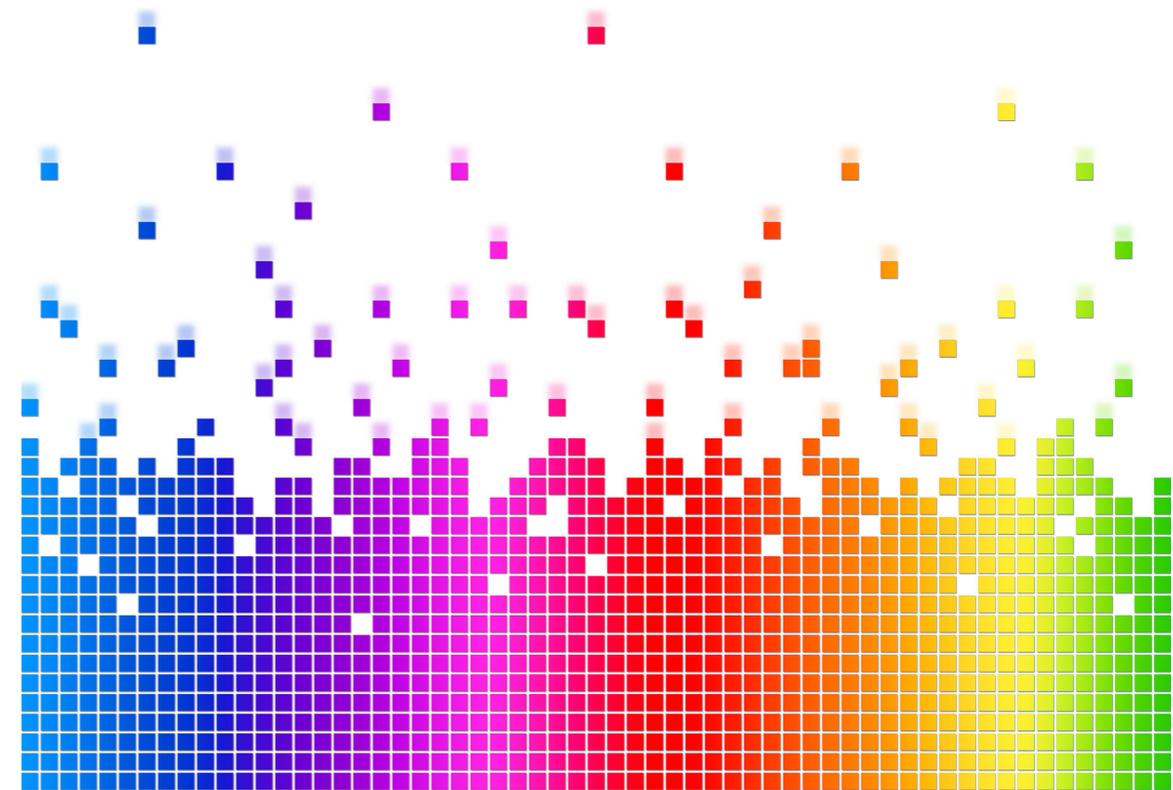


Thesis for licenciate degree
2022

On the clinical assessment of persistent fatigue and pain



Gabriella Bernhoff

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Institutet**

Stockholm 2022

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Published by Karolinska Institutet.

Printed by Universitetservice US-AB, 2022

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ISBN 978-91-8016-100-8

On the clinical assessment of persistent fatigue and pain

LICENCIATE THESIS

By

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The thesis will be defended in public at Zanderska Building, Stockholm, Friday February 3rd 2023 at 9 a.m.

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Salus populi suprema lex

Cicero

Popular science summary of the thesis

It has been more than 100 years since physician William Osler urged clinicians to actively listen to patients' stories about their disease – and then find out the diagnosis. This advice remains a beacon in clinical assessment, especially when it comes to persistent fatigue and pain. For several reasons, the clinical management of these conditions is an area with a high risk of mistakes.

Screening for hypermobility/reduced resistance to load and neuropathies is crucial. The results of such screenings can inform special considerations for self-care and treatment.

A majority of patients have neck or low back problems that hinder physical exercise and persist despite numerous treatment attempts. There are often secondary psychological issues, such as anxiety. The symptom picture is quite diverse; delayed diagnosis is common and leaves the patient not getting the help they need. These patterns highlight the shortcomings in the interaction between the patient and the healthcare system.

Any assessment for these patients must take into consideration the indefinite nature of these disorders (subjective, migratory, absence of detectable structural pathology) and ensure that the patient's narrative is not lost because it communicates much about the disease mechanisms. Screening (hypermobility, neuropathic pain) can contribute to systematic evaluation. Screening instruments must be reliable, evidence-based, interpretable, and easy to handle.

The goal of this thesis is to add to the evidence of utility of some common measuring instruments and of experiences patients with persistent fatigue and pain have. The project included more than 270 patients with suspected chronic fatigue syndrome and was conducted at a specialist clinic for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) in Stockholm. Data collected in the investigation (before diagnosis) were analysed in three studies.

First, the Beighton score was investigated for its relevance (validity) in determining generalized hypermobility, with a comparator reference in the form of an integrated assessment by an experienced physiotherapist (Beighton score, Five-part questionnaire/5PQ, and semi-structured anamnesis). The results showed only weak agreement and provided support for using the Beighton score together with a targeted history. The measurement stability was fair despite tests in a field environment.

The second study focused on a standardized reading of pain drawings by patients reporting neck-related headaches. The pain drawing template or pattern used in the screening appeared to be condition-specific because analyses showed a clear link to dizziness/imbalance and a comparatively more serious pain problem. Screening with

pain drawing may support patient centredness in the consultation and is a target area for development within the diagnostics for patients with persistent fatigue and pain.

In the third study, self-perceived health was investigated from a diagnostic perspective. The results provided preliminary evidence of a condition-specific health experience of reduced tolerance to exertion and low energy levels in comparison with similar conditions. This finding added clarification to the diagnosis of ME/CFS.

In summary, the results reported in this thesis increase knowledge about how screening within persistent fatigue and pain can be used in clinical assessment and in studies in a correct, optimally effective way. The condition ME/CFS is made clearer in terms of its identity.

Abstract

Patients with persistent fatigue and pain, most of them women, often struggle with decreased function and related concerns. They commonly receive an inconclusive investigation and a delayed diagnosis. Neuropathic aspects of the condition may be missed. Clinical screening is vital because it can support medical and healthcare decision-making early in the course of an illness. Two go-to tools of the typical assessment, the Beighton score and the pain drawing, are appreciated in praxis but lack substantial evidence base. The overarching aim of this thesis was to contribute to improvements in the management and diagnostics for these patients. All research questions originated from clinical praxis.

The studies are based on data from one group among the very large population of patients who have persistent fatigue and pain: those presenting with suspected myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).

In study I, the Beighton score was evaluated within clinical routine assessment for its capacity to identify a physique with systemic joint laxity. Systemic joint laxity is a risk factor for developing persistent health issues and should warrant considerations in treatment. Normally, this feature would need to be assessed routinely in the investigation of persistent fatigue or pain. This study involved different competencies of the assessors (physician and physiotherapist). Despite these differences and a lack of joint training in the method, inter-rater reliability was acceptable, demonstrating the stability of the Beighton score as a measurement. The sum score, however, must not be interpreted as a definitive answer regarding whether systemic joint laxity is present but must be read instead within the context of a targeted medical history.

Study II concerned the pain drawing used to assess body pain extent. Methods of interpretation, however, have not been standardized in clinic and little evidence is available regarding its use for assessing the cervical spine. Study II involved evaluation of a method of screening for cervicogenic headache using a standardized reading in which a predefined C2 pain pattern was applied. Dizziness/imbalance was strongly associated with the C2 pain pattern and those who presented with this pattern had more severe pain and lower health-related quality of life compared with those who did not present with it. Thus, the pain drawing with the C2 pain pattern could distinguish patients with a more complex pain picture. The strong association with dizziness/imbalance strengthened the relevance of the pattern in clinical assessment of cervicogenic headache.

Paper III describes self-perceived health in the population with persistent fatigue and pain, from a biopsychosocial perspective. A comparison was made for two subgroups

within the study population – those diagnosed with ME/CFS and those who were not but had a related symptom picture. Data were collected with several questionnaires on health-related factors. Characteristics of ME/CFS in this context were impaired tolerance for exertion (mental or physical), impaired energy levels, worse pain, and poorer general health. No between-group differences were found for signs of anxiety and depression, mental role functioning, and mental well-being, so that the identified ME/CFS characteristics did not emerge as causal in the health status of the ME /CFS-subgroup.

In conclusion, the Beighton score and the pain drawing can aid in determining the nature and degree of a condition with persistent fatigue and pain. They appear to be tools to retain in the clinical assessment. Screening with the pain drawing also may be beneficial in supporting a patient-centred management and merits further development within the clinical assessment. The experience patients have with ME/CFS places this condition at the far end of the spectrum of persistent fatigue and pain.

List of scientific papers

This thesis is based on studies reported in the following papers, referred to in the text by their respective roman numerals.

- I. **Assessment of systemic joint laxity in the clinical context: relevance and replicability of the Beighton score in chronic fatigue.**
Bernhoff G, Huhmar H, Bunketorp Käll L.
J Back Musculoskelet Rehabil. 2022; 35: 859–866.
- II. **The significance of pain drawing as a screening tool for cervicogenic headache and associated symptoms in chronic fatigue.**
Bernhoff G, Huhmar HM, Rasmussen-Barr E, Bunketorp Käll L.
J Pain Res. 2022; 15: 2547–2556.
- III. **A comparison of health-related factors between patients diagnosed with ME/CFS and patients with a related symptom picture but no ME/CFS diagnosis: a cross-sectional exploratory study.**
Bernhoff G, Rasmussen Barr E, Bunketorp Käll L.
J Transl Med 20, 577 (2022).

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List of abbreviations

BPE	Body pain extent
C2	Second cervical nerve root
CFS	Chronic fatigue syndrome
EQ-VAS	EuroQol vertical visual analogue scale
HAD	Hospital Anxiety and Depression Scale
ICF	International Classification of Functioning, Disability and Health
IQR	Interquartile range
MAP	Multimodal assessment model of pain
ME	Myalgic encephalomyelitis
MRI	Magnetic resonance imaging
OR	Odds ratio
PROM	Patient-reported outcome measure
RAND	Research and development
VAS	Visual analogue scale
WAD	Whiplash-associated disorders
WAI	Work ability index
WHO	World Health Organization

Introduction

When subjected to stress, the body adapts to manage that stress more effectively, as it does with physical exertion by increasing the overall efficiency of the circulatory system. Another example is the constant multitasking of everyday life: At all levels of the central nervous system, different stimuli are efficiently integrated, and filter systems especially in the brainstem and thalamus prioritize inputs relevant to the individual's needs and goals while suppressing less important or distracting afference. The body is "silent" (symptom-free) from the descending regulation of pain and other stimuli, and when in balance, is a fine-tuned machine.

Decreased function can become a main concern when these systems falter and persistent symptoms arise, mainly persistent fatigue and pain. These symptoms are often classified as musculoskeletal complaints and considered to be the cause of up to about a third of primary care consultations [1,2], as well as being a major cause of disability [3]. As such, conditions of persistent fatigue and pain are resource-intensive for society in terms of both healthcare interventions and income loss.

The back and the neck/shoulder are among the most frequently affected areas, which also include the knee [1,4]. The curvature of the spine and its hard and soft structures make it elastic while also supporting its purpose as a protective shell for the spinal cord. As with other joints, however, osteoarthritis can develop in the spinal joints and progress to trigger symptoms involving virtually any part of the body because of nerve irritation. Patients may try a variety of rehabilitative efforts, sometimes for years, with no lasting effect, and many will undergo several MRI scans [5]. Overload from common treatments such as overly strenuous physical therapy [6], manual neck manipulation [7,8], and spinal surgery [9–11] poses substantial risks for continuation or even worsening of symptoms. Normally, clinicians encounter the worry that follows from these experiences of a long journey through the healthcare system and too little constructive information [12–14].

Medical care and healthcare have a key role in offering patients an appropriate investigation and adequate management. The investigation is aimed at early diagnosis. By the late 1900s, the physician William Osler was urging engagement in active listening to a patient's narrative of illness, advising clinicians, "Listen to the patient; and you will learn the diagnosis". This advice remains a guidepost in clinical assessment, not least with regard to the numerous groups who experience persistent fatigue and pain as symptoms are mainly subjective. For several reasons, though, the process in the healthcare system carries high risk for errors [15,16]. Routines for effective triage of patients can improve outcomes, including patient safety and patient satisfaction.

1 Literature review

1.1 Scope and delimitations

Fatigue in this thesis refers to “extreme tiredness resulting from mental or physical exertion or illness” [17]. *Pain* refers to an “unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage” [18]. *Persistent* refers to symptoms lasting at least 3 months [19,20].

All patients included in the project were enrolled for investigation of possible myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) at a publicly funded private secondary clinic specialized in this condition. Issues are addressed here for clinical assessment irrespective of type of healthcare provision, but with relevance especially in the context of primary care. Early correct assessment is important for these conditions and for promoting health, and highlighted below are some aspects related to issues in first-line care for ensuring a good, patient-centred approach. Primary care is the hub of care, and proactive working methods at these encounters can limit the unnecessary use of resources in secondary care. Initial management must ensure safe handling and consider the patient’s needs.

1.2 Persistent fatigue and pain – hallmark symptoms of associated disorders

ME/CFS is classified as a neurological disease and the term was coined in the 1950s [21,22]. It is characterized by severe disabilities, fatigue and pain [23]. Many patients improve slowly, but complete recovery is rare [24]. The condition poses a diagnostic challenge due to the large variation in symptoms, intra- and interpersonal variation [25]. ME/CFS is a so called exclusionary diagnosis – there are no diagnostic tests – based on the International Consensus Criteria [21], developed to support clinical diagnostics. The criteria have mandatory symptoms, including a post-exertional exacerbation of fatigue (“post-exertional malaise”). The prevalence of ME/CFS has not been determined but is estimated to about 0.1% of the population [26].

Among syndromes of persistent fatigue and pain, where no serious illness or injury is found to be the cause, the most well-known are perhaps ME/CFS [23], fibromyalgia [27,28], and whiplash-associated disorders (WAD) [29]. The common denominator among these disorders is an off-balance nervous system, with an emphasis on persistent fatigue and widespread pain including headache and jaw pain, dysautonomia, impaired cognitive functions, sleep problems and functional gastrointestinal symptoms [23,27–30]. Not least, they are tied together by the subjectivity of complaints (fatigue and pain). The earlier collective designation in the literature was as “central sensitivity syndromes” [31]. Pain sensitization is considered to develop partly because of persistent

pain that acts to lower pain thresholds, and partly because of increased mental vigilance [32,33]. Different types of inflammation are contributing factors in the development of persistent central sensitization, and research has highlighted activation of the immune system, perhaps through interference from glial cells [34]. Trauma to the spine and stress in the medical sense can contribute to the development of central sensitization [34–36]. Such persistent sensory dysregulation is believed to be possible for all sensory stimuli, as in fibromyalgia [37]. To standardize understanding of the presumed discrepancy between perceived pain and identifiable tissue pathology, the term “nociplastic pain” [38] has been introduced, describing pain characterized by an altered nociception.

Research has shown that these patients rate their quality of life as very low [39]. Of course, disease reduces body functions. The experience of increased bodily limitations can produce a feeling of hopelessness and loss of meaning. As the body changes, experience of the world changes and can leave the patient feeling alienated and alone with less motivation to live [40,41].

1.3 Disease as a biopsychosocial construct

Health issues are considered to arise and be maintained in a biopsychosocial context [42]. Apart from the pathophysiology (biomedical aspect), the psychological (e.g., fear of movement) and social parts (e.g., support from others), with a behavioural and chemical impact on the nervous system, may either facilitate or suppress symptoms and disability [43–45]. Combinations of stressors can throw the autonomous antagonist systems of the sympathetic and the parasympathetic and their substances out of balance, and lead to persistent fatigue and pain [46–49] (Figure 1). Prolonged dysautonomia has been associated with central sensitization and post-exertional malaise [50].

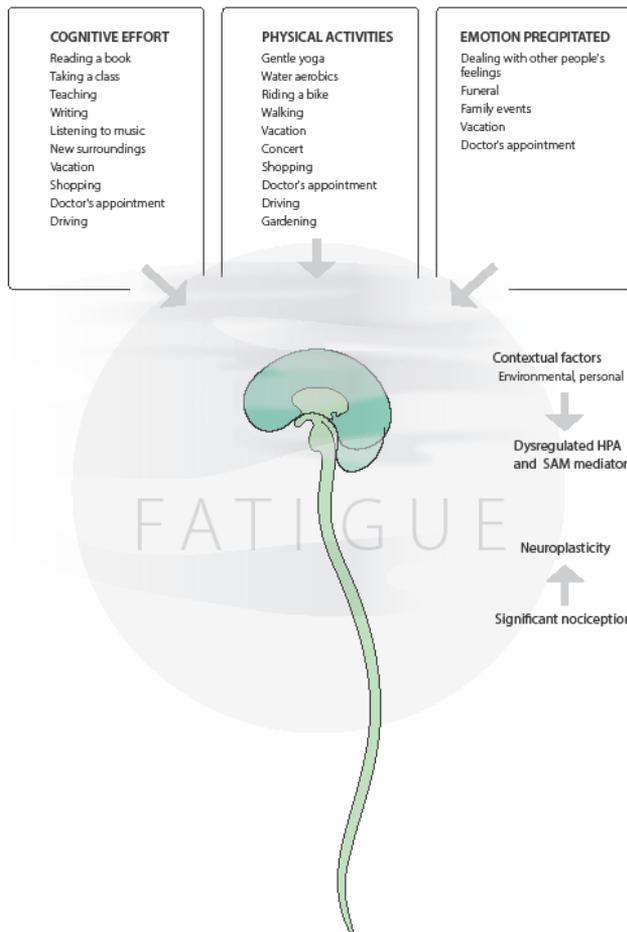


Figure 1. A diagram of the biopsychosocial etiology of persistent fatigue and pain and significant mechanisms of pathophysiology. Activity of pain pathways and pathways of responses to stressful external stimuli upset homeostasis of the nervous system. Upper part of figure shows examples of stressors (cognitive effort, physical activities, emotion precipitated) that can cause exacerbation of fatigue (post-exertional malaise) according to Stussman B, Williams A, Snow J, Gavin A, Scott R, Nath A, et al. Characterization of post-exertional malaise in patients with myalgic encephalomyelitis/chronic fatigue syndrome. *Front Neurol.* 2020; 11: 1025 [25]. The concept of contextual factors as a determinant of health from the ICF [42]. HPA = hypothalamic–pituitary–adrenal. SAM = sympathetic–adrenal–medullary. Illustration: Airi Iliste

1.4 Liabilities of hypermobility

A person's phenotype is a determinant of health [51–53]. Individuals with overly elastic connective tissue are among those most likely at risk of developing persistent fatigue and pain, as described below.

Muscle aches (myalgia) arise from prolonged static muscle work, which is common for those who have to compensate with the musculature for weak or compromised joint stability. When motor units are contracted generally for a long time, as with static work, the resulting increased intramuscular pressure hampers blood supply to the muscle (ischemia) resulting in oxygen depletion (hypoxia) [54]. Prolonged low-intensity static muscle work leads to metabolic crisis and neurogenic inflammation. Substances (prostaglandins and cytokines) that can sensitize muscle nociceptors are released, and a normally high threshold for the nociceptors is lowered (peripheral sensitization) so that they are more easily triggered [55–57].

Hyperactivity of the pain system, central sensitization. Spinal trauma and emotional stress are thought to contribute to the development of central sensitization [34,35] and are likely overrepresented among patients with overly elastic connective tissue [58]. Prolonged nociception, inflammation, negative expectations (fear, anxiety) and nerve damage can act in facilitating pain with control from the periaqueductal grey and the rostral ventromedial medulla [59]. Instability in joints can cause glutamate-mediated hyperactivity in secondary pain neurons in the spinal cord from repeated stimulation of afferent fibres of mechanoreceptors [60]. Stretching the collagen fibres in the facet joint capsule in the cervical spine beyond the physiological range of motion initiates nociceptive signalling, considered to eventually cause modifications in neuronal signalling that can lead to both acute and persistent pain [61,62]. Consequently, this group can exhibit the cardinal symptoms of various "central sensitivity syndromes", such as jaw pain, post-exertional malaise, brain fog or impaired bowel function/miction [63–65].

Disabled pain-inhibiting networks (disinhibition). Pain depends on the balance between activity in the facilitating system (mediated mainly by cholecystokinin) and the pain-inhibiting systems (mediated primarily by opioids) [66]. Reduced attenuation for patients with systemic joint laxity also can be central to maintaining widespread pain in this group. Mechanisms in part may relate to the fact that proprioceptive stimulation has an anti-nociceptive effect (i.e., the gate control theory) [67]. Some tissue properties may partially deprive these patients of endogenous pain suppression, including reduced joint sense, decreased total muscle work in case of minimized daily physical activity, or weaker torque/contraction in a muscle where the connective tissue components have a pronounced elasticity [68,69].

With a propensity to develop fatigue and pain and without some typical endogenous pain regulation, "net pain" would be aggravated among those who have these features. Whether such characteristics really are overrepresented among those with persistent fatigue and pain is not well researched, however. The lack of information is mainly the result of the multifaceted histology, which has yielded poorly defined research populations and compromised the transferability of research results [70]. Still, neuropathic pain is most likely a common trait in the clinical presentation of these patients [71].

1.5 Gender perspectives on persistent pain

More women than men have persistent pain [72]. Approximately 75 % of patients with ME/CFS are women [26,73]. Gender has been conceptualized as a process where social identities are created, then ranked and valued differently [74]. These identities in turn act to form exposures and health behaviours [74,75]. Gender bias has been proposed as a factor in diagnostics, especially in the patient-caregiver contact when data are to be interpreted and where the more neutral/biomedical body is out of focus [76]. This issue involves both men and women, but more often women and non-binary people [77]. In 2019, Nature Communications published a study analysing healthcare data for almost 7 million men and women in the Danish healthcare system over a 21-year period. The study showed that women were diagnosed later than men across 700 examined diseases [78]. In primary care, very little research has addressed how to avoid gender bias [76] (the gap is considered in this sector not to lie with gaps in data collection, which indeed may be more comprehensive for women; research there thus has been said to have a greater chance than other healthcare areas of reflecting women's health issues) [76]. A lack of patient-centred care for women has been reported [79]. Despite proven differences when it comes to women's health and lobbying to improve women's health, a long road remains to achieving fully patient-centred care for women who have conditions of persistent fatigue and pain.

1.6 Patient-centred care in the clinical consultation

The most important part of clinical diagnostics is the patient's story [80]. The verbal account of experiences of illness proposes pathological mechanisms. Legitimization of patient narratives has historically tended to depend on whether the details could be linked to pathology [81]. The consequent management depended on symptoms being confirmed as "real" and if they could not be, symptom reports could be more or less dismissed and neglected clinically (i.e., "Invalidation") [82]. The complex clinical presentation of persistent fatigue and pain, for example in fibromyalgia and chronic low back pain, may be met by this approach although it is not consistent with available evidence or the biopsychosocial models of practice [81,83–86]. Many clinicians still find it challenging to accept pain without a clear link to pathology [87].

A faulty diagnosis has been identified as the most common cause of harm by the healthcare system (patient harm) in primary care [88]. Of influencing factors, approximately 72% were found to be patient-related and concerned traits that also define the group with persistent fatigue and pain such as multi-morbidity, fragility and the complex nature of a disorder [88]. Nerve involvement that manifests in persistent fatigue and pain may be overlooked in the clinical assessment, not unlike in circulatory conditions in which disrupted blood supply can manifest as various other medical conditions [89]. A common example is nerve involvement in the cervical spine, which can be misinterpreted in clinical assessment as shoulder problems [90]. Other relevant examples are multiple sclerosis [91], thoracic nerve involvement [92], postural tachycardia syndrome [93], and dystonia [94]. A faulty diagnosis may pass as a temporary inconvenience for a patient, but for some it can have a serious impact by diverting them to a path of self-care that may undermine health. Ethical principles guide behaviour towards patients, stated in terms of autonomy and "not doing harm" ("The risk of harm in the investigation must be no greater than in ordinary life") [95].

In ensuring patient-centred care the caregiver's role has been defined primarily as being supportive and trying to understand the patient's life [96], as well as respecting their dignity [97,98] and can be brought into praxis from active listening [99,100]. Healthcare-seeking primarily sorts into the psychosocial domain within the biopsychosocial perspective on pain; purely physical (biomedical) reasons for consultations are a motive, but once you know the cause of your symptoms, even when they are pronounced, many refrain from seeking medical care [101]. Rather, worrying about the symptoms is often the main reason for seeking care [102]. If the caregiver focuses only on the physical aspects and does not address other concerns, the patient will feel that they were not properly treated, despite an otherwise correct consultation [103]. The most important factor in the health care consultation is probably relational, to be seen and respected by the caregiver [104,105].

Requirements for delivery of healthcare are phrased in terms of patient-oriented care, but the conditions are financial, necessitating efficient management [106]. Thus, investigative methods are needed for conditions of persistent fatigue and pain that can successfully register and accurately interpret the patient's narrative without being cost-prohibitive.

1.7 Clinical screening

The clinical assessment of musculoskeletal pain must always include a pain classification [107], which is key to success in diagnosing the condition. Here, listening to the patient is central for mapping the symptom profile and can spare them from superfluous examinations and consultations [108]. E-health has contributed to labour-saving data collection methods in which some of the interaction with healthcare is web-

based. Research indicates that improved accessibility and less stress in web-based history taking means strengthened patient empowerment and patient-centredness, which are important benefits for the patient group described here [109]. To what extent primary care performs structured assessments for patients with persistent fatigue and pain is unclear [110], but research emphasizes the time shortage [111].

Screening is not equivalent to diagnosis but is a way to identify people who are likely to have a condition, such as cervical nerve involvement. Guidelines support use of screening for severe conditions, i.e. that cause significant limitations, and for conditions that have a high prevalence at the preclinical stage, both of which are true for hypermobility and headaches [112]. A screening tool must have sound measurement properties, be easy to administer, and be inexpensive. For screening to be appropriate, an approved and effective treatment must be available for the illness in question. This requirement reflects well the conditions of systemic joint laxity and emerging persistent fatigue and pain, where early administered adequate treatment can be very helpful [24].

1.8 Pain drawing

The pain drawing is a cornerstone of clinical assessment [113]. Its primary role is to form the basis of pain classification, and a first step is deciding whether the pain is neuroanatomically represented [114]. The pain drawing was initially scientifically evaluated around 1950 [113] and for a long time only gave information about pain location and distribution. Instructions for completing it varied. Pain could be indicated approximately with an X or a body part could be circled or shaded, leaving considerable room for interpretation [115]. Pathognomonic descriptors have been included in some drawing designs (e.g., burning, shooting) for neuropathic pain, although a patient typically uses several different descriptors to describe their pain, sometimes overlapping for neuropathic and nociceptive pain [116].

Digital applications on smartphones and tablets are considered similar to paper drawings in terms of measurement properties [117]. In addition, digital solutions have helped to quantify pain, showing that the number of marked body regions could be linked to disability [118] and have aided in the discovery of pain patterns of use [119].

1.9 Conceptual basis for this thesis

The interpretation of results in this thesis has theoretical underpinnings in the International Classification of Functioning, Disability and Health (ICF) [42]. As a framework, ICF has complexity as well as specificity and enables understanding a condition from new perspectives (Figure 2). This framework enable a systematics of the biopsychosocial definition of health for clinical observations and where the various components related to health are coded [42].

The components of the ICF are grouped into two categories, (1) Functional state and disability (consisting of the component body structures, activity and participation) and (2) contextual factors (consisting of personal and environmental factors) that interact. If one component is affected, it can change another component or the disorder.

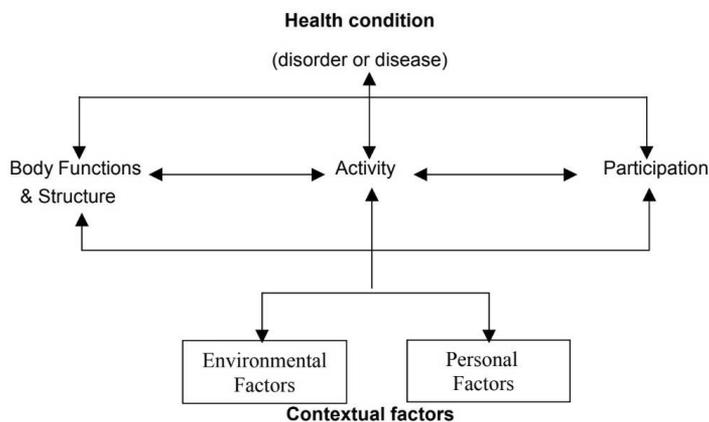


Figure 2. Interaction within the individual's health context, according to the International Classification of Functioning, Disability and Health (ICF) [42].

To contextualize the findings, two more theories are used. The second theoretical basis is a framework for patient-reported outcome measures (PROMs) [120]. This framework provides perspectives for unifying the questions examined in this work through the assumptions of quality concepts for both screening tools and the patient-caregiver interaction. Subjective outcomes in the clinical assessment cannot be defined unambiguously with the laws of physics, and guidelines for their measurement thus are more like recommendations. When PROMs are used quantitatively, this framework advises taking into account a need for an ongoing evaluation to better understand both the instrument's validity and the question design. According to McClimans and others, PROMs would ideally be instruments made to facilitate or strengthen a genuine dialogue about self-perceived health, and not be about promoting predetermined judgments (described as quasi-questions) [120]. This concept relates to Hans Georg Gadamer's logic for questions and answers and addresses the issue of PROMs being only partially validated and lacking a gold standard [120–122].

A third theory serving as a basis for this work is the multimodal assessment model of pain (MAP) [123]. It was chosen as the study population's perhaps most important characteristic vis-à-vis diagnostics being of subjectivity in disorders. MAP, in short,

assumes that the patient's narrative of the condition is the best possible proxy for a diagnostic gold standard; that the experience itself cannot be measured but that some manifestations of a condition are measurable; and that qualitative and mixed methods have a unique ability to provide access to the subjectivity of the condition and thus offer great value. Wideman et al. argues that previous theory has not been clear about how different types of assessment relate to the subjective experience of the condition. In other words, there has been a lack of consideration of what can be uniquely accessed through qualitative forms of assessment such as conversation and listening. The MAP framework builds on the biopsychosocial model with the aim of bridging the dividing line between purely objective measurements and the patient's story. Doing so can, according to Wideman et al., counteract the risk that well-validated pain experiences are expected to be closely linked to identification of the underlying causes, with the result that patient reporting without this correlate would be ignored. Wideman et al. saw the clinical assessment as encompassing the pain experience (not measurable), pain manifestations (can be followed with qualitative measures), and measures of pain (quantifiable), as well as the interaction between the patient-as-sender and the assessor ("third-person perspective ") (Figure 3). This concept parallels PROMs being seen as conversations [120].

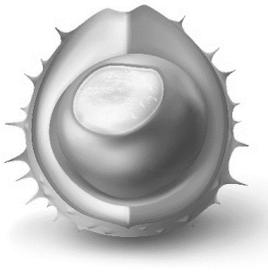


Figure 3. The MAP illustration of the preferred assessment situation of the individual with persistent fatigue and pain, modified after Wideman et al. [123]. The core would represent the pain experience (not measurable), the shell corresponds to pain manifestations (can be surveilled with qualitative measures), and thorns correspond to pain measures (quantifiable). The model of Wideman et al. also includes the assessor who stands on the side-lines and observes/measures (not shown in above figure). Image by macrovector on Freepik.

1.10 Rationale for this thesis

The inspiration for this PhD project came from an intersection of some clearly distinguishable medico-societal currents: Hampered functioning from fatigue and pain is common, as are patients' subsequent significant, related concerns; despite

technologization, most results from medical and healthcare very much depend on the “human factors” (of patients and of personnel); and a strained healthcare sector means that many patients could be directed toward a harmful everyday life more or less unnoticed. An aim of healthcare is for its provision to be equal for all. In the clinic, however, realizing equal healthcare means prioritizing seeing people's differences, as there are as many phenotypes of humans as there are humans. Perhaps the most common questions in the initial physiotherapy consultation from patients with the health issues described here are, “What type of exercise is good for me?” and “What should I avoid?” Most people are aware that a healthy amount of stress hones the system, even though the optimal dose varies. Proper management for the complaints of patients with persistent fatigue and pain calls for an easily administered assessment of musculoskeletal phenotype and whether symptoms trace to any neuropathies. Such an assessment can go a long way toward ensuring adequate interventions. The Beighton score and PROMs, especially in the form of a pain drawing, are investigated in this thesis to address the shortage of evidence with the goal of contributing to the clinical decision-making for patients with persistent fatigue and pain.

2 Research aims

The overarching aim of this doctoral project was to investigate key clinical tools used in the assessment of patients with persistent fatigue and pain, such as ME/CFS. The specific aims of the studies were to:

- evaluate the Beighton score's performance in screening for systemic joint laxity among patients with suspected ME/CFS. (Study I)
- investigate the pain drawing's performance in screening for cervical nerve involvement among patients with suspected ME/CFS by means of estimating any relationship between occurrence of dizziness/imbalance and a presumed C2 involvement. (Study II)
- investigate and compare self-perceived health-related factors in the population with suspected ME/CFS – a comparison of those diagnosed with ME/CFS and those who did not receive this diagnosis. (Study III)

3 Materials and methods

3.1 Study sample population

All three studies involved patients 18 years or older with suspected ME/CFS who were referred from primary care to the specialist clinic to undergo an investigation for ME/CFS. During the period of data collection, February 2019–February 2020, a total of 278 patients were eligible for the project, of whom 149 patients qualified for study I (Table 1). Study II included the 275 patients who submitted a completed pain drawing and had had a first physician consultation. Study III included 262 patients who completed questionnaires for health-related factors. All data were collected prior to the diagnosis assessment.

The number of participants to include was based on requirements for the pain drawing. The power calculation relied on estimates of a ~50 % prevalence of neck-arm symptoms in the population (in the general population about 25 % among women and about 15 % among men) [124]. A CI of 0.20 both ways was expected for the kappa values. Good agreement was predicted between the pain drawing and the neurological examination, with a kappa value of about 0.7, as was an inferior agreement between the pain drawing and MRI, with a kappa of about 0.5. Based on these parameters and margins for dropout of participants, approximately 270 participants were planned in total.

3.2 Beighton score

The Beighton score was developed as an instrument adapted for use in large groups for the assessment of overly elastic connective tissue in general [125]. It is practical and suitable for screening. In total, 9 points are possible, which would be interpreted as a physique with pronounced systemic joint laxity. A physique with a standard type of connective tissue has been defined by a Beighton score of 0–2 points [126]. No consensus exists for optimal thresholds, and different point limits have been recommended, e.g., the recommended threshold according to the 2017 international classification of Ehlers–Danlos syndrome is ≥ 6 for prepubertal children and adolescents; ≥ 5 for pubertal boys and girls and men and women up to 50 years; and ≥ 4 for those age > 50 years [127].

3.3 Dizziness/imbalance

Dizziness or imbalance was assessed from the patients' medical files [128]. Examples of file notes of verbally reported dizziness/imbalance by the patient at the first visit to the physician (different physicians): "All along he has had [...] and balance issues", and "Bouts of dizziness".

Table 1. Overview of studies I–III.

	Performance of Beighton score and pain drawing		Health factors in the study group
	Study I	Study II	Study III
Design	Observational diagnostic study	Cross-sectional correlational study	Cross-sectional comparative study
Participants Mean age, years (SD)	Patients with suspected ME/CFS		
	Total (149): 45.5 (11.2)	Total (275): 45.8 (12.2)	Total (262): 45.7 (12.0)
	Women (137): 45.6 (11.1)	Women (227): 45.2 (12.0)	Women (219): 45.2 (12.1)
	Men (12): 44.0 (11.7)	Men (48): 48.7 (12.8)	Men (43): 47.9 (11.4)
Data collection	Semi-structured history taking, screening with Beighton score	EQ-VAS, VAS, retrieval from patient files, screening with pain drawing	Questionnaires*
Data analysis	Cohen’s kappa, Spearman’s rho, sensitivity, specificity	Logistic regression, Kruskal-Wallis test	Mann-Whitney U test, Chi-square test, Student’s t-test, regression analysis

EQ-VAS = EuroQol 100 mm vertical visual analogue scale. ME = myalgic encephalomyelitis. CFS = chronic fatigue syndrome. VAS = Visual analogue scale. * Physical activity questionnaire, Work Ability Index (WAI), Hospital Anxiety and Depression Scale (HAD-A/HAD-D), RAND-36.

3.4 Patient-reported outcome measures

The prevailing definition of health, according to the World Health Organization, is health as a “physical, mental and social well-being and not merely the absence of disease or infirmity” [51]. PROMs offer a way to clarify health issues from the patient’s perspective. According to the U.S. Food and Drug Administration, a PROM is a report on the status of a patient’s health that comes directly from the patient, without interpretation of the account by a clinician [129]. PROMs are tools that measure a patient’s perceived symptoms, functioning, or health-related quality of life [130]. PROMs thus are important because they can enhance clinical decision-making.

3.4.1 EuroQol vertical visual analogue scale

Self-reported current health status (health-related quality of life) was assessed with a paper version of the EuroQol 100 mm VAS (EQ-VAS) with the endpoints 0 = “worst imaginable health” and 100 = “best imaginable health”, generally considered to have acceptable validity and somewhat uncertain test-retest reliability [131,132].

3.4.2 Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) consists of two subscales: HADS anxiety/worry and HADS depressiveness/depression, which screen for anxiety symptoms and depressive symptoms, respectively [133–135]. Evidence for its psychometric properties is solid [136,137]. The subscales have seven statements each (a total of 14 claims), relating to the preceding week, and responses are given on a four-point Likert scale that can generate between 0 and 3 points (maximum 21 points per subscale). The total score translates to any of three “risk levels”: low, moderate, or high risk of depression or anxiety of clinical importance. The recommended threshold has been set at 8 [136,137]. Totalling 11 points or more on a subscale likely implies a condition of clinical significance [137]. Scores between 15 and 21 are interpreted as severe anxiety or depression. We used the respondent’s average value on the subscale for dropout and allowed a maximum of two items per subscale [138].

3.4.3 Physical activity

Physical activity was measured as the total amount of physical activity per week, for different aspects [139]. The first question indicates how much time the patient spends in high-intensity activity, and the second question addresses moderate intensity, i.e., practicing daily physical activity. Fixed answer options are used (time categories). The two results are merged into an outcome of “activity minutes” (150 activity minutes or more per week is the recommended level). The form has been evaluated for psychometrics and was found to be equivalent to other self-reported questions about physical activity [139].

3.4.4 RAND-36

RAND-36 (formerly Short Form-36, or SF-36) was used to measure self-perceived health [140,141]. It is intended to reflect health according to the WHO. The instrument has eight subscales with a total of 36 multiple-choice questions and is considered to have adequate measurement properties [140,142]. The eight subscales are Physical Function, Role Limitations Due to Physical Health Problems, Role Limitations Due to Personal or Emotional Problems, Social Function, Energy/Fatigue, Bodily Pain, Emotional Well-Being, and General Health. These each give an outcome or index of 0–100 %, where 100 % is

interpreted as excellent health. (Emotional well-being and energy/fatigue have sometimes been expressed as general mental health and vitality, respectively). Loss of items was not taken into account in the calculation, and the subscale index thus represents the average value of the items answered. We allowed one missing item per subscale [140].

3.4.5 Visual analogue scale

Data on patients' current pain intensity was collected with a paper version of the 100 mm visual analogue scale (VAS): endpoints 0 = "no pain" and 100 = "worst possible pain" [143] The instruction read, "How much pain are you experiencing at this moment? (Please mark with an X on the line)".

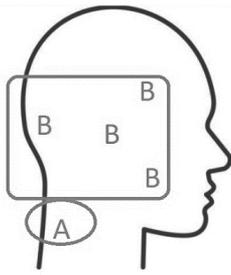
3.4.6 Work Ability Index

The Work Ability Index (WAI) was designed for screening for ill health in workers [144]. It consists of 10 questions for seven domains [145,146]. In the present project, only the first question, WAI 1, was used, which asks the respondent to estimate on a scale of 0–10 self-perceived work ability in the present compared to their lifetime best ability. WAI 1 also has been validated for use as a proxy for WAI [147–149]. Thresholds for classification of work ability are usually given as follows: poor, 0–5; moderate, 6–7; good, 8–9; and excellent, 10 [147].

3.4.7 Pain drawing

A paper pain drawing with the human body as a silhouette (frontal and dorsal view) was used to assess headaches and pain distribution (in the same drawing). All markings by the patient for the head, including the scalp and face, were interpreted as a headache. For a standardized reading for intended screening for C2 involvement, a template with C2 pain patterns was developed [150] (Figure 4). A confirmed C2 pain pattern meant that two criteria (A and B) were met (Figure 4): There must be neck pain (criterion A), and either the back of the head or the side of the face (temple/ear/jaw) must be marked (criterion B). The patients were then grouped based on the pain drawing into three categories: 1) cervical headache in accordance with the specified C2 pain pattern, 2) headache without C2 pain pattern, and 3) no headache.

Possible body pain extent was assessed using the body region method by Margolis [151] in which each region (45 in total) is assigned a percentage area, and areas are summed to a score of 0–100 %.



Criterion A:

Upper half of the neck, bordering to the head (dorsal view of the drawing)

and

Criteria B:

B) lower half of head (dorsal view)

B) side of head: temple or ear or jaw (front view)

Figure 4. Standardized C2 pattern pain drawing key. From, Bernhoff G, Huhmar HM, Rasmussen-Barr E, Bunketorp Käll L. The significance of pain drawing as a screening tool for cervicogenic headache and associated symptoms in chronic fatigue. *J Pain Res.* 2022; 15: 2547–56 [152].

3.5 Measurement properties

Study design was considered with a view to consequences for the relevance of the outcome after statistical processing. In studies I and II, variables were defined from a statistical perspective (theoretically, operationally), with a pre-analysis depending on the instruments' application and context [154]. The clinical questions addressed the benefit of screening to detect indications of a neuropathic disorder. The research question in turn was about the measurement properties of screening tools, so the operational definition was joint range of motion, pain localization, and body pain extent. This definition determined the statistical properties of the data and thus methods suitable for analysis (Figure 5). For example, where screening with pain drawing was aimed at grouping individuals by having headache/no headache, the patient markings were categorized as ordinal data

3.5.1 Measurement reliability: criterion validity

Robustness of psychometric properties is a prerequisite for clinical tools to be reliable, i.e. useful in decision-making [130,155]. Validity was previously seen as a property of test tools but is now viewed as an evolving judgment on the extent to which accumulated evaluation supports intended interpretation in a given context [156]. Criterion validity is the agreement between operational definitions of an outcome – for the measurement that one intends to evaluate versus an established and proven measurement method intended to measure exactly the same thing (gold standard). In study I, criterion validity was agreement between the studied definition for determining systemic joint laxity in a standardized screening and the comprehensive routine expert assessment. In study II, relevance (validity) of a standardized reading with a C2 pain pattern was studied with an agreement analysis and the spontaneously reported dizziness/imbalance as a proxy

operational definition of gold standard. The goal was finding procedures that could realize more of the pain drawing’s diagnostic potential.

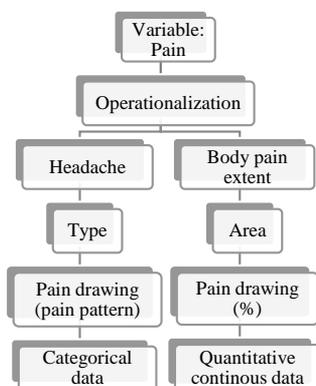


Figure 5. Data characteristics derived for analysis from the studied clinical variable pain.

3.5.2 Measurement stability: repeatability

Inter-rater reliability is a prerequisite for validity and refers to the degree of consensus between assessors who test the same phenomenon independently (reproducibility) [157]. The outcome value describes the deviation of test results when the same test is measured repeatedly, but with changed measurement conditions (assessor). Clearly stated criteria, as with the Beighton score and the pain drawing patterns used in these studies, are necessary for measurement stability to aid in ambiguous measurement scenarios. Otherwise, the observer is believed to drift in judgement towards what they expect. When the number of categories used is small (2 for paired data), the likelihood of two raters agreeing by pure chance increases, so coefficients corrected for chance were used.

3.6 Study I

In this study, Beighton score was investigated for its diagnostic ability on its own in screening for overly elastic connective tissue manifesting as systemic joint laxity in patients with suspected ME/CFS (Table 1). Inter-rater reliability of the Beighton score also was assessed. Clinical identification of the phenotype of overly elastic connective tissue can allow for preventing degeneration and nerve involvement by adaptations to avoid unfavourable stress or load pattern. The performance of the Beighton score alone was explored with a group of patients from the cohort of those enrolled at the clinic for investigation for suspected ME/CFS. The study was intended to investigate the concordance between the screening (often considered decisive in assessing for

systemic joint laxity) (evaluated in terms of cut levels normally applied in praxis; i.e., dichotomous outcome of 3-, 4-, and 5-cut level) against the gold standard of comprehensive expert assessment. The study was carried out in a routine examination. There is also a general assumption that the performance of the Beighton score could be weaker when used for clinical decision-making than for research purposes, as the latter would require skill and experience in using the method. Field studies provide insights into the actual performance of a structured assessment of hypermobility and help expose factors that affect reliability. Thus, two caregivers from different professions conducted a parallel assessment as part of the investigation routine, evaluated with Cohen's kappa for agreement and with sensitivity and specificity.

3.7 Study II

For study II, the pain drawing was evaluated as a screening tool for signs associated with neuropathic pain/cervical pain (Table 1). The aim of this observational clinical study was to estimate the relationship between exposure in the form of C2 influence and the occurrence of dizziness as an outcome. To achieve this aim, the strength was calculated by determining the odds ratios (ORs) for patient-reported "C2 pain" and dizziness/imbalance. Any co-occurrence of ORs also alternatively could be taken to indicate the relationship between the probability of dizziness/imbalance occurrence versus non-occurrence. Logistic regression analysis was applied, with confidence intervals (CIs) and p values used to interpret whether random errors had an impact.

3.8 Study III

The third part of the thesis was a continuation of the study of PROMs, examining their information value in diagnostics. Possible differences were surveyed between two similar population subgroups (Table 1). The study was justified based on a lack in the literature of comparisons between the associated conditions of persistent fatigue and pain for self-perceived health. The aim of study III therefore was to broaden the factual basis of health-related factors in the investigation of ME/CFS for both clinic and research purposes. Clinical questions addressed whether the results from different measures of self-perceived health could contribute to diagnostic precision in persistent fatigue and pain, and whether self-perceived health varies enough between groups to justify considering it in the planning of interventions. The study design was a comparison of two clinical groups with suspected ME/CFS, one group that was subsequently diagnosed with ME/CFS and another that was not. The data collection took place in connection with the routine clinical investigation by means of questionnaires. The results were evaluated using non-parametric analyses because variables for self-rated health are rarely normally distributed in these conditions, and the groups were compared.

3.9 Ethical considerations

All studies were conducted in accordance with the Declaration of Helsinki and were granted ethical permission by the Swedish Ethical Review Authority (Diary No. 2018/1754–31 and 2022–00868–02) [158]. Risks of participating were deemed low and concerned transient symptoms such as tenderness and dizziness associated with the clinical examination. Furthermore, some medicalization of perceived health was anticipated from what emerged during the study (e.g., information about the onset of narrowing of the spinal foramen), which could have negative consequences (e.g., fear of movement). However, this group was considered to have already been exposed to lasting medicalization from continuous contact with the healthcare system. Also possible, however, was developing an increased sense of self-efficacy and freedom of action from obtaining additional information through participating in the project.

4 Results

4.1 Study I

The analysed group for study I consisted of 149 patients, all screened for hypermobility by both a physician and a physiotherapist. Incomplete cases (n = 91) in which there was no second screening were ruled out, so that there may have been a discrepancy between what emerged and the outcome from the population as it would have been if it were complete. The mean age of the analysis group was 45.5 years (range 21–74 years), and the proportion of women was 92% (n = 137) (Table 1). Screening with the Beighton score alone did not appear to have “diagnostic ability” when evaluated against the gold standard chosen for the study (comprehensive expert assessment). The prevailing dichotomized interpretation of the Beighton score was analysed for different cut values. When a cut value ≥ 3 was used as an indication of systemic joint laxity, the percentage agreement between the physician’s assessment with the Beighton score and the physiotherapist’s integrated assessment was 74%, with a kappa of 0.39, interpreted as weak agreement. When a higher threshold was applied, the agreement was similar, as shown in Table 3.

Inter-rater reliability outcomes added to the evidence of an acceptable measurement stability of the Beighton score performance: Similar outcomes could be obtained in the current study, despite a clinical setting, in terms of no joint training in the screening and with assessors from different professions. Inter-rater reliability was moderate (rho 0.66) when a categorized outcome for the sum score was used. A dichotomous interpretation with a cut value ≥ 5 showed moderate agreement as well (percentage agreement 81% and kappa 0.61). However, when applying a cut value ≥ 4 , agreement was weak (percentage agreement 74% and kappa 0.43).

Table 3. Estimates of criterion validity of the Beighton sum score in the assessment of systemic joint laxity, using different cutoff values, with a routine comprehensive assessment as gold standard.

Cut level	Percent agreement	Cohen’s kappa	Sensitivity	Specificity
≥ 3	74 %	0.39	92 %	43 %
≥ 4	73 %	0.39	85 %	52 %
≥ 5	73 %	0.45	71 %	77 %

4.2 Study II

Study II participants' characteristics are shown in Table 1. For 96% of the drawings, the researchers agreed in their interpretation using the standardized C2 pain pattern template. Presuming cervicogenic headache according to the pain drawing, a C2 pain pattern was common in the study group (found for 116 patients, 42%), and dizziness/imbalance occurred more frequently in this group. The dizziness/imbalance association with the C2 pain pattern was strong compared with the non-headache group: OR 6.50 (95% CI 2.42–17.40, $p < 0.001$). Even compared to the group with other headaches (no C2 pain pattern), the association was significant and clear (OR 3.15; (95% CI 1.54–6.41, $p = 0.002$). No effects on the outcome could be observed from sex, age, pain intensity, and pain distribution ($p > 0.05$). The broad CI reflected the relative occurrence of events within the sample. Regarding other types of headache (no C2 pain pattern), the odds of dizziness/imbalance were higher than for those with no headache, but not statistically significantly so. Of the study population, 25% had indicated dizziness/imbalance during the first physician consultation.

Furthermore, the symptom picture was more severe for the group that reported a C2 pain pattern: Pain intensity was higher (VAS median 66.5 mm, range 49.0–79.0), and pain distribution was more extensive (61.4%, range 44.6–76.3) than in both other groups (Table 4). Reported quality of life was lower (EQ-VAS median 26.5 mm, range 20.0–38.3) than for those who had no headache according to the pain drawing ($p < 0.001$) (outcomes for quality of life not significant for comparison with the subgroup with other types of headache and no C2 pain pattern). Missing data consisted of 30 reports (11%) of self-rated quality of life and 4 reports of pain intensity (1.5%).

4.3 Study III

In study III, 262 patients were included, of whom 205 (78 %) were diagnosed with ME/CFS at the specialist clinic. The amount of missing data was $< 10\%$ for all variables. Missing cases were not included in the analyses. Measurement of the various health-related factors showed that the group diagnosed with ME/CFS was distinct from the group without an ME/CFS diagnosis established by impairments in physical or mental effort (measurements of physical and social functioning and energy), worse pain, and worse general health ($p \leq 0.05$) (Figure 6). Apart from significant associations with the ME/CFS diagnosis, the reported health factors were generally not associated with demographics, with some exceptions: RAND physical functioning and bodily pain were associated with sex, and general health was associated with age. No significant between-group differences were found, however, regarding assessed activity in minutes per week, work ability, anxiety/depression, emotional role limitation, and well-being ($p > 0.05$).

Table 4. Presentation from study II of between-group differences for pain and health-related quality of life. Subgroups based on the pain drawing [152].

Patient-reported outcomes	1 Headache with C2 pain pattern n = 116	2 Headache (no C2 pain pattern) n = 86	3 No headache n = 73	P-value (between groups)
Pain intensity, VAS (0–100 mm) Median (IQR)	66.50 (49.00–79.00)	48.50 (31.00–65.25)	40.00 (19.00–57.00)	1–2 < 0.001 2–3 0.066
Body pain extent, BPE (0–100 %) Median (IQR)	61.38 (44.62–76.31)	46.25 (28.19–64.31)	31.50 (15.50–51.00)	1–2 < 0.001 2–3 0.002
Health-related quality of life, EQ-VAS (0–100 mm) Median (IQR)	26.50 (20.00–38.25)	30.00 (20.00–40.00)	35.00 (25.00–50.00)	1–2 0.069 2–3 0.039

BPE = body pain extent. IQR = inter-quartile range. VAS = visual analogue scale. EQ-VAS = EuroQol vertical visual analogue scale.

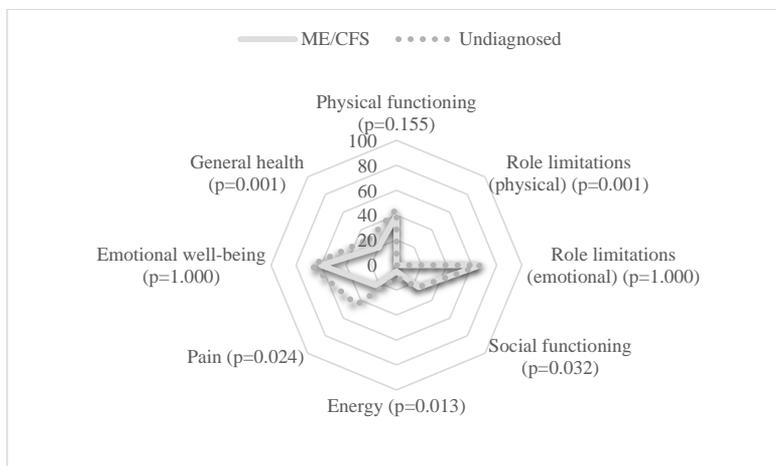


Figure 6. Self-perceived level out of the best possible level (100 %), for the factors measured with RAND-36, with between-group differences for physical functioning, energy, pain, and general health. Data shown are group median percentage. From

Bernhoff G, Rasmussen-Barr E, Bunketorp Käll L. A comparison of health-related factors between patients diagnosed with ME/CFS and patients with a related symptom picture but no ME/CFS diagnosis: a cross-sectional exploratory study. *J Transl Med.* 2022; 20(1): 577 [159].

5 Discussion

5.1 Summary of the main results

This thesis aimed to study measurement properties of the Beighton score (paper I), after which the pain drawing in relation to cervicogenic headache was focused for a standardized method of reading (paper II). Lastly, the self-perceived health from a diagnostic perspective was studied in the population of patients with persistent fatigue and pain (paper III).

Regarding whether the Beighton sum score accurately reflects the presence/absence of systemic joint laxity, with the overall assessment as gold standard, results showed a weak relevance for this intended purpose even if the screening showed a fair interrater reliability. An implied accuracy, however, was found for the standardized C2 pattern pain drawing key among patients with persistent fatigue and pain. The pattern was supported in part by the relationship between dizziness/imbalance and the C2 pain pattern. Because the pattern also distinguished patients with comparatively more serious pain problems using the pain drawing, it could be argued that the pattern was condition-specific. Thus, the standardized reading might be helpful as a complement in investigations to understand more about the nature and degree of severity of persistent fatigue and pain, headaches, and associated disorders. "Field" inter-rater reliability was found to be acceptable for the Beighton score; the same seemed to apply for the double or parallel assessment made for the pain drawing (by means of a standardized reading). Such stability enables permanent use for bedside assessment. Study III indicated initial evidence that aspects of self-perceived health may to some extent reflect the diagnoses of ME/CFS. In line with some earlier research, the results supported the role of the RAND-36 subscales Physical role limitation and Social functioning for diagnostic use, as they showed outcomes that were consistent with the final diagnosis.

5.2 Theoretical integration of results

This thesis work contributes to the empiricism of assumptions about measurement qualities for some key instruments in the clinic. The aspects of measurement quality that were investigated in studies I and II were partly of a presumed diagnostic ability, i.e. the ability to identify systemic joint laxity and possible nerve involvement from the cervical spine, respectively. Measurement stability was investigated.

The correspondence between the Beighton sum score and the presence of systemic joint laxity was relatively weak in study I. In previous research, the usual thresholds for interpretation have not infrequently been used as a proxy for systemic joint laxity without problematizing its diagnostic ability. The variable "systemic joint laxity" in studies thus may have had an unclear definition, whereupon conclusions about those groups

lost some validity [160]. There are probably many different phenotypes with overly elastic connective tissue, which makes it a challenge to evaluate.

A suggested link between a C2 pain pattern and central sensitization emerged in study II, with a large proportion with neck pain in the study population. The C2 pain pattern seemed to reflect or indicate a condition in the upper neck, based on a clear association between the pattern and an impaired sense of balance and the ability of the pattern to identify patients with relatively more severe pain. Among other things, central sensitization involves increased pain sensitivity and generalized pain, which were implied in the pain picture to a significantly higher degree among those who reported a C2 pain pattern. Because central sensitization has been associated with status after neck distortion, such a relationship seems plausible for the group with presumed cervicogenic headache in study II. Why are such problems with hyperactivity in pain nerve pathways associated with cervical influence? Irritation of the spinal cord has been suggested as a significant factor in the development of central sensitization [36]. Other generally recognized triggers are joint degeneration, especially of spinal origin [34,35,62], and stress [161], which appear prevalent in the population with persistent fatigue and pain, and especially the subgroup that also has systemic joint laxity, offering a potential explanation [162,163].

Stress as a frequent facilitator of post exertional malaise (a manifestation of central sensitization) should be highlighted. According to clinical experience, the measured impaired physical function and energy level in study III could have served as a breeding ground for a “trap” for many: an unfavourable pattern of activity in daily life and non-functioning recovery strategies. This imbalance is believed to lead to continuous physiological stress and secondary dysautonomia [47,164]. The results of study III also fit logically within the interconnected ICF system, which constitutes a representation of health aspects according to the biopsychosocial model: Conditions with persistent fatigue and pain are characterized by a decrease in activity levels. It has been argued about chronic fatigue, fibromyalgia and WAD that they are so-called culture-bound diseases, which is true in the sense that they arise partly because of the near and social environment, but the discussion has often circumvented the search for pathological processes and the dyshomeostasis that gives the disease a bodily source [165,166]. The environments around the individual affect health and function, which is conceptualized within the ICF as contextual factors (Figure 2). At the same time, states of persistent fatigue and pain represent a heterogeneous phenomenon that includes multiple diagnoses or different degrees of severity of the same condition [23] making it complex and challenging to elevate to the general state of knowledge. Environments that are blind to a condition, i.e., not aware of its causes and manifestations and related function influences, can further burden the systems [14,78,88]. When it comes to contextual factors in the ICF, sex and coping strategies especially can be of great importance.

Women are more likely to develop these conditions than men – about 80% of the study population were women, which is consistent with previous research [26,73]. One hypothesis is that women have fewer openings for recovery in everyday life [167], and energylessness may mistakenly be considered natural for women because of how gender is encoded [168]. This situation could contribute to symptoms being overlooked as not disease-related. The impact of those close to the patient is also most likely of great importance for persistent fatigue and pain.

Below are some reflections on the instruments' ability to support a listening approach in assessment, an important aspect in assessment for the patient group. Structural or organ-related deviations can often be absent, but the narrative presented for assessment for the often shifting manifestations of the disease can be turned into a diagnostic concept. In particular, in study II, the results showed that when patients gave their statement about their condition within and to the healthcare system, to some extent they also expressed something about how the healthcare system listened to them. The pain drawing uses visual symbols for reporting. Often the patient adds instructions for the reader, such as explanatory words or short messages, that to some extent provide information about how the question in the form is asked. Theoretical work in clinical assessment highlights this aspect as valuable and even necessary for the development of measuring instruments.

PROMs play an important role in diagnostics of persistent fatigue and pain because symptoms are predominantly subjective and PROMs convey the health status that comes directly from the patient, without interpretation of the account by a clinician [169]. The standardization of data from PROMs, however generally creates an unwanted locked or artificial interaction, according to both McClimans and Wideman et al. [120,123]. A disadvantage, then, is that the usual mechanisms for controlling the intended meaning of questions are prevented. McClimans believes that data collected with a PROM should always be seen as incompletely understood. The same will then also apply to questions that have been asked. McClimans' theory – A theoretical framework for patient-reported outcome measures – instead advocates for an active and continuous evaluation of the questions asked in the clinical assessment. By processing the effects of the questions, eventually the right questions can be asked to generate the most relevant information in the investigation [120]. McClimans also argues that PROMs should not be locked or standardized, but like the pain drawing should ask the patient "genuine questions" – i.e., questions to which the answer is not known in advance, so that the question also will be open to reinterpretation. A genuine question is asked to better understand something that is not already known [120]. It is not the same as data being incomplete, but as a carrier of importance tied to the question. These frameworks describe the activity in which the patient fills out a questionnaire as primarily socially and contextually oriented, or more precisely as a conversation. Thus, PROM data are

considered to be produced socially, although recorded in a standardized and strongly limited way.

McClimans calls for genuine questions – in the sense that they may need to be revised – to estimate the subjective in the condition and prioritize the patient's narrative in the assessment. Wideman et al. does so, as well, stating that the narrative should be documented and used as a starting point for a well-considered triangulation for assessment instruments.

The pain drawing can meet these criteria for effective PROMs, and study II focused on standardized reading of the drawing. From the perspective of preferably using measuring instruments that ask genuine questions, the use of an interpretive template in study II can be said to be a variant of meeting that need: The pain drawing is allowed to be indefinite in both question and answer when submitted to the patient for completion, and by applying a template for reading, it operationalizes the theoretical basis of communicative capacity and transparency.

The problems of unclear context in PROMs has to do with the fact that the patient's story is not just raw data, but as a patient, one usually makes an effort to build a story that makes life's events understandable [170]. This can be highlighted by the so-called speech acts, most often described for oral conversations, but applicable also for questionnaires. A speech act describes and studies what takes place in interpersonal communication, social actions performed using language, e.g. protesting against something or demanding something from someone [171]. Characteristics of speech acts are interaction and context-dependence (social structures or environments); for example, the statement takes on meaning when pronounced in a healthcare environment, which narrows the selection of expected answers. Context dependence thus means that the same speech act can have different functions depending on the situation, usually categorized as either an intended or actual effect on the listener [171]. Regarding design, the pain drawing can provide clear "clues" to conversational context that are directly visual in that they are limited to the body of the respondent. The mechanisms of communication in PROMs (as in conversations) mean that the person asking the question always has greater insight into the context than the person who receives the question [171]. For example, a patient may be asked by the physiotherapist to estimate pain intensity as 0–10. The patient reports "9" to answer a question about how great the need for pain relief is (the intended effect of the response act), while the physiotherapist interprets this as a pure measure of pain intensity (actual effect). According to McClimans, this distinction facilitates being able to answer in the desired way when a PROM question can be understood both regarding the explicit question and the meaning of the wider domain in which the question was formulated. The pain drawing gives opportunity to convey even the nature of the question domain, better than in surveys where the explicit question always has several possible (unknown)

dimensions and with the answer options fixed. Although “genuine” open-ended questions are to be asked, however, questions need to be produced that make the instrument both interpretable and measurable. This need was met in study II using the standardized reading template: In the question situation, the question was open-ended, and a sharp question was later asked in the assessment situation when the drawings were screened.

Furthermore, the pain drawing offers adherence to prioritizing subjectivity in the assessment of conditions of persistent fatigue and pain. The pain drawing allows a very varied reporting, which suits the heterogeneous manifestation in conditions of persistent fatigue and pain. The patient’s experience of the condition, however, is considered not measurable because the pain experience is a function of the whole individual in their context [123]. This situation calls for addressing the described complexity of the clinical assessment and once again highlights that the pain drawing may be a solution. The MAP illustration thus is indeed a replica of the pain drawing in both content and design (though without touching on the area of pain drawing), even when it comes to the inclusion of the assessor’s role. The pain drawing reciprocates all the constituents of MAP and could be employed for this purpose. The drawing, paper or electronic version, offers recording and monitoring of pain manifestations as illustrated by the “shell” in MAP (Figure 3). Furthermore, available methods for standardized reading of the pain drawing should be seen as applicable to the “spikes” in MAP – pain measures with bearing for diagnostics. At the same time, an expanded mandate of the conversation is called for in the clinical assessment to arrive at effective ways of evaluating subjective measures [120]. It is advisable to connect this to the pain drawing, which provides patients and caregivers the means to meet in the subjective dimensions that are the reality of these conditions, in ways that allow discussion and evaluation. This approach can support the “strategic triangulation” that Wideman advocates for clinical assessment by potentially being labour-saving and unifying.

For other instruments with the ability to take advantage of subjective manifestations in conditions of prolonged fatigue and pain, an activity diary has been studied in chronic fatigue to assess the level of physical activity and was found not to correspond with accelerometer-measured performance [172].

5.3 Methodological considerations

5.3.1 Study design

Among the strengths of studies I–III is foremost that they addressed research gaps and added to knowledge on the diagnostic performance of the Beighton score in routine assessment of systemic joint laxity (study I); on the capacity of pain drawing in screening to identify nerve involvement from a specific spinal segment – where the

factual basis is meagre (study II); and on the diagnostic concept of ME/CFS in view of self-perceived health.

Several weaknesses of the study designs should be noted. First, the studies involved relatively narrow research questions because of a conscious choice to consider quality criteria for study design. In study III, actions to address this limitation could have been a more detailed report of the two patient groups (background, health issues, clinical findings), which could have helped in better understanding the findings. Study III might have been conducted by contrasting with other control groups. The associated conditions of persistent fatigue and pain, however, are rarely well defined in practice even if they are given different names. A risk would therefore have been retention of the ambiguity associated with such a control group and with less transparency than in the current implementation. Second, the studies in the thesis were based on cross-sectional data, which is suitable only for investigating associations, but it was suitable for the intended evaluation of measurement properties. Because studies I and III were based on baseline data from prospective studies, the data could also be used to investigate prediction models or for outcome studies. This use would lead to a contribution of higher scientific quality to existing evidence and the use of other methods of inference. Third, there was a question of whether observer bias (detection bias) may have affected the validity of the data. The assessors were aware of the role of the findings sought in relation to the research questions and could possibly thus have been inclined more or less deliberately to over-interpreting or undervaluing what they found. Especially with subjective outcomes such as pain, blinding is considered important in counteracting the influence of the assessor. Having blinded assessors was not practical, but in study I, both assessors 1 and 2 were blinded to whether the patient participated in the study, and assessor 2 used multiple sources of information (triangulation). In studies I and II, predetermined criteria were used in each measurement in the form of a detailed assessment procedure and the pain pattern key, which helped to make results credible.

5.3.2 Assessment methods

In study II, the scientific background arguably was limited for the clinical issue investigated regarding associations between dizziness and pain extent/pain site, as well as the means of reporting. Still, subjective complaints are at the core of the condition, which justifies their having been the focus of the research. Each symptom separately has a body of evidence, as synthesized in paper II. The fact that dizziness can be found in most groups with persistent pain (often called a nonspecific symptom) would not have diminished the validity of the outcomes in study II; an approach was used with spontaneously reported dizziness for data collection, reasonably placing this symptom at the centre of the patient's condition. Another gain of highlighting dizziness was the

lack of clear evidence regarding its aetiology and pathophysiology in the patient group, so that new knowledge was needed.

The problem remains with the space created for false reporting by fully embracing the narrative as the focus of the investigation. It would be possible to fabricate ill health with PROMs. How this possibility should be handled is not resolved, but is an issue outside of this work.

The PROMs in study III were relevant given that they were generic and comparable across multiple clinical conditions, and this PhD project focused on early adequate care for patients with persistent fatigue and pain. Acceptable psychometric properties were a must and needed to contribute to the decision-making basis for the group, i.e., capture current health domains. However, disease-specific instruments could have better identified activity limitations, and the CFS-APQ could have been an alternative [173]. Nonetheless, the instruments included in the study can measure relevant health domains for persistent pain and were included in the National Quality Register for Pain Rehabilitation for use in clinical assessment, which was a strength.

RAND-36 best showed clinically significant differences in study III, confirming previous research regarding outcome assessment of CFS (from research on SF-36) [174]. For implementation aspects, on the other hand, for the current group, RAND-36 is considered to have a relatively large response burden and also was the measuring instrument within the study that had the greatest dropout, which may have reflected this burden. An alternative is EuroQol five dimensions (EQ-5D), which has a lower response burden but poorer responsiveness than the RAND-36 [175].

5.4 Generalizability and clinical gains

This thesis builds on an understanding of the state of knowledge of screening instruments in the clinical assessment of persistent fatigue and pain. The evidence added regarding measurement stability of the Beighton score and pain drawing promises good conditions for their use in different types of environments (e.g., primary health care centres with varying competencies). For the latter, a template for standardized reading in practice can lead more professionals to use the instruments routinely and increase the degree of standardized documentation. The clinical value of pain drawing is clear and suggests that such a simple and manageable test can be used to map the nature and severity of the condition. This addition would contribute to the effectiveness of investigation in people who have persistent fatigue and pain. Another of the advantages of the work is that it discusses underlying validity theory for pain drawing.

The relatively large study population provided statistical strength (despite the lack of data). The study population was representative in terms of age range (ME/CFS most

commonly between 40 and 60 years) and gender distribution (about 80% women), according to the U.S. Centers for Disease Control and Prevention [26]. The measurement characteristics were evaluated in a completely clinical setting – that is, without any training of assessors regarding the relevance of the test or the condition itself. As far as is known, this is a first for the Beighton score. For these reasons, the results seemed to have a very high external validity.

The work also is a contribution to protecting the study group from patient harm. The physical integrity of the individual and their autonomy is fundamentally inviolable. Everybody has the right in healthcare to be extended the opportunity to protect their health. For the care to be ethically justifiable, patients must be informed and educated about the management of persistent non-malignant neurological conditions that can manifest themselves almost exclusively with subjective problems.

6 Conclusions

The studies in this thesis involved empirical examinations of the performance of central instruments to improve knowledge about their contribution in clinical investigations. Key points of the current work are as follows:

- The measurement stability of the Beighton score was confirmed for patients with persistent fatigue and pain, for assessment in a bedside context.
- The accuracy of the Beighton score alone for identifying systemic joint laxity in suspected ME/CFS is uncertain; it appears to be useful in screening when combined with a targeted history taking.
- Screening for a C2 pain pattern using pain drawing may be useful for promoting early adequate interventions for patients with persistent fatigue and pain, as the pattern can possibly indicate the nature and degree of severity of the condition (signs associated with neuropathic pain/cervical pain).
- The pain drawing merits further research and development as meeting virtually all criteria of a high-quality PROM, especially good potential for registering the condition's non-measurable manifestations as well as pain measures, with relevance for diagnostics.
- The hallmark symptoms of ME/CFS, when compared to a similar symptom picture – a very low tolerance for exertion and very low energy levels – seem to be condition-specific also when measured with PROMs, adding evidence to the definition of the diagnosis.

7 Future perspectives

It would be valuable to interview patients with ME/CFS to through qualitative data gain a deeper knowledge about their experiences of conveying information about their health condition, for example with pain drawings and questionnaires. It is justified to create additional evidence for the pain drawing as it was assessed as particularly relevant for a patient-centered approach in the present project. Much remains to be done in following up on how patients with persistent fatigue and pain handle filling out PROMs. Deficiencies in the ability to correctly interpret and report for PROMs are challenging for people with these diagnoses.

The associated conditions, particularly fibromyalgia, WAD and ME/CFS have been suggested to have a common pathophysiology. They could be linked in new studies where these theories are tested and data material from these patient groups is examined with the same research question, e.g., regarding central sensitization.

With the benefit of pain drawing in being designed for subjective reporting, there is likely potential for refinements in the drawing's query design. Research has shown that patients in estimating PROMS behave in ways consistent with making an effort to engage in a conversation. From that follows a call to create a better context for conversation or dialogue, e.g., through instructions. Also, new useful ways to standardize readings would be of interest. With this background, the question design for the pain drawing can be developed in several ways to become more useful regarding subjective data. Implications can be seen for 1) drawing design, 2) instruction, and 3) standardized reading.

Treatment for this patient group should be based on activity adaptation and recovery strategies. Pacing is a strategy in which patients are encouraged to achieve an appropriate balance between activity and rest to avoid aggravation and to set realistic goals to increase activity. More studies are needed that can investigate common treatment methods in occupational therapy and physiotherapy for people with persistent fatigue and pain and ascertain their role in evidence-based practice.

8 Acknowledgements

Many thanks for invaluable assistance, encouragement and patience throughout the duration of this project, to

Erik Carsjö

Peter Alexanderson, VD Bragée Kliniker

Lina Bunketorp Käll

Moundheur Zarroug

Eva Rasmussen Barr

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