9), were sent to the patients. GP's appointment was scheduled for the patients responding to the letter. Functional ability was derived from FIQ and depression from PHQ-9. American College of Rheumatology (ACR) 2010 diagnostic criteria form was filled with the patients at the beginning of consultation. Only the patients filling the criteria for fibromyalgia were included in the study.

Information from thyroid hormone treatment and TSH and free thyroxine (T4-V) levels were gained from the electronic patient record. Reference values for TSH and T4-V were provided by the Fimlab Laboratories, which provides laboratory services to the Tampere University Hospital area. We used the Finnish guidelines for hypothyroidism [12]: TSH level over 4.2 mU/l was defined as subclinical hypothyroidism if the T4-V level was normal. The T4-V level under 11.0 pmol/l was defined as central hypothyroidism if TSH level was normal or low. TSH level over 4.2 mU/l and T4-V level under 11.0 pmol/l was defined as overt hypothyroidism. TSH levels between 0.27 and 4.2 mU/l and T4-V levels between 11.0 and 22.0 pmol/l were defined as normal thyroid function.

Data were analyzed using SPSS version 23. Cross-tabulation and Chi-square test were used when categorical variables were present and two-sample t-test was performed with variables following a normal distribution. Paired samples t-test was used when the means of two measurements taken from the same individual was compared. When needed, Kolmogorov–Smirnov test was used to confirm normal distribution of variables.

The Regional Ethics Committee of Tampere University Hospital has approved the study plan.

Results

Demographic features of study population

Altogether 208 fibromyalgia patients (17 male and 191 female) were included in the study. 103 patients returned mailed questionnaires and GP's appointment was scheduled. There was no statistically significant difference between those not answering the study invitation and those participating in the study regarding age, gender, number of regularly taken medicines, GP's visits before the study and number of other diseases (Table 1).

Features of patients with levothyroxine treatment

Altogether 96 patients had fibromyalgia according to ACR 2010 criteria and seven patients did not fill the criteria for fibromyalgia at the time of the study. From that group 33 (34%) had thyroid hormone treatment and 63 (66%) had not. No statistical significant difference was found between those taking thyroid hormone replacement and those not taking it in functional ability ($p = 0.36$) or depression ($p = 0.71$). Information regarding regular medication was present in their electronic patient record (Table 2).

Table 1 Features of study population

	Participants N = 103		Not participating N = 105		p-value
	%	n	%	n	
Gender					0.19
Male	10.7	11	5.7	6	
Female	89.3	92	94.3	99	
	Mean and 95% CI for mean				
Age	55.1 (52.1–58.1)		57.4 (54.4–60.5)		0.30
Number of regularly taken medicines	3.3 (2.7–3.4)		4.0 (3.3–4.7)		0.15
GP's visit 12 months before the study	5.3 (4.0–6.5)		5.0 (4.0–6.0)		0.52
Number of other chronic diseases	2.5 (2.2–2.9)		2.8 (2.4–3.2)		0.39

Table 2 Characteristics of study population

	No levothyroxine N = 64	Levothyroxine N = 33	p-value
	Mean and 95% CI for mean		
Number of other diseases	2.4 (1.91–2.90)	2.79 (2.32–3.25)	0.32
Number of regularly taken medicines	3.05 (2.15–3.95)	3.45 (2.63–4.28)	0.65
FIQ score (mean)	44.42 (39.87–48.97)	41.07 (34.36–47.77)	0.36
PHQ-9 score	10.05 (8.64–11.46)	10.52 (8.39–12.64)	0.71

All characteristics were normally distributed

FIQ Fibromyalgia Impact Questionnaire, *PHQ-9* Patient Health Questionnaire for depression

Thyroid hormone levels before and after treatment

From those 33 patients with levothyroxine treatment, 16 had information regarding the initial TSH and T4-V levels before thyroid hormone treatment: ten (10/16) patients had hypothyroidism based on the laboratory tests. Subclinical hypothyroidism was present in six cases (6/16), central hypothyroidism in three cases (3/16) and overt hypothyroidism in one case (1/16). The diagnosis of central hypothyroidism was confirmed with specialist of internal medicine working in the Nokia Health Center in all three cases. Of the 16 patients with thyroid hormone treatment, six patients (37%) had normal thyroid function at the beginning of the treatment (Table 3).

Discussion

In our study, over one-third of the fibromyalgia patient using thyroid hormone treatment—whose initial thyroid hormone levels were available—did have normal thyroid function. This indicates that the guidelines of care are not followed in one-third of the cases when levothyroxine treatment is prescribed to a patient presenting fibromyalgia symptoms.

The occurrence of thyroid hormone treatment was much higher in our study population (34%) than the known prevalence of hypothyroidism among general population in Finland [4].

There are likely several explanations to the relatively weak adherence of the guidelines of care for treatment of hypothyroidism with fibromyalgia patients. One might be that one of the main symptoms of fibromyalgia is fatigue, which also is common with hypothyroidism. Patients are aware of this and some may want to try out the thyroid hormone treatment even though their thyroid function is normal. On the other hand, it might be tempting for a physician to diagnose a somatic disease—instead of a functional syndrome—causing the fatigue and try out if levothyroxine treatment would reduce patient's symptoms. Altogether, further studies are needed to study these hypotheses.

In our study, three patients had central hypothyroidism and only one patient had overt hypothyroidism. These patients have obvious indication for the treatment. Rest of the patients (12 patients) had either subclinical hypothyroidism (6 patients) or normal thyroid function (6 patients) at the beginning of the treatment. These patients might not benefit from levothyroxine treatment.

Our findings that 37% of patients had normal thyroid hormone levels at the beginning of the treatment is

Table 3 Thyroid function of patients (n = 16) with levothyroxine treatment whose initial TSH and T4-V level information was present in patient records

Patient	Daily thyroxine dose (µg)	TSH (mU/l) before threatment	T4-V (pmol/l) before treatment	Current TSH (mU/l)	Current T4-V (pmol/l)	Year of hypothyroidism, dg
1 overt hypothyroidism	75	7.3	10.0	2.5	13.6	2012
2 subclinical hypothyroidism	37.5	7.9	11.2	1.4	15.1	2012
3 subclinical hypothyroidism	93	7.1	11.0	0.31	19.1	2008
4 subclinical hypothyroidism	75	6.7	13.8	3.2	15.7	2004
5 subclinical hypothyroidism	50	5.7	13.0	2.5	16.0	2016
6 subclinical hypothyroidism	50	4.9	13.7	2.6	18.6	2011
7 subclinical hypothyroidism	50	4.4	14.1	2.8	14.1	2014
8 central hypothyroidism	75	2.6	10.8	0.78	19.3	2012
9 central hypothyroidism	125	2.6	10.7	1.3	11.6	2012
10 central hypothyroidism	71	0.24	10.9	0.18	14.2	2011
11 normal thyroid function	50	3.5	12.1	1.6	16.2	2013
12 normal thyroid function	100	1.6	16.6	1.2	16.0	2015
13 normal thyroid function	50	1.9	12.6	1.3	13.6	2013
14 normal thyroid function	150	4.2	11.9	0.01	20.2	2012
15 normal thyroid function	100	1.2	13.9	0.87	20.3	2014
16 normal thyroid function	25	1.1	11.0	0.87	13.9	2016
Mean (p-value)	73.5	3.9	12.3	1.5 (< 0.001)	16.1 (< 0.001)	
Median	73	3.83	12	1.3	15.85	

Overt hypothyroidism (TSH > 4.2 mU/l and T4-V < 11.0 pmol/l), subclinical hypothyroidism (TSH > 4.2 mU/l and T4-V = 11.0–22.0 pmol/l), central hypothyroidism (TSH = 0.27–4.2 mU/l and T4-V < 11.0 pmol/l), normal thyroid function (TSH = 0.27–4.2 mU/l and T4-V = 11.0–22.0 pmol/l). Paired samples T-test was used to determine the statistical significance for chance of TSH values and T4-V values

consistent with the suggestion that every third levothyroxine treatment might be unnecessary in Finland [6]. On the other hand, it is probable that subclinical hypothyroidism is diagnosed more often from fibromyalgia patients than from general population, because guidelines give instructions to test thyroid function when fibromyalgia diagnosis is set [10]. Based on literature, it is unknown whether patients benefit from levothyroxine treatment in that case [13, 14].

In addition, the mean daily dose of levothyroxine was 73.5 µg in our study, which is lower than 92.6 µg described by Virta and Eskelinen in their study [3]. In our study, seven patients (44%) had a low daily dose of levothyroxine (< 51 µg) comparing to 13.9% in Finnish prevalence study 1. Furthermore, we found no association between thyroid hormone treatment and functional ability or depression. This finding is consistent with previous studies [3].

Even though fibromyalgia is not regarded as an autoimmune disease, several autoimmune diseases are associated with it [2]. There is evidence that autoimmune diseases such as type 1 diabetes, multiple sclerosis and Hashimoto's thyroiditis could be derived from pathogens like *Mycobacterium paratuberculosis* [15, 16]. Furthermore, inflammatory, infectious, and autoimmune disorders have also been suggested to be etiological events in the development of fibromyalgia, but there is limited evidence to support that hypothesis [17].

To conclude, our findings suggest that there is considerable unnecessary prescribing of levothyroxine to patients with fibromyalgia syndrome with normal thyroid function. However, small sample size and data gathered from a single health center effects on the generalizability of our findings. Further studies are needed to confirm the potential association between functional syndromes like fibromyalgia and inappropriate thyroid hormone treatment. Moreover, it is not clear do fibromyalgia patients benefit from diagnosis of subclinical hypothyroidism, which might be an incidental finding from thyroid function screening at the time of the diagnosis of fibromyalgia. Further studies are also needed from that subject.

Limitations

The main weakness of our study is small sample size. Furthermore, data were collected only from one health center, which has an impact on the generalizability of our findings. In addition, we do not know for sure what kind of symptoms patients had at the moment of the diagnosis of thyroid dysfunction, but we know from the fibromyalgia questionnaires that all patients experienced

symptoms that are also linked to hypothyroidism—such as fatigue—at the moment of the study. Another weakness is that only half of patients identified from patient records participated in the study. On the other hand, there was no statistically significant difference between participants and those not participating (Table 1).

Furthermore, altogether 33 patients had levothyroxine treatment, but we had information only from 16 patients' thyroid function before the treatment. It is likely, that patients without this information, either had had levothyroxine treatment for a long time or it was prescribed from occupational health care or from specialized health care using different electronic patient records. For this reason, we believe that these 16 patients are rather representative sample of fibromyalgia patients with levothyroxine treatment in a Finnish health center.

Abbreviations

ACR: American College of Rheumatology; FIQ: Fibromyalgia Impact Questionnaire; GP: General practitioner; PHQ-9: Patient Health Questionnaire-9; T4-V: Free thyroxine; TPO: Anti-thyroid peroxidase; TSH: Thyroid-stimulating hormone.

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Authors' contributions

AV, EK and TK made substantial contributions to conception, design, analysis and interpretation of data. AV examined the patients and performed statistical analyses and write the first draft of the manuscript. AV, EK and TK have been involved in revising it critically for important intellectual content and have given final approval of the version to be published. AV, EK and TK have agreed to be accountable for all aspects of the work. All authors read and approved the final manuscript.

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Availability of data and materials

The data that support the findings of this study are available from Nokia Health Center but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Nokia Health Center.

Declarations

Ethics approval and consent to participate

The Regional Ethics Committee of Tampere University Hospital has approved the study plan (R15041). All participants have given their written consent to participate in the study and for the publication of results.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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ORIGINAL ARTICLE

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Experiences of patients with fibromyalgia at a Finnish Health Centre: A qualitative study

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KEY MESSAGES

- Several patients had faced uncertainty and contradictions regarding fibromyalgia syndrome, and at least some of these feelings appeared to originate from physicians' varying attitudes and knowledge.
- Patients valued an excellent doctor-patient relationship and continuity of care.
- There is a need to develop the diagnostic process and treatment of fibromyalgia in primary care.

ABSTRACT

Background: Fibromyalgia is a functional syndrome. Despite recent findings, there is still considerable uncertainty about its diagnostic process.

Objectives: This study aimed to explore patients' experiences with fibromyalgia during the diagnostic process in primary health care. Moreover, we tried to determine how diagnostic consultation could be improved.

Methods: This study is based on data from patients with fibromyalgia in a primary health care study conducted in Nokia, Finland. Patients with fibromyalgia were identified from electronic medical records. Focus-group participants with fibromyalgia diagnoses were selected using a purposive sampling method to gather a maximum variation sample. Qualitative thematic analysis was used for the coded data from four focus-group discussions in 2018. A description of the coding tree was provided and researchers organised the codes. Finally, all researchers identified themes from the data.

Results: The main unifying entities were the uncertainty and contradictions fibromyalgia patients faced on several occasions. Physicians sometimes offered other diagnoses – like depression – as an explanation for the symptoms, or used repetitive tests to eliminate other possible diagnoses. Furthermore, patients expressed their wishes for a holistic, empathetic, and up-to-date approach to their symptoms.

Conclusion: In our interviews, a good doctor-patient relationship and continuity of care were necessary, as were the physician's attitude and knowledge of fibromyalgia. Our findings also suggest avoiding repeated or unnecessary rule-out tests and the overdiagnosis of psychiatric disorders is necessary.

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Fibromyalgia; qualitative study; focus group; continuity of care; doctor-patient relationship

Introduction

In the eyes of many physicians, fibromyalgia is still a questionable disease entity, partially because of its mysterious pathophysiology [1]. It is a functional syndrome characterised by central sensitisation [2]. In addition to pain, patients can experience fatigue, poor sleep quality, cognitive problems, and various other symptoms [3].

There are several challenges relating to a fibromyalgia diagnosis. Various diagnostic criteria have been developed chiefly for research purposes but these criteria are also used for diagnostic purposes [4]. These criteria also received criticism over the confusion that the role of the tender points caused [5]. Based on the criticism, the ACR 2010 criteria were developed to

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give physicians an alternative that did not require tender point examination [5]. The original criteria also included the stipulation that the symptoms cannot be explained by any other disorder but this was later removed [6]. In clinical practice, laboratory tests are unnecessary for a fibromyalgia diagnosis but clinical guidelines recommend them to rule out diseases (such as anaemia or hypothyroidism) causing fibromyalgia-like symptoms [7].

Previous studies show there is significant under- and overdiagnosis concerning fibromyalgia, and the diagnosis often fails to provide an adequate clinical concept fit to the experience of the illness [8,9]. Indeed, many symptoms of fibromyalgia overlap with other diseases, which might lead to the overdiagnosis of subclinical manifestations of these diseases, as rule-out laboratory tests are often ordered during the diagnostic process [10,11]. It also appears likely that some physicians do not accept the diagnosis of fibromyalgia and are not willing to diagnose it even if the patient has typical symptoms, which may result in underdiagnosis [9]. In part, the reluctance might be caused by the belief that by not setting the diagnosis, they will avoid the overdiagnosis and medicalisation of fibromyalgia symptoms [12]. Furthermore, the diagnosis of fibromyalgia often fails to provide a valid explanation of the patient's symptoms [8]. On the other hand, some physicians find the treatment of fibromyalgia frustrating because of the difficulty in controlling the symptoms and the patient's emotional response, and there are no pharmacological interventions that are suitable for all patients and all symptoms [13,14].

A meta-ethnography study focussed on the diagnostic experiences of patients with fibromyalgia found that patients had often searched for a long time in their health care for the correct diagnosis [15]. A meta-synthesis of qualitative studies from illness experiences of fibromyalgia reported the same finding and this period before the diagnosis was difficult for patients [16]. In another study, patients found the overlapping symptoms confusing and this caused uncertainty and doubts regarding the accuracy of the diagnosis [17]. When the diagnosis was set, it validated and made sense of the symptoms. However, this relief was short and patients began to question the validity of the diagnosis and medical authority [15]. In addition, the invisibility of symptoms raised questions regarding the patients' credibility [16].

To conclude, from previous studies, it is known that the time before a diagnosis is burdensome from the patient's perspective. Diagnosis offers some help and validates the symptoms but usually, this does not last long, as the patient realises that, life has changed forever due to fibromyalgia. However, most patients eventually learn to cope with the symptoms [15,16,18,19]. These coping mechanisms vary from one patient to the next, and patients also desire longer consultation times in primary health care, continuity of care, and correct information on the aetiopathogenesis of fibromyalgia [16,20,21].

To the best of the authors' knowledge, there are no previous qualitative studies on the diagnostic experiences of fibromyalgia patients in terms of the under- and overdiagnosis of fibromyalgia or the comorbidities of fibromyalgia from the patients' viewpoint. This study aims to determine the patients' experiences with fibromyalgia during the diagnostic process, especially in terms of possible diagnostic inaccuracies, and to ascertain how diagnostic consultation could be improved.

Materials and methods

The research team and reflexivity: Aleksi Varinen (AV, male, GP) and Tiina Vuorio (TV, female, GP) conducted the focus-group interviews. In addition, Tuomas Koskela (TK, male, GP, professor of general practice) and Elise Kosunen (EK, female, professor of general practice) also designed the study and interpreted the data. AV works as a clinical lecturer at Tampere University, and at the time of the interviews, TV worked as a clinical lecturer at Turku University. AV had established prior contact with all the patients in one research appointment during the previous phase of the fibromyalgia study. Three of the patients were formerly patients of AV at Nokia Health Centre. However, they were not AV's patients during or after the study, and their fibromyalgia diagnosis was set before they became AV's patients. Therefore, the researchers were not involved in the diagnostic process of the study patients. All patients had previously received an information letter on this study and the researchers' interest in the topic.

The methodological orientation of this study is a thematic analysis based on the phenomenological theory of the description of the participants' personal subjective experiences [22]. The participants were selected using purposive sampling. The study is based on data from patients with fibromyalgia participating in the Finnish Primary Health Care study conducted at Nokia Health Centre. Fibromyalgia patients were sourced from electronic medical records. The inclusion criteria were the ICD-10 code corresponding to fibromyalgia (M79.7) or a diagnosis of fibromyalgia in the

patient records with some other code (M79.0, M25.5, R52.9, and M79.1). Altogether, 208 patients with fibromyalgia were identified. An information letter containing five questionnaires was sent to the patients. A GP's (AV) appointment was scheduled for the 103 patients who responded to the letter. Altogether, 96 patients had fibromyalgia according to the ACR 2010 criteria and seven patients did not meet the ACR 2010 criteria for fibromyalgia at the time of the study. During the appointment, patients who met the criteria had the chance to ask questions about the syndrome.

Finally, for the qualitative part of the study, patients with fibromyalgia were selected using the purposive sampling method. AV selected the patients based on the information gathered from the previous stage of the fibromyalgia study to create a maximum variation sample. The criteria used for this were age, gender, educational level, and years since the original diagnosis of fibromyalgia. All patients were initially approached by mail to obtain written consent for the fibromyalgia study. Patients selected for the focus groups were contacted by telephone by AV. Initially, the four focus-group sessions were planned based on the estimate that four groups would be enough to achieve data saturation [23]. Each group was planned to contain five patients because of the topic's complexity and possibly controversial content [23]. Four patients declined the invitation to participate in the focus-group interviews due to timetable constraints. At this point, 20 patients were selected for the study, however, two patients cancelled their appointment at the last minute.

As a result, the study sample consisted of 18 patients divided into four focus groups (two groups with five participants and two with four participants). The participants were referred to the different groups according to their age to keep the conversation pace comfortable for all participants [24]. The interviews took place in the Nokia Health Centre auditorium on 19–20 March 2018. No one else was present besides the participants and researchers. The characteristics of the participants are shown in Table 1. The age of the patients and the years since the diagnosis are shown in Supplementary Table 1.

The interview guide (Supplementary File) was available to the interviewers. A preliminary interview guide was developed based on previous research findings, and all of the researchers participated in formulating it to facilitate the data collection. The three main questions considered the patients' desires for their treatment in primary health care, how the diagnostic process of fibromyalgia started, and the patients' thoughts about the diagnostic tests used. The first session was also a pilot for the interview guide and no modifications were made based on that session.

Table 1. Demographic features.

Characteristic	Participants ($n = 18$)
Age (mean & standard deviation, SD)	54.7 ± 15.5
Gender (*n*)	
Female	15
Male	3
Educational level (*n*)	
Primary school	6
Upper secondary school or vocational school	11
University or polytechnic	1
Employment status (*n*)	
Engaged in working life (full- or part-time)	5
Unemployed	2
Unable to work (absence due to illness or disability pension)	9
Old-age pension	2
FM severity: PSD[a] score (mean & SD)	22.5 ± 4.0
Years with FM[b] (mean & SD)	13.8 ± 9.9
FM diagnosis set in (*n*)	
Primary health care	6
Secondary health care	12
Number of other diagnoses (mean & SD)	1.8 ± 1.2
Regular medication (*n*)	
Yes	9
No	9
Number of GP visits last year (mean & SD)	3.5 ± 2.0

[a]The PSD score is derived from the American College of Rheumatology (ACR) 2010 diagnostic criteria as the widespread pain index and symptom severity scale are combined into one index ranging from 0 to 31. A patient who fills the ACR2010 criteria for FM will always have at least 12 points from the PSD score. The PSD score is strongly related to somatic symptom severity [29].
[b]The time since the FM diagnosis ranged from 2 to 32 years.

The interviews were recorded (by audio). Field notes were also made during the sessions. The continuity of questioning was maintained by following the interview guide in every focus-group interview. Four sessions were carried out and after that, the researchers agreed that data saturation had been reached based on the field notes and no more focus-group interviews were needed. All participants participated equally, except for one patient who had suffered a stroke earlier; this slightly affected her ability to speak as fluently as the other patients. The duration of the interviews ranged from 61 to 95 min.

The data were coded according to the thematic analysis process [23]. We identified subordinate codes within group interviews and arranged them into more prominent themes across the interviews. Initially, 61 codes were generated. Due to overlaps, some codes were unified, resulting in 55 codes altogether (Supplementary Table 2). Finally, seven themes were formulated. Researchers used back-and-forth translation to verify that the citations were translated adequately. COREQ and SRQR checklists were used in reporting this study. The demographic features of the study population are presented in Table 1.

Table 2. Main themes from the focus-group interviews.

Searching for a reason for their illness
Prolonged diagnostic process
Contradictory and suspicious thoughts regarding the diagnosis
Need for compassion and understanding
The importance of the doctor-patient relationship
Illness and identity
Conceptions of the treatment

Results

The following seven themes (Table 2) emerged from the data:

Prolonged diagnostic process

The patients felt that physicians ordered diagnostic tests for rheumatoid arthritis and other various somatic diseases, but as they were negative, receiving the fibromyalgia diagnosis was a slow process:

> *'Laboratory tests for rheumatoid arthritis had been taken quite regularly since I was 14 or 15 years old, and nothing had ever been found'. (Woman, 40 years, 16 years since the diagnosis)*

In many cases, the participants mentioned that the rheumatologist had set the final diagnosis of fibromyalgia. In addition, the patients felt that on several occasions, physicians considered the symptoms of fibromyalgia (e.g. fatigue) to be a sign of depression, even though the patients did not feel their mood was low:

> *'When I went to clinical examinations for my pain, the only diagnosis that I got was depression'. (Woman, 33 years, 4 years since the diagnosis)*

Some participants felt that physicians did not set the diagnosis and tried to provide treatment advice instead:

> *'At some point I was getting frustrated and the doctor just said that there is nothing wrong with me: a person can have pain that comes from an unknown origin'. (Man, 62 years, 3 years since the diagnosis)*

Sometimes patients thought that physicians knew more than they revealed, but they were not allowed to tell everything, especially if there was a lack of sound scientific evidence:

> *'But I think that many doctors know more, but they cannot – is it their ethics or what – but they just can't tell you what to do even if it would ease the symptoms. They have to use that medical jargon'. (Woman, 40 years, 16 years since the diagnosis)*

Uncertainty was more evident if the patients were told they had a fibromyalgia-like syndrome or if the patients were atypical (e.g. young or male). The role of tender points was also confusing, as many patients had more severe pain elsewhere. Some participants had different pain syndrome diagnoses (e.g. fibromyalgia and chronic pain syndrome), which was also considered confusing.

Contradictory and suspicious thoughts regarding the diagnosis

This theme included negative attitudes toward the diagnosis of fibromyalgia as well as from the patient's, physician's, and society's side because of the negative stigma:

> *'But at the moment when the diagnosis was set, the doctor said to me that you have to understand that this is a disease which is not taken seriously. So shall I set this diagnosis or not? And I replied that you have to do it if the symptoms match'. (Woman, 65 years, 9 years since the diagnosis)*

Patients often felt it hard to accept the diagnosis of fibromyalgia, and they would have wanted more tests to find out what was wrong with them. Sometimes the patients received only the diagnosis but no treatment or instructions on how to cope with the situation:

> *'It was actually the only thing that I did not want – the diagnosis – I wanted instructions for treatment'. (Woman, 49 years, 13 years since the diagnosis).*

On the one hand, some patients argued that fibromyalgia did not explain all of their symptoms. On the other hand, some patients reported that they were diagnosed quickly, as the GP seemed familiar with the syndrome and a few patients already suspected they had fibromyalgia.

In some cases, the participants felt that the physician had kept the diagnosis secret from them or made them decide whether they wanted the fibromyalgia diagnosis to be written in the medical record:

> *'I felt so embarrassed about that disease, because the occupational health doctor said to me, that do you want … are you really sure that you want me to put this diagnosis in your medical records'. (Woman, 65 years, 9 years since the diagnosis).*

Furthermore, many patients felt that they did not go to see their GP because of the fibromyalgia symptoms but due to other symptoms or because they did not know if the symptoms resulted from fibromyalgia. They thought it was tough to tell which condition was causing the symptoms, especially when they had many comorbidities:

> *'I have gout and other diseases. And osteoarthritis. I have several diseases that cause pain. Fibromyalgia is not the only one. You don't always know which the pain is from'. (Woman, 50 years, 10 years since the diagnosis)*

Searching for a reason for the illness

This theme included the patients' thoughts about heritability and psychological factors (e.g. adverse life events) that could trigger fibromyalgia and thoughts about defects in their body (e.g. the hypermobility of joints) predisposing them to fibromyalgia:

'I am the third generation of women with this disease'. (Woman, 49 years, 13 years since the diagnosis)

'I have guessed that I have it, because we have that in my family and the symptoms are the same'. (Man, 59 years, 3 years since the diagnosis)

'I have also too straight a spine'. (Woman, 49 years, 13 years since the diagnosis)

Lack of compassion and understanding

A lack of empathy and understanding of the effects of fibromyalgia were the main features of this theme. The participants felt that close relatives and health care workers did not understand them. Furthermore, they felt that physicians questioned their credibility because they did not look sick:

'Even strangers tell you that you look so lively and happy that how can you not go to work'. (Woman, 49 years, 13 years since the diagnosis)

In addition, the patients reported that physical examinations were often painful and the physicians did not seem to understand this:

'When doctors say that checking blood pressure can't hurt, and it hurt so much that I almost fainted'. (Woman, 47 years, 14 years since the diagnosis)

Moreover, patients felt that there was a lack of understanding also from society, as the diagnosis of fibromyalgia does not entitle one to a disability pension. On the other hand, one patient described how she regained her credibility when she was granted a disability pension:

'When I got my disability pension, it did not make me healthy but I felt that my dignity was restored'. (Woman, 69 years, 27 years since the diagnosis)

Furthermore, some patients felt that fibromyalgia was not taken into consideration in the care planning for other medical conditions:

'After the fibromyalgia diagnosis, when I have visited doctors for other symptoms, no one has considered that they may be from fibromyalgia'. (Woman, 65 years, 9 years since the diagnosis)

On the contrary, some felt that physicians thought that every symptom they had derived from the fibromyalgia syndrome:

'It takes time to understand the symptoms and how they present. It takes time to know yourself and your symptoms'. (Woman 65 years, 9 years since the diagnosis)

The importance of the doctor-patient relationship

The doctor-patient relationship was essential for the patients. Additionally, patients appreciated it if the physician was familiar with the treatment of fibromyalgia:

'If you have a good doctor, he understands the correct treatment for you'. (Woman, 40 years, 16 years since the diagnosis)

Listening and understanding the condition was the key element for a good relationship. Still, many physicians seemed to lose interest after setting the diagnosis and did not give any instructions for self-treatment. Patients also reported that the physician they saw changed all the time and the consultations were too short:

'The consultation time is short. Or if you get on-call appointment, then it is even shorter'. (Woman, 33 years, 4 years since the diagnosis)

Furthermore, the patients desired consultations where specialists and their GP would plan the treatment together:

'Sometimes you hope that there would be some joint consultation with your GP and the rheumatologist or some other specialist'. (Man, 62 years, 3 years since the diagnosis)

Some patients also recognised the limitations of the effective treatment methods for fibromyalgia.

Illness and identity

The patients stated that when they realised there was no curative treatment for fibromyalgia they were forced to adopt a new identity. GPs often tried to provide reassurance by pointing out that the condition is not malignant. This, however, did not always work:

'Doctors often try to comfort you that this does not kill you. But I think that it is not comforting when you have forty or fifty years left to live and you know that the pain is not going anywhere'. (Woman, 49 years, 13 years since the diagnosis)

Some patients felt that the illness burden of fibromyalgia was very high and experienced desperation due to the fact there is no cure for the syndrome:

'I have noticed that some older patients would rather have cancer, which can either be cured or it kills you. With fibromyalgia you have constant pain and no-one can help you'. (Woman, 49 years, 13 years since the diagnosis)

On the one hand, the younger patients, in particular, described difficulties accepting the restrictions on their

functional ability. On the other hand, older patients tended to accept fibromyalgia better as a part of their burden of illness. Some patients mentioned that for a while, they had even forgotten they had fibromyalgia when they got some more severe diseases:

'I had breast cancer a few years ago, and I have not visited the doctor because of fibromyalgia for about 20 years'. (Woman, 72 years, 25 years since the diagnosis)

After accepting the diagnosis, it was easier to find coping strategies. Most patients said that listening to one's body was the best advice for coping with the symptoms. As a result, they felt their life had to be organised according to the disease:

'On a holiday trip I have to schedule my life. Today I go walking and tomorrow I will lie by the pool. Makes you laugh (ironically), but that's how it is'. (Woman, 40 years, 16 years since the diagnosis)

Conceptions of the treatment

The patients had different opinions on the effectiveness of different medications, nutritional guidance, physiotherapy, psychological interventions, cold therapy, peer support, and acupuncture:

'I was in a rheumatology clinic, and when they examined my tender points I yelled like a dying swan, and there was no question about the diagnosis, and then they started trying different medications: oral corticosteroids, etc. and nothing helped'. (Woman, 69 years, 32 years since the diagnosis)

In general, some patients have experienced short-term benefits from corticosteroids and long-term benefits from exercise:

'Exercise helps, even if it is only ten minutes of walking'. (Woman, 65 years, 9 years since the diagnosis)

More information on fibromyalgia and meaningful pursuits in daily life were also seen as beneficial:

'Maybe the best thing to do is to exercise, but not too much and try to clear your mind of pain-related issues to with meaningful daily life pursuits'. (Man, 62 years, 3 years since the diagnosis)

Furthermore, the patients recognised the importance of sleep:

'You are more sensitive to pain if you do not sleep well'. (Man, 62 years, 3 years since the diagnosis)

Discussion

Main findings

An excellent doctor-patient relationship and continuity of care were meaningful from the patients' perspective, as were the physician's attitude and knowledge of fibromyalgia. Furthermore, it is necessary to avoid repeated tests to eliminate other possible diagnoses and the overdiagnosis of psychiatric disorders in the diagnostic process of fibromyalgia.

We expected the patients to talk more about diagnostic procedures and the uncertainty relating to positive or negative findings. However, during the conversations, only repeated laboratory tests for ruling out rheumatoid arthritis and some other somatic diseases were raised. Instead of mentioning diagnostic procedures, the patients expressed their need to discuss the uncertainty and contradictions regarding the diagnosis and treatment of fibromyalgia they had faced on several occasions.

Interpretation of the study results in relation to existing literature

From previous studies, it is known that patients face some uncertainty relating to the diagnosis and treatment of fibromyalgia. In our study, one potential source of the overdiagnosis of subclinical manifestations of other diseases was the physicians' repetitive use of exclusion tests for other diseases. This might occur because the former diagnostic criteria for fibromyalgia syndrome required that other conditions possibly causing similar symptoms be ruled out. However, in the revised criteria, a diagnosis of fibromyalgia is valid irrespective of other diagnoses, though it is still vital to diagnose comorbidities that may cause similar symptoms [6]. Thus, fibromyalgia should not be seen as a rule-out diagnosis. On the other hand, sometimes, patients felt that physicians did not even set a preliminary diagnosis and provided treatment instructions instead.

The controversy is also present from the physicians' point of view, as there are no specific diagnostic criteria for fibromyalgia developed especially for clinical work [5]. This and the difficulty of treating the symptoms can also confound physicians [14]. In our study, we discovered that patients experience this contradiction on many levels in health care, as well as in personal relationships and, more broadly, in society. Even though fibromyalgia is a medical diagnosis, the patients felt that some physicians did not believe that the patients benefitted from the diagnosis and were reluctant to set it. Epidemiological data from a previous study have shown similar results [9]. This may highlight that some physicians think the diagnosis is not helpful and by not setting the fibromyalgia diagnosis, they can avoid medicalisation [12]. Moreover,

most of the patients had been diagnosed over a decade ago, which may reflect former attitudes towards fibromyalgia syndrome as well as problems with the former fibromyalgia criteria relating to clinical work [5]. On the other hand, our sample also included several patients who had been diagnosed only a few years ago, and these patients had similar experiences. Furthermore, various other diagnoses, such as depression, were offered as an alternative explanations for the symptoms. These alternative explanations might lead to the misdiagnosis or overdiagnosis of psychiatric conditions if the diagnostic guidelines for these diseases are not followed since there is some overlap in functional syndrome symptoms (e.g. poor sleep and cognitive problems) and depression.

Patients had also received different chronic pain diagnoses from other medical specialities (e.g. psychiatry), and the role of these alternative diagnoses was confusing to patients. A new unifying diagnostic construct of bodily distress syndrome including four symptom clusters (cardiopulmonary, gastrointestinal, musculoskeletal and general symptoms, or fatigue) has also been suggested instead of several speciality-specific functional syndrome diagnoses such as fibromyalgia, and this might reduce the diagnostic incoherence from that perspective [25].

From the physician's viewpoint, it is also difficult to distinguish which symptoms derive from fibromyalgia and which might be symptoms of some other undiagnosed disease requiring further investigation. The continuity of care and an excellent doctor-patient relationship that patients emphasised during the interviews might help with this.

The patients' treatment conceptions mainly were in line with the previous literature. Treatment should be individual and some medications may benefit some patients but cause severe side effects in others [13]. Several participants in our study found exercise beneficial, which is in line with findings from previous studies [2]. Previous literature and our findings also highlight the importance of the continuity of care and longer appointments in primary health care [20,21].

Strengths and limitations

The strengths of this study include a comprehensive group of patients, including three male participants. The participants were of various ages and their symptoms vary from mild to severe. None of the participants had a current patient-doctor relationship with either of the interviewers, and the interviewers were not employees of the health centre at the time of the study. The questions presented at the interview were open-ended, and the participants started conversations without further encouragement. The interviews were carried out face-to-face. During the interviews, patients also brought up several themes identified in previous studies.

The inclusion of only one health centre is a limitation of this study. However, many patients had also had consultations in specialised and occupational health care and the patients had faced the same kind of attitudes and uncertainty in these contexts as at the health centre. Additionally, in the focus groups, not all the patients participated equally, and some might have left something unsaid.

Implications for further studies and clinical practice

Based on our findings and other studies, there is a need to improve the diagnostic process for fibromyalgia in primary care to avoid the overdiagnosis of subclinical manifestations of diseases when rule-out tests are repeatedly used in the diagnostic process of fibromyalgia [9,10]. There also may be a need to adopt a concept for functional syndromes or bodily distress syndrome that is meaningful for both patients and GPs in order to clarify the role of overlapping functional syndrome or pain syndrome diagnoses and the symptoms they are causing. A holistic view and good communication skills are important factors in patient communication [8].

Conclusion

Many patients have faced contradictions and uncertainty regarding fibromyalgia syndrome, and some of these feelings appear to originate from physicians' varying attitudes and knowledge. On the other hand, a good doctor-patient relationship and continuity of care were highly valued: these core values of general practice need to be supported. Our findings suggest that it is necessary to develop the diagnostic process and treatment of fibromyalgia in primary care to avoid repeated or unnecessary rule-out tests and the overdiagnosis of psychiatric disorders based only on pain or functional syndrome symptoms.

Geolocation information: This study was conducted in the Pirkanmaa region of Finland.

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Ethics statement

The study protocol was approved by the Regional Ethics Committee of Tampere University Hospital (R15041).

Authors' contributions

AV, TV, EK, and TK participated in the planning and organising of this study. AV and TV were moderators in the focus groups. All authors participated in the data analysis and reporting and reading and approving the final manuscript.

Disclosure statement

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