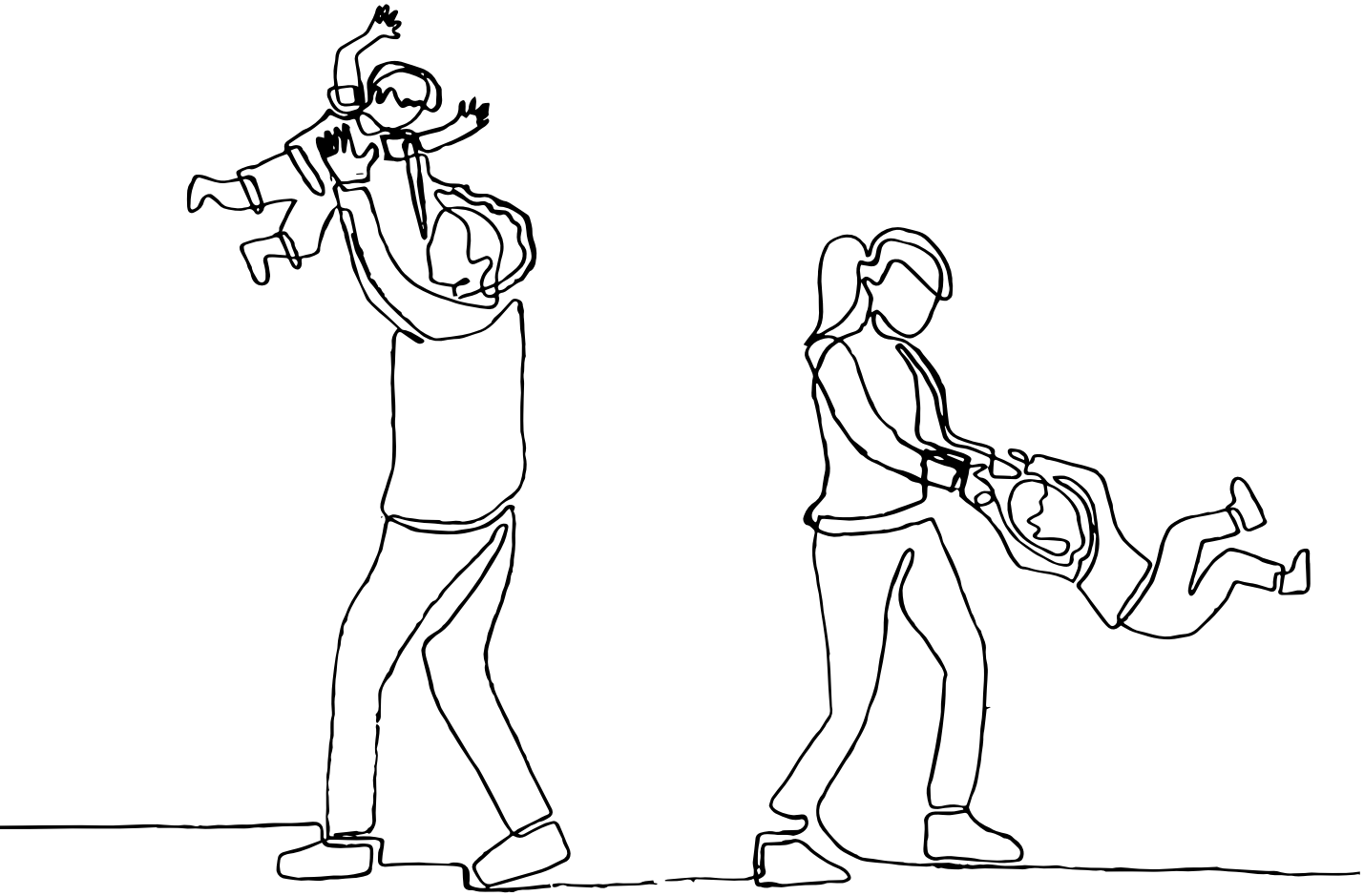
Physical activity, participation and health-related quality of life in chronic fatigue syndrome and multiple osteochondromas

PHYSICAL ACTIVITY, PARTICIPATION & HEALTH-RELATED QUALITY OF LIFE

In chronic fatigue syndrome and multiple osteochondromas



Dissertation submitted to obtain the degree of Doctor of Medical Sciences
at the University of Antwerp and Doctor at Maastricht University by

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Stellingen
behorend bij het proefschrift

Physical activity, participation and health-related quality of life in chronic fatigue syndrome and multiple osteochondromas

Kuni Vergauwen
Maastricht, 25 april 2024

1. De conclusie vanuit verkregen data is krachtiger als de validiteit en betrouwbaarheid van een meetinstrument aangetoond zijn bij de gemeten populatie. *(dit proefschrift)*
2. Patiënten met het chronisch vermoeidheidssyndroom zijn niet goed in staat om een realistische inschatting te maken van hun fysieke activiteitenniveau met behulp van een zelfrapportage activiteitendagboek. *(dit proefschrift)*
3. Patiënten met multiple osteochondromen in het huidige onderzoek ervaren minder vaak psychologische symptomen dan personen met het chronisch vermoeidheidsyndroom, maar bij aanwezigheid hiervan is de negatieve impact op hun levenskwaliteit groot. *(dit proefschrift)*
4. Fysieke activiteit heeft niet voor elke persoon met chronische vermoeidheid en pijn een even heilzaam effect op de levenskwaliteit. *(dit proefschrift)*
5. De positieve relatie tussen het kunnen uitvoeren van persoonlijk relevante activiteiten en gezondheid staat buiten kijf.
6. Participatie mogelijk maken, bevorderen of behouden is de kracht van de ergotherapeut, waarbij betrokken zijn bij het dagelijks handelen even waardevol is als actief deelnemen.
7. De ergotherapeut is een cruciale partner in de eerste lijn, zowel bij preventie, herstel als compensatie.
8. Het inzetten op persoonlijk relevante activiteiten en preventie van psychologische belasting bij personen met chronische vermoeidheid en pijn heeft het potentieel om de levenskwaliteit van patiënten te verbeteren en maatschappelijke belasting te verminderen.
9. Waarom binnen je comfortzone blijven als daarbuiten veel meer te beleven valt? *(Loesje)*
10. Onderwijs is niet het leren van feiten, maar de training van de geest om na te denken. *(Albert Einstein)*
11. De mooiste job is tegelijk de moeilijkste: het opvoeden van kinderen.

University of Antwerp

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Maastricht University

Faculty of Health, Medicine and Life Sciences
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Physical activity, participation and health-related quality of life in chronic fatigue syndrome and multiple osteochondromas

Fysieke activiteit, participatie en gezondheidsgerelateerde levenskwaliteit bij chronisch vermoeidheidssyndroom en multiple osteochondromen

Kuni Vergauwen

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List of abbreviations

95% CI	95% Confidence Interval
AC	Activity Counts
ADL	Activities of Daily Living
ANOVA	Analysis of variance
API	Activity Pattern Interview
AUC	Area Under The Curve
BDI	Beck Depression Inventory
BMI	Body Mass Index
BPAQ	Baecke Physical Activity Questionnaire
BPS	Bio-Psycho-Social model
CDC	Centers of Disease Control and Prevention
CF	Chronic Fatigue
CFS-APQ	Chronic Fatigue Syndrome – Activities and Participation Questionnaire
CFS-AQ	Chronic Fatigue Syndrome – Activity Questionnaire
CI	Confidence Interval
CIS	Checklist Individual Strength
CLBP	Chronic Low Back Pain
COSMIN	Consensus-based Standards for the selection of health Measurement Instruments
CFS	Chronic Fatigue Syndrome
DN4	Douleur Neuropathique en 4 Questions
EQ-5D	Euroqol Questionnaire
EXT	Exostosis
FABQ	Fear-Avoidance Beliefs Questionnaire
FDR	False Discovery Rate
FIS	Fatigue Impact Scale
HADS	Hospital Anxiety and Depression Scale
HADS-A	Hospital Anxiety and Depression Scale – Anxiety
HADS-D	Hospital Anxiety and Depression Scale - Depression
HME	Hereditary Multiple Exostoses
HRQOL	Health-Related Quality Of Life
ICF	International Classification of Functioning, Disability and Health
IPAQ-SF	International Physical Activity Questionnaire – Short Form
MA	Moderately Active
MCID	Minimal Clinical Important Difference
MCS	Mental Component Summary
MD	Major Depression
MD	Mean Difference
MDD	Major Depressive Disorder
ME	Myalgic Encephalomyelitis
MET	Metabolic Equivalent of Task
MO	Multiple Osteochondromas
NRS	Numeric Rating Scale
PA	Physical Activity
PAL	Physical Activity Level
PCS	Physical Component Summary
PCS	Pain Catastrophizing Scale
PDI	Pain Disability Index
PEM	Post-Exertional Malaise
PP	Pervasively Passive

PRISMA	Preferred Reporting Items For Systematic Reviews And Meta-Analyses
QOL	Quality Of Life
ROC	Receiver Operating Characteristics
SD	Standard Deviation
SF-36	Short Form – 36
SIP	Sickness Impact Profile
VAS	Visual Analogue Scale
VIF	Variance Inflation Factor
WHO	World Health Organization
WHOQOL-100	The World Health Organization Quality of Life Assessment Instrument
WSAS	Work and Social Adjustment Scale

CHAPTER 1

Introduction

Background

"Well basically it was like somebody had taken . . . zapped me of all my energy for one, and my life had to change because I couldn't do things like I did before." [1]

Indeed, fatigue often co-occurs with pain in different chronic conditions and both symptoms can be debilitating in nature [2–4].
Fatigue is defined as *"extreme and persistent tiredness, weakness or exhaustion – mental, physical or both"* [5] and it becomes chronic if it is persistent or relapsing in nature and present for six or more consecutive months [6]. **Chronic pain** is defined as *"pain that lasts or recurs for longer than three months"* [7], with **pain** being defined as *"an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage"* [8]. According to these definitions, both symptoms are personal experiences and can be expressed and experienced differently on various occasions depending on a variety of personal and contextual factors [8,9]. Chronic fatigue syndrome (CFS) and hereditary multiple exostoses / multiple osteochondromas (MO) are both chronic disorders that are accompanied by chronic fatigue and/or pain [6,10–13].

Chronic fatigue syndrome (CFS) is, according to the CDC-1994 criteria, a disorder characterized by unexplained, persistent or relapsing fatigue of a new or definite onset, which is present for at least six months. The fatigue is not the result of exertion, is not alleviated by rest and leads to a significant reduction in previous levels of occupational, educational, social and personal activities. In addition, the fatigue has to be accompanied by at least four of the following symptoms, which have to be present for at least six months: impaired short-term memory or concentration, sore throat, tender cervical or axillary lymph nodes, muscles pain, pain in several joints, headache of a new type, pattern or severity, unrefreshing sleep or post-exertional malaise lasting more than 24 hours [6]. Besides the CDC-1994 criteria [6], over 20 other case definitions have been developed with differences in main symptoms, inclusion and exclusion criteria [14,15]. Consequently, these case definitions vary in sensitivity and specificity, but consensus on a uniform case definition has not been reached. Since the CDC-1994 case definition is the most frequently cited and most extensively validated [14], this case definition will be used throughout this thesis to define CFS.
Estimates of prevalence rates vary in relation to case definitions and study designs [16,17], and range between 0.2% – 2.2% for developed countries [16–18]. The total prevalence of CFS in Europe is estimated around 2 million [19]. CFS is 1.5 to 2 times more prevalent in women than men [16,17] and is most common in young adults with its peak at 20-40 years of age [16]. Information on incidence rates is even more scarce and is estimated at 15/100.000 adults per year in de United Kingdom [18].
Limited attention has been given to the societal impact of CFS in Europe [19], but a significant economic burden has been identified due to both direct as indirect or hidden costs. Direct costs encompass mainly various medical costs, and indirect costs consist of occupational limitations (productivity loss, absenteeism, work incapacity) and non-medical, often hidden costs such as informal care given by the patient's social context

[16,20]. There is also a great impact on the mental and physical quality of life (QOL) of the patient and the emotional well-being of his carer(s) [16,21]. Overall, CFS causes significant economic, personal and societal burden which should receive healthcare policymakers' and society's attention [16,21].

Up to now, multiple hypotheses regarding the aetiology of CFS have been proposed. Prins et al. (2006) summarized various predisposing, precipitating and perpetuating factors proposed by previous research, assuming that one or multiple factors from all categories are conditional, but insufficient for the development of CFS, and more complex interactions of other biological regulation systems are expected to underlie its origin [22].
A more recent overview regarding the etiopathogenesis of CFS lists infection, dysfunctions of the immune and/or endocrine-metabolic system, sleeping disorders and neuropsychiatric factors as proposed hypotheses. However, clear biomarkers of the hypothesized disorders or dysfunctions and direct relationships with the onset of CFS have not yet been identified [20]. One hypothesis of particular interest is neuroinflammation caused by alterations in the neuroimmune system, which presumably plays a central role in CFS [23]. Increased levels of pro-inflammatory cytokines and disturbances in glial cell functions, which contribute to neuroinflammation, appear to be involved in CFS and the development of fatigue [24], but results remain conflicting and no definite conclusions on their role can be drawn. Central sensitization, a mechanism involved in the development and perpetuation of chronic pain, causes hypersensitivity to somatosensory stimuli (e.g., touch, light, sound) and is often co-occurred by fatigue [25–28]. Sensitization of the central nervous system, influenced by infectious agents, dysfunctions of the immune and endocrine system and psychological factors [27], is suggested as an explanation for CFS symptomatology. Sensitized fatigue pathways as a cause of post-exertional malaise in CFS were found in patients with CFS [29], also suggesting involvement of central processes [24,26,28,29].
As yet, **no clear aetiology** has been found and the diagnosis is determined based on a clinical examination and the exclusion of other medical and psychiatric pathologies explaining patient-reported symptoms [22,30].

Hereditary Multiple Exostoses / Multiple Osteochondromas (MO) is a condition characterized by the development of numerous cartilage-capped benign exostoses, usually in the metaphysial region of long bones and mainly growing on the metaphysis towards the diaphysis [31], but can develop from all bones that arise from endochondral ossification [32]. The disorder is autosomal dominant inherited [32], with approximately 90% of the affected individuals having a family history [33], and for the remaining individuals being the result of a new onset mutation [33]. Prevalence is estimated at 1:50.000 in Western countries [31] with an equal distribution across gender.
Exostoses can develop from childbirth into puberty [31,32] but cease to grow when grow plates close [32,34]. In general, by the age of 12 all affected individuals who have affected family members are diagnosed [31]. Secondary complications of MO could be osteoarticular complications, such as skeletal deformities or limited range of motion of joints, or compression of adjacent structures, such as peripheral nerves, blood vessels

or the spinal cord [31,32,34,35]. The most important complication is malignant degeneration, mostly into chondrosarcoma, but in more rare cases also osteosarcoma. Malignant degeneration into chondrosarcoma is reported to occur in 5.8% in patients of 16 years and older [36]. MO is in approximately 80-90% of affected individuals associated with a mutation in the exostosis (EXT) genes (EXT1 or EXT2) [37]. In about 10% of the affected persons, no mutation in the EXT-genes is found and it remains unclear why MO occurs [38].
In patients with MO, more than 80% reported having pain [12,13], with both local pain as well as generalized pain being reported by patients [12]. This finding suggests that, besides the structural deformities, underlying processes contribute to the development of chronic generalized pain in MO [12]. Darilek et al. (2005) found that surgery was significantly related to pain in patients with MO and hypothesize that patients who undergo multiple surgeries may have a more severe phenotype causing more pain. Surgery itself could be an eliciting factor of central sensitization causing generalized pain [39]. Reddi et al. (2014) identified several risk factors for the development of chronic post-surgical pain. Preoperative risk factors include repeated surgery, preoperative pain lasting more than one month, catastrophizing and anxiety; intraoperative factors are a surgical approach with risk of nerve damage and postoperative factors include pain, depression, anxiety and catastrophizing. Additionally, high prevalence of severe fatigue (71%) has been identified but this was in a study including only 21 patients with MO. Furthermore, no research regarding its pathophysiology has been undertaken [10]. Primarily, one would expect the presence of physical complaints which are related to the development of exostoses in MO, but not fatigue complaints. Up to now, there is **insufficient information** regarding fatigue (prevalence, intensity, duration etc.) and pain in patients with MO. Also, the **pathophysiology of the chronic (generalized) pain and fatigue** have not been thoroughly investigated in relation to the aetiology of MO, requiring more research regarding underlying processes of both symptoms.

In summary, while CFS is a relatively rare syndrome characterized by chronic fatigue among other debilitating symptoms, (chronic) fatigue as a symptom appears to be frequently present in other chronic diseases as well. Fatigue and pain are also common in patients with MO as is the case with numerous other chronic disorders, such as cancer [5], fibromyalgia [40] and multiple sclerosis [5,40,41]. In CFS, the aetiology and pathophysiology are still completely unknown [22,30]. Due to its unknown aetiology, CFS can be considered a **non-specific disorder** characterized by chronic fatigue that may be accompanied by chronic pain. The aetiology of MO is clear and, consequently, MO can be classified as **a specific disorder** explaining the localized (nociceptive) pain due to the structural deformities**.** However, as with many chronic disorders, the pathophysiology of chronic fatigue and chronic pain remains not fully understood. The pathophysiology of chronic fatigue and chronic pain complaints is hypothesized to be multifactorial and can differ depending on the underlying disease [42–44]. This thesis is particularly interested in the impact of chronic fatigue in patients who also experience chronic pain.

Recent research proposed that severe fatigue is a generic symptom that can be (partly) explained by transdiagnostic factors and that fatigue-related research should not focus on disease-specific factors alone [3]. Several transdiagnostic factors, including pain, reduced activity and physical functioning were significantly and positively associated with fatigue severity in the majority of the included chronic disorders. Other factors, such as depressive symptoms, gender and age, were inconsistently related with fatigue severity across disorders [3]. These findings indicate that fatigue severity seems to be associated with both transdiagnostic and disease-specific factors, underpinning the relevance of investigating both in fatigue-related research.

Because chronic fatigue complaints cannot be (fully) explained by the aetiology and pathophysiology of MO and CFS and a generic rather than disease-specific pathophysiology of fatigue is proposed, it seems valid to hypothesize that multiple factors contribute to the development and perpetuation of fatigue in both disorders. From this point of view, the **biomedical model** that was primarily adopted in the 19th century [45] is too narrow and cannot provide a sufficient explanation. Therefore, the use of more comprehensive model is necessary. In 1977, George Engel proposed the **bio-psycho-social model (BPS)** as an alternative to the biomedical model. In his opinion, the biomedical model was too limited and failed to recognize the importance of psychological, social and behavioural factors on the development and perpetuation of an illness [45–48]. The BPS model on the other hand posits a complex interplay between the biological system and psychological, social and behavioural factors which all can contribute, separately or simultaneously, to the development and perpetuation of an illness [45,47,48]. The view of the BPS model on illness and health is therefore adapted to the proposed multidimensional character of fatigue and appropriate to use within research and rehabilitation.

The International Classification of Functioning, Disability and Health

All different perspectives of health proposed by the BPS model were incorporated in the International Classification of Functioning, Disability and Health (ICF), a taxonomy developed by the World Health Organization (WHO) in 2001 [49]. Figure 1 is a schematic overview of the basis of the ICF that presents the relationship between all domains related to health as proposed by the BPS model [45,47,48]. It is important to note that the biomedical part is an essential part, but that the BPS model has a more holistic view on illness and its symptoms that takes more determinants into account than only the biological system as proposed by the biomedical model [48]. Rehabilitation uses the ICF to operationalize the concepts of the BPS model and consequently adopts a system-oriented perspective and holistic view on disability that addresses all individually determined factors influencing an individual's health to enable an **optimal recovery** from the presented illness or disorder and the **most optimal quality of life (QOL)** [48].

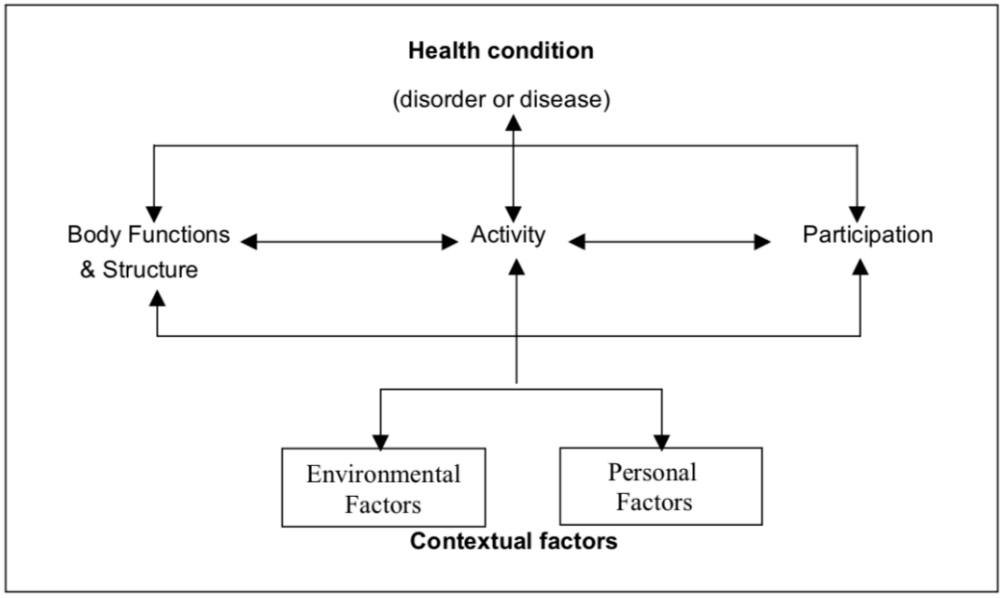

Figure 1. Diagram of the International Classification of Functioning, Disability and Health [49]. *Reproduced with permission of the publisher from International Classification of Functioning, Disability and Health: ICF – © World Health Organization 2001.*

Health-related Quality of Life (HRQOL)

Quality of life (QOL), an essential primary outcome of medical care [50,51], is defined by the WHO as:

> *An individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, personal beliefs, social relationships and their relationship to salient features of their environment.*[52]

Based on this definition, it can be concluded the concept of QOL is related to health, but encompasses more factors than only health-related elements [53,54]. Even though individuals with a chronic disease often experience a significant impact on their QOL, especially when this is accompanied by chronic fatigue [50,55–57], one's QOL is affected by many key elements of which physical and mental health-related factors are just a few contributing elements. Since a person's QOL is not only affected by health-related factors, the term **'health-related quality of life' (HRQOL)** was developed [53,54]. HRQOL includes the effect of health, illness and treatment on QOL and excludes all other factors influencing QOL that are not related to health [54].

HRQOL is individually determined and based on a patient's personal perception of their health, based on their aspirations and expectations which are shaped by individual values and beliefs systems [53,58]. The importance of the personal perception of an illness and health status is acknowledged by the BPS model by incorporating the individual's personal, social and temporal context [48]. Even though personal and environmental factors are part of the ICF framework, the personal perception of a patient is not explicitly included in the framework of the ICF, but essential to define a patients' HRQOL [48,58]. The ICF, however, can be used to operationalize HRQOL [59] and it is suggested to

include a patient's personal perspective in the personal context section of the ICF [58]. The ICF framework is therefore suited to investigate HRQOL and its determinants.

HRQOL in CFS and MO

Both in patients with CFS [56,60–63] and with MO [12,13,64], **lower levels of HRQOL** have been identified in comparison to healthy controls. Remains the question whether this lower HRQOL is associated with similar or different **determinants in a specific and non-specific disorder** with comparable symptoms, i.e., MO and CFS respectively.

Based on the model of HRQOL, determinants of HRQOL can be disease-specific or transdiagnostic, i.e., independent of an underlying chronic disorder. They can also be unmodifiable, which include characteristics of the individual (e.g., age, gender, ethnicity, marital status, psychological traits) or some environmental factors (e.g., family, neighbourhood) [53], or they can be modifiable, such as psychosocial factors [50,53]. These determinants should therefore be included in further research and have their place within the ICF.

Insight into transdiagnostic determinants of HRQOL will support clinical practice and future scientific research by providing an overview of factors that have an impact on HRQOL regardless of the underlying disorder and should be assessed systematically when a patient presents with chronic pain or fatigue. In addition, these insights will support the development of efficacious and comprehensive rehabilitation interventions aimed at maximizing patients' HRQOL by ensuring that all relevant modifiable biopsychosocial factors are identified and addressed during treatment for patients presenting with specific or non-specific pain and fatigue complaints.

Current rehabilitation interventions for CFS aimed at minimizing symptom severity and maximizing HRQOL, are only moderately effective [65,66]. Treatment interventions for CFS include a multidisciplinary rehabilitation treatment, cognitive behavioural therapy and graded exercise therapy [22,65–67]. Determinants of HRQOL in patients with MO and rehabilitation interventions for improving their HRQOL have not yet been addressed in scientific research. Therefore, more research regarding determinants of HRQOL in CFS and MO and the comparison between both disorders is needed to improve the knowledge of transdiagnostic and disease-specific determinants of HRQOL in patients with chronic pain and fatigue and support the further development of efficacious rehabilitation interventions.

Physical activity

One determinant of specific interest in the exploration of determinants related to an individual's HRQOL in CFS and MO is *physical activity.*

In the general population, a significant negative effect of physical inactivity on health has been described and has been identified as an important risk factor for the development of non-communicable diseases [68]. The WHO recommends regular moderate physical activity for adults to reduce the risk of developing non-communicable diseases, to enhance their level of cardio respiratory and muscular fitness, and to achieve a healthier body composition among other health benefits [69]. Additionally, previous

research identified physical activity of moderate intensity to be positively associated with HRQOL in the healthy adult population [70]. Significant relationships between physical activity and HRQOL, more specifically the domains of physical functioning and vitality, have been established [70]. It seems from these results that physical activity is most related to physical domains of HRQOL [70–72]. However, smaller positive relationships between physical activity and mental HRQOL have also been identified [70,73].

Evidence regarding the **influence of physical activity on HRQOL** in patients with CFS is scarce and in MO even lacking.
In patients with CFS, lower levels of physical activity have been identified in persons with CFS in comparison to healthy controls [74,75]. Mainly less activities of moderate and high intensity are performed [76,77] enhancing the risk for additional health problems [68]. This reduction of activities is reflected in a substantial reduction in previous levels of occupational, educational, social or personal activities is part of the CDC-94 criteria for CFS [6], making the experience of participation restrictions almost inevitable.
A Cochrane review concerning exercise therapy for CFS [72] found that increased physical activity had a positive effect on physical functioning, but no conclusions could be drawn on overall QOL, indicating that PA has an influence on at least one domain of HRQOL in patients with CFS. Similar results were found for exercise therapy in patients with chronic pain reporting that exercise therapy seemingly has little adverse effects, may improve pain severity and physical functioning, and consequently has a beneficial influence on QOL [71]. It is important to note that both reviews investigated exercise therapy as an intervention, a subcategory of physical activity [78].

Up to now, no studies focused on the physical activity level (PAL) of patients with MO. However, due to the chronic nature of the disorder, the severity of its currently known associated impairments and impact on patients' HRQOL, it is valid to hypothesize that at least a proportion of the patients with MO has a lower PAL compared to healthy persons. In addition, lower levels of HRQOL have been identified in comparison to healthy controls [12,13,64]. However, no study investigated the association between PAL and HRQOL in patients with MO.

Apart from a positive relationship between physical activity and HRQOL, the ability to be physically active, and more specifically the ability to perform meaningful activities of daily living (ADL), enables participation, a concept included in the ICF as 'involvement in a life situation' [49] (Figure 1). Participation is considered a more objective outcome measure, while HRQOL, among other things, includes a person's satisfaction with their participation.
Impairments in bodily functions caused by a chronic disorder such as CFS or MO (health condition) can cause **limitations in activities** and consequently **participation restrictions** [49]. All factors are thus inextricable linked to HRQOL. Additionally, environmental and personal factors can either be facilitating or restricting [49].
As presented by the ICF (Figure 1), all concepts are inseparable and insight into the association between all concepts is necessary *to clarify the impact of CFS and MO (health condition) on a person's physical activity level (PAL), activities, participation and HRQOL*.

This clarification will help future research and clinical practice in developing evidence-based interventions aimed at minimizing patients' impairments, limitations and/or restrictions and maximizing their HRQOL.

Because studies investigating HRQOL, physical activity and the direct association between both constructs in patients with CFS and MO are scarce, this thesis focusses on the **exploration of HRQOL and physical activity** separately, the **association between both concepts**, and aims at identifying **transdiagnostic and diseases-specific determinants** associated with HRQOL [3,51].

Outline of this thesis

Part 1: Assessment of (physical) limitations and restrictions in chronic fatigue syndrome

In order to explore HRQOL and physical activity in patients with chronic fatigue, the first aim of the present thesis is to identify reliable and valid measurement instruments for measuring these constructs. A large number of measurement instruments for measuring HRQOL and physical activity are available. Even though research regarding HRQOL and physical activity has been performed in patients with chronic fatigue, and more specifically patients with CFS, consensus on the psychometric characteristics of these measurement instruments in patients with CFS is lacking. Consequently, it is unclear which measurement instruments are most suited to use in research, but also in clinical practice. In patients with MO, insufficient research regarding patients' HRQOL and no research on their PAL has been performed. The investigation and selection of appropriate and suitable measurement instruments was based on previous research results in patients with CFS, since the primary diagnostic criterium in CFS is chronic fatigue; this group is therefore a valid representation of patients with chronic fatigue. A systematic review of the literature and critical appraisal of the psychometric properties of identified measurement instruments measuring HRQOL and physical activity in patients with CFS was deemed necessary as a starting point to address the overall aim of the present thesis. The results of the **systematic review** on **measurement instruments to assess activity limitations and participation restrictions** in patients with **CFS** are described in *chapter 2*. The results of the **systematic review** on the psychometric assessment of **measurement instruments to evaluate the physical activity level and pattern** in patients with **CFS** are described in *chapter 3*.

Both objective measures and self-report measures are often used to assess a person's PAL. Objective measures fairly accurately estimate patients' actual PAL in terms of activity intensity, but most currently used measures do not take environmental and contextual factors into account and they do not provide a detailed overview of the kind of activities patients perform. This information would provide more insight in patients' meaningful activities of daily living and would help to tailor activity management programs to each patient's individual needs. Self-report measures could provide this information, but previous studies have shown that current self-report measures are not capable of measuring patients' actual PAL [79–81]. Therefore, a measurement instrument (activity diary) that addresses the limitations of previously used self-report measures was developed and it was investigated whether the activity diary could accurately estimate patients' actual PAL by comparing it to an objective measure. *Chapter 4* evaluates the ability of the activity diary to estimate the actual PAL in patients with CFS and explores which factors explain the **discrepancy between the objective and self-report measure of physical activity**.

Part 2: Health-related quality of life and physical activity in chronic fatigue syndrome and multiple osteochondromas

Up to now, there is only limited knowledge on the HRQOL of patients with MO and no information regarding their PAL is available. Consequently, the impact of MO and associated symptoms on patients' HRQOL and PAL is unclear. Therefore, the second part of this thesis will first investigate the **HRQOL and PAL in patients with MO** and identify **biopsychosocial factors** associated herewith through a survey amongst Dutch patients with MO. These results are described in c*hapter 5*.

Second, more insight is needed to identify which biopsychosocial factors, including physical activity, are associated with HRQOL in patients with chronic pain and fatigue complaints, and whether these factors are disease-specific or can be considered to be transdiagnostic. Therefore, c*hapter 6* will **compare HRQOL** in a specific (**MO**) and non-specific (**CFS**) pain and fatigue disorder to identify transdiagnostic and diseases-specific biopsychosocial determinants of HRQOL.

Chapter 7 provides a **general discussion** evaluating the main results, formulates methodological considerations and presents the conclusions of all studies in this thesis. Furthermore, implications for clinical practice will be given followed by recommendations for future research and the potential added value of the findings for society (valorisation).

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PART 1

Assessment of physical activity limitations and restrictions in chronic fatigue syndrome

CHAPTER 2

Assessment of activity limitations and participation restrictions with persons with chronic fatigue syndrome: a systematic review

This chapter is published as:
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Abstract

Purpose: To summarize measurement instruments used to evaluate activity limitations and participation restrictions in patients with chronic fatigue syndrome (CFS) and review the psychometric properties of these instruments.

Method: General information of all included measurement instruments was extracted. The methodological quality was evaluated using the COSMIN checklist. Results of the measurement properties were rated based on the quality criteria of Terwee et al. Finally, overall quality was defined per psychometric property and measurement instrument by use of the quality criteria by Schellingerhout et al.

Results: A total of 68 articles were identified of which eight evaluated the psychometric properties of a measurement instrument assessing activity limitations and participation restrictions. One disease-specific and 37 generic measurement instruments were found. Limited evidence was found for the psychometric properties and clinical usability of these instruments. However, the CFS-activities and participation questionnaire (APQ) is a disease-specific instrument with moderate content and construct validity.

Conclusion: The psychometric properties of the reviewed measurement instruments to evaluate activity limitations and participation restrictions are not sufficiently evaluated. Future research is needed to evaluate the psychometric properties of the measurement instruments, including the other properties of the CFS-APQ. If it is necessary to use a measurement instrument, the CFS-APQ is recommended.

Introduction

Chronic fatigue syndrome (CFS) is a complex, clinically defined illness characterized by severe fatigue that cannot be explained by another medical or psychiatric condition and is not sufficiently reduced by resting. Patients also have to experience substantial reductions in previous levels of occupational, educational, social or personal activities, leading to limitations in one or more areas of life [1]. These limitations may result in financial problems, because some patients are unable to stay at work [2,3]. Another characteristic of CFS is the exacerbations of symptoms after performing too much physical or mental activities [1,4]. Patients perform fewer activities to avoid an increase of their symptoms and develop an activity-related strategy of complete rest expecting that this strategy will cause improvement. However, this strategy results in social isolation, depression, increased limitations and restrictions or even leading to a situation of being homebound. Re-activation and reduction of social isolation is therefore one of the most important therapeutic goals in CFS [3,5].

One of the core concepts of rehabilitation is to support patients in performing their daily life activities in a client centered way that promotes or maintains their health, well-being, participation and autonomy [6–11]. It is therefore important to be capable of identifying possible restrictions in activities and participation by means of standardized, reliable and valid measurement instruments and registration documents [3,7,9,10].

The number of assessment tools measuring activity limitations and participation restrictions has strongly increased during the last years. As a result, it has become more difficult to choose the most appropriate measurement instrument that covers the desired construct [7,12]. Different aspects, such as the target group and psychometric properties within the desired population, are important to consider to organize a good health service and to support the patient's rehabilitation [7,10].

Given the relevance of a correct identification of restrictions in activities and participation in a disabled and generally inactive group like the CFS population, insight in the characteristics and psychometric properties of the different measurement instruments within this specific population is required. Till now, different (generic) measurement instruments are used. However, consensus on the psychometric characteristics of these measurement instruments in patients with CFS is lacking.

The present systematic literature review aims to summarize answers to the following research questions.

(1) Which measurement instruments are currently used to evaluate activity limitations and participation restrictions in patients with CFS?

(2) What are the psychometric properties of these measurement instruments in patients with CFS?

(3) Which of these measurement instruments are appropriate to use in patients with CFS?

Methods

This systematic review is reported following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines, which is an updated statement

addressing the conceptual and methodological issues of the original QUOROM Statement [13].

Eligibility criteria

To be included in the present systematic review, studies had to report the use of measurement instruments evaluating activity limitations and participation restrictions in patients with CFS.

The definitions for activity, participation, limitations and restrictions from the International Classification of Functioning, Disability and Health (ICF) were used to identify relevant measurement instruments [14]. Quality of life (QOL) measurements assessing a person's satisfaction or limitations with performing daily activities or participation restrictions were also included.

Information sources and search strategy

The literature search was executed by use of the electronic databases PubMed and Web of Science from 1 July 2012 until 31 October 2012. A sensitive search filter, developed by Terwee et al. in 2009 was used [15]. This search filter consists of a combination of search terms and is designed to find studies on psychometric properties of measurement instruments in the electronic database PubMed. As the sensitivity of this filter is 97.4%, other searches were also used to make sure no relevant studies were missed [15]. Reference lists of included articles were screened as well. No limits were set for the date of publication. The search strategy was built by combining "chronic fatigue syndrome" both as free text word and MeSh-term with different key words related to the assessment (assessment, "outcome measure", survey, questionnaire) or activities and participation ("activities of daily living", disability, "daily functioning", limitations, participation).

Study selection

The study selection was performed in two different screening phases.

Following inclusion criteria were applied:
(1) The study had to be executed on adult humans;
(2) Studies were written in English or Dutch;
(3) Studies included at least one measurement instrument that identifies limitations in activities of daily living or participation restrictions.

Following exclusion criteria were applied:
(1) Studies about medication, genetics, epidemiologic research, immunology, prevalence, endocrinology, alternative therapy, diagnostics by use of medical imaging;
(2) Systematic reviews and meta-analyses.

The first selection was based on title and abstract. Articles that met the first two inclusion criteria were included for full text reading. The third inclusion criterion was only applied during full text reading, because not all articles mention the measurement instrument in their abstract. All articles identified during the literature search are included in the first

part. Studies evaluating the psychometric properties of relevant measurement instruments are included in the second part.

Data-extraction and rating

Part 1: Overview of measurement instruments used in scientific research

All data concerning measurement instruments evaluating activity limitations and participation restrictions in individuals with CFS were extracted with the help of a form based on ''Worksheet 12: Test critique form'' by Fawcett [16] and compiled in one table (Supplementary Material).

Part 2: Evaluation of psychometric properties of measurement instruments

All articles evaluating the psychometric properties of measurement instruments used with CFS were included in the further analysis of the systematic review. General information (Table 4) was retrieved with the help of the ''Generalizability'' box of the COSMIN checklist [17]. The research methodology used to evaluate the psychometric property was rated with the help of the COSMIN checklist. The COSMIN checklist was developed in 2010 according to a Delphi study by international experts in health related measurement instruments [18]. The COSMIN checklist evaluates 10 psychometric properties and consists of four possible answers: ''excellent'', ''good'', ''fair'' and ''poor''. A general score for the methodological quality was provided for every individual psychometric property for every measurement instrument by taking the lowest score from every box (Table 2) [17]. The ''Interpretability'' box was filled in for every article and scored based on the number of questions that could be answered with ''yes'' (1 or 2=poor; 3 or 4=fair; 5 or 6=good; 7=excellent). The results of the psychometric properties were rated based on the quality criteria of Terwee et al. [12].

Synthesis of best evidence

The level of evidence for every psychometric property was defined by combining the rating of the methodological quality from the COSMIN checklist and rating of the research results according to the quality criteria of Terwee et al. (2007) (Table 3) [12].

A general score was given to each measurement instrument and was either ''strong'', ''moderate'', ''limited'', ''conflicting'' or ''unknown''. The levels of evidence for the overall quality, similarly as proposed by the Cochrane Collaboration Back Review Group and modified by Schellingerhout et al. (2011) were used to determine the score [19,20].

Results

From 249 unique hits, 99 articles were identified based on their title and abstract. Full text reading resulted in the exclusion of another 31 articles. A total of 68 relevant articles were included. Only five articles evaluated the psychometric properties of a measurement instrument (Figure 1).

All information regarding the measurement instruments was compiled in a table (Supplementary Material). The references of all included articles, except the five evaluating the psychometric properties of a measurement instrument, were checked. Based on this additional search, three more articles that evaluated the psychometric

properties of a measurement instrument in CFS were identified. A total of eight articles were included for further analysis and five unique measurement instruments were evaluated. The methodological quality of these eight studies is presented by psychometric property for every individual measurement instrument in Table 2. The ratings of the results are presented by psychometric property in Table 3.

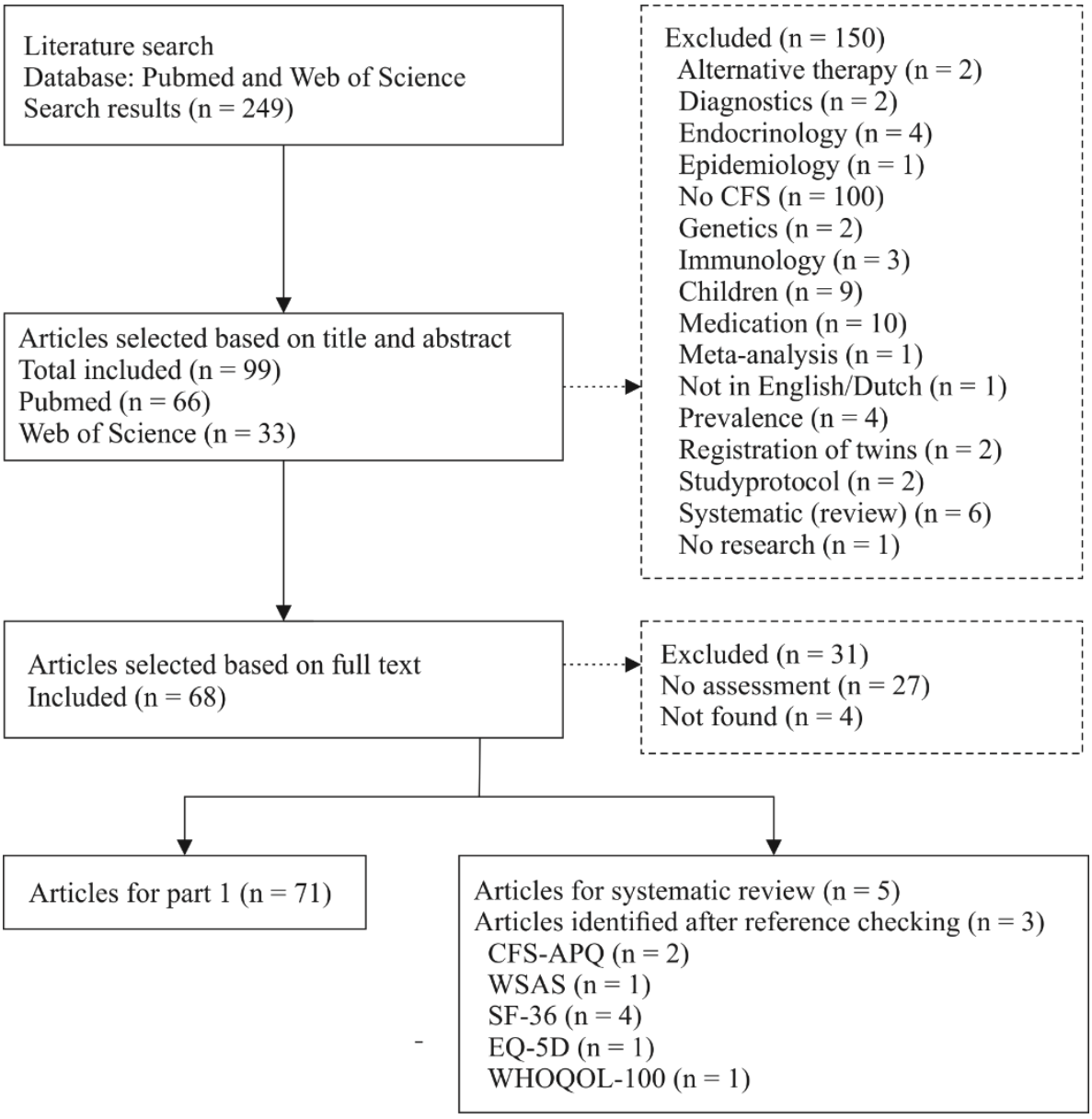

Figure 1. Flowchart of search strategy.
CFS-APQ, Chronic Fatigue Syndrome-Activities and Participation Questionnaire; WSAS, Work and social adjustment scale; SF-36, Short Form-36; EQ-5D, Euroqol Questionnaire; WHOQOL-100, The World Health Organization quality of life assessment instrument.

Table 1: Information regarding all included measurement instruments from part 1

Content	Measurement instrument	Goal	Psychometric properties	Ref.
Activity	Activity and symptom diary	To monitor activities	None mentioned	[21]
	Activity Restriction Index (ARI)	To measure a person's current ability to engage in activities	Intraclass Correlation Coefficient (ICC) = 0.84	[22]
	General questions regarding daily functioning (Vercoulen et al., 1994)	To measure the interference of complaints with daily activities	None mentioned	[23]
	Assessment of functional status (Solomon et al., 2003)	To measure hours spend on meaningful activities	None mentioned	[24]
	Baecke Physical Activity Questionnaire (BPAQ)	To assess habitual leisure and occupational physical activities	Reliability coefficients of the BPAQ and associations with other measurements were mentioned	[22,25]
	Barthel Activities of Daily Living Index	To measure the degree of independence in ADL	None mentioned	[26]
	Canadian Occupational Performance Measure (COPM)	To measure the performance of and satisfaction with ADL	None mentioned	[27]
	Subsidiary measures of functioning (Sharpe et al., 1996)	To measure ADL and employment status	None mentioned	[28]
	Frenchay Activities Index	To measure the degree of involvement in domestic tasks, social events, hobbies, and employment	None mentioned	[26]
	One-Time Measure (Andersen et al., 2004)	To rate symptoms and measure functional changes	None mentioned	[29]
	Human Activity Profile (HAP)	To measure daily activities and relate them to a known amount of average energy expenditure (MET)	None mentioned	[30]
	Patient-Reported Outcomes Measurement Information System, Health Assessment Questionnaire (PROMIS HAQ)	To assess a person's ability to carry out ADL	None mentioned	[31]
	Physical Activity Questionnaire (PAQ)	To measure functional patterns	None mentioned	[32]

Table 1 (continued)

Content	Measurement instrument	Goal	Psychometric properties	Ref.
Activity	Questionnaire (Assefi et al., 2003)	To measure a person's financial, occupational and social status	None mentioned	[2]
	Questionnaire (Nijs et al., 2008a)	To assess work participation and social activity	None mentioned	[33]
	Stanford Health Assessment Questionnaire (HAQ)	To assess a person's functional capacity to perform ADL	None mentioned	[34]
	Work and Social Adjustment Scale (WSAS)	**To measure a person's ability to work, engage in household management and participate in social and private leisure activities and relationships**	**Part 2**	[35,36]
General health	19- Item Medical Outcome Study Short-Form General Health Survey (MOS-19)	To measure general health on the basis of multiple subscales	Reliability coefficients were mentioned	[37,38]
	20-Item Medical Outcome Study Short-Form General Health Survey (MOS-20)	To measure general health on the basis of multiple subscales	Pearson product-moment correlation coefficient that measured the correlation between the scores of the MOS-20 and the Wood Mental Fatigue Inventory was described	[22]
	Euroqol Questionnaire (EQ-5D)	**To measure general health and subdivide patients in 243 different health states**	**Part 2**	[39]
Disability / limitations	Brief Disability Questionnaire (BDQ)	To measure functional impairment	None mentioned	[21]
	Functional Status Questionnaire (FSQ)	To measure functional disability over the previous month	None mentioned	[40]
	Karnofsky Performance scale	To assess a person's degree of disability	Good agreement (Cohen's K greater than 0.8 at every time point) Valid and reliable in several patient populations, but no exact values were mentioned	[22,28,41,42]
	PROMIS HAQ	To measure a person's degree of functional impairment	None mentioned	[31]
	Questionnaire (Gadalla 2008, 2008a)	To asses short-term disability	None mentioned	[43,44]
	Questionnaire (Perruccio et al., 2007)	To measure limitations in activities due to a disease or illness	None mentioned	[45]

Table 1 (continued)

Content	Measurement instrument	Goal	Psychometric properties	Ref.
Disability / limitations	Questionnaire (Wilson et al., 2001)	To measure functional impairment	None mentioned	[46]
	Self-assessment of functional impairment (Butler et al., 1991)	To assess a person's ability to work, home management, social and private leisure activities	None mentioned	[47]
	Sickness Impact Profile (SIP)	To measure disability/functional limitations associated with health problems	Reliable and valid for a variety of patient groups, but no exact values were mentioned	[42,48–51]
	SIP 8	To measure disability/functional limitations associated with health problems	Cronbach's alpha (Dutch version) = 0.91	[23,52–56]
	SIP short version	To measure disability/functional limitations associated with health problems	Reliable and valid , but no exact values were mentioned	[57]
Participation	**Chronic Fatigue Syndrome Activities and Participation Questionnaire (CFS-APQ)**	**To measure both activity limitations and participation restrictions**	**Part 2**	[25,27,33,58–65]
Quality of Life (QOL)	Manchester Short Assessment of Quality of Life (MANSA)	To measure satisfaction with life as a whole and in specific life situations	High concordance with the Lancashire Quality of Life Profile, but no exact values were mentioned	[66]
	Danish CFS Questionnaire Repeated Measure	To measure a person's coping with ADL	None mentioned	[29]
	Medical Outcome Study Short-Form General Health Survey (SF-36)	**To measure functional status and QOL**	**Part 2**	[27,32–34,39,52–54,58–60,64,66–90]
	Quality of Life Scale	To measure the satisfaction with different life activities with persons with chronic illnesses	High test-retest reliability, convergent and discriminate construct validity, but no exact values were mentioned	[76]
	Quality of Life Questionnaire	To assess QOL	Good internal consistency (Cronbach's alpha = 0.851)	[88]
	The World Health Organization Quality Of Life Assessment Instrument (WHOQOL-100)	**To measure different facets of QOL**	**Part 2**	[51]

Table 1 (continued)

Content	Measurement instrument	Goal	Psychometric properties	Ref.
Impact of fatigue / other symptoms	Activity and symptom diary	To measure the influence of fatigue and other symptoms on activities	None mentioned	[21]
	General questions regarding daily functioning (Vercoulen et al., 1994)	To measure the interference of complaints with ADL	None mentioned	[23]
	Multidimensional Assessment of Fatigue (MAF)	To evaluate the influence of fatigue on ADL	Good internal consistency (Cronbach's alpha = 0.92)	[30,87]
	SIP	To measure the impact of an illness on ADL	Reliable and valid for a variety of patient groups, but no exact values were mentioned	[23,42,48–50,52,54–57]

Table 2: Results COSMIN checklist

Measurement instrument	Internal consistency	Reproducibility Reliability	Reproducibility Agreement	Content validity	Criterion validity	Construct validity	Responsiveness	Interpretability
CFS-APQ								
Nijs et al. (2003)	poor	poor		good		poor		poor
Nijs et al. (2004c)	poor					good		poor
SF-36								
Myers et al. (1999)								poor
Buchwald et al. (1996)	poor					poor		poor
Ware et al. (1992)				poor				
EQ-5D								
Myers et al. (1999)						poor		good
WHOQOL-100								
De Vries et al. (1997)	poor			good		fair		poor
WSAS								
Cella et al. (2011a)	excellent					poor	poor	poor

Table 3: Results quality psychometric properties of measurement instruments: synthesis of best evidence

Measurement instrument	Internal consistency	Reproducibility Reliability	Reproducibility Agreement	Content validity	Criterion validity	Construct validity	Responsiveness	Floor and ceiling effects	Interpretability
CFS-APQ	unknown	unknown		moderate		moderate			unknown
SF-36	unknown			unknown		unknown			unknown
EQ-5D						unknown		limited	moderate
WHOQOL-100	unknown			moderate		limited			unknown
WSAS	strong					unknown	unknown		unknown

Levels of evidence for the overall quality of the psychometric property (based on Schellingerhout et al. 2011) [20] combined with Quality criteria for psychometric properties (based on Terwee et al. 2007) [12].
strong = consistent findings in multiple studies of good methodological quality OR in one study of excellent methodological quality; moderate = consistent findings in multiple studies of fair methodological quality OR in one study of good methodological quality; limited = one study of fair methodological quality; conflicting = conflicting findings; unknown = only studies of poor methodological quality

Part 1: Overview of measurement instruments used in scientific research

A total of 38 different measurement instruments were used to evaluate activity limitations and participation restrictions in scientific research with a patient population with CFS. All measurement instruments and their psychometric properties are compiled in Table 1 (Supplementary Material).

Part 2: Discussion of psychometric properties of measurement instruments

Psychometric studies of the CFS-APQ, SF-36, EQ-5D, WHOQOL-100 and WSAS were found and therefore included for further analysis. They were rated by use of the COSMIN checklist and quality criteria of Terwee et al. (2007) [12].

Chronic fatigue syndrome-activities and participation questionnaire

The chronic fatigue syndrome-activities and participation questionnaire (CFS-APQ) evaluates a person's health status over the past 7 days [65]. It is based on the "International Classification of Functioning, Disability and Health" (ICF) and was constructed based on self-reported activity limitations and participation restrictions of 141 patients with CFS [64,65]. It consists of 26 items that are scored on a four point Likert-type scale (range 1–4; range total score 1: 1–16; range total score 2: 1–4) [91]. The average application time is 8 min. [61].

The literature search identified nine studies that used the CFSAPQ in their study to measure activity limitations and participation restrictions with persons with CFS. Four of these studies mentioned information about its internal consistency, test–retest reliability, content validity, convergent validity and criterion validity and mentioned the exact values that were evaluated by two other studies [25,33,61,63].

Although two studies evaluated its psychometric properties, no studies of good methodological quality were found that evaluated the internal consistency, reliability, agreement, criterion validity or responsiveness [64,65].

The **content validity** was evaluated according to a good methodological quality and found to be good [64].

Two studies evaluated the **internal consistency** (Cronbach's α > 0.80 for total score 1 and 2; variation from 0.87 to 0.94), but did not evaluate the factor structure [64,65].

Test–retest reliability was measured in different test conditions and was 0.80 for all items and total scores except for items 6 and 18 [64].

One study of good methodological quality evaluated the convergent validity with the MOS SF-36. Correlations of the CFS-APQ total scores varied from 0.53 to 0.78 for the subscales "physical functioning", "social functioning" and "bodily pain", the other correlations were lower than 0.50 [65]. No information is available about the ability of the CFS-APQ to discriminate between patients with CFS and other conditions where fatigue causes limitations [64].

Medical outcomes study short-form 36

The short-form 36 (SF-36) is a generic, self-reporting measurement instrument that evaluates functional status and well-being or quality of life [69]. It contains 36 items and eight subscales. The application time of the English version is 10 min or less [68]. A higher score on the scale indicates a better health and less bodily pain [68,69].

Thirty-two articles were found that used the SF-36 in their study. One mentioned the internal consistency of the SF-36 in persons with CFS (Cronbach's α 0.86) that was evaluated in another study [79]. There was little information mentioned in the articles on the (other) psychometric properties of the SF-36. Three studies evaluated the psychometric properties of the SF-36, but no studies of good methodological quality were found that evaluated the internal consistency, reliability, agreement, content validity, construct validity, criterion validity and responsiveness.
Correlation between the own subscales of the SF-36 varied from 0.26 to 0.84, except for the subscale ''role limitations due to physical problems'' which did not correlate with any other subscale [39]. **Internal consistency** was calculated for each subscale (Cronbach's α 0.74 to 0.90), but a factor analysis was not performed [68].
The SF-36 is capable of **discriminating** between patients with CFS [and chronic fatigue (CF)] and major depression (MD) based on intensity of impairment and heterogeneous patterns of disability [68]. According to research the SF-36 is too sensitive in the subscales ''role limitations due to physical problems'' and ''role limitations due to emotional problems'', mostly because a limited range of scores. This causes a floor effect and makes the measurement instrument unable to adequately discriminate
between persons with mild, moderate and severe limitations [39,68]. One study used the receiver operating characteristics (ROC) to identify the subscales that discriminate best between persons with CFS and healthy persons in two study samples, a community sample and one from tertiary care. Three subscales (''vitality'', ''role limitations due to physical problems'' and ''general health'') had an area under the curve of 0.91 ($p<0.05$) in the study sample from tertiary care and three subscales had a moderate sensitivity: ''vitality'', ''role limitations due to physical problems'' and '''social functioning'' in both study samples [69].

Euroqol questionnaire
The Euroqol questionnaire (EQ-5D) is a short questionnaire that can be completed in a short time span. The first part consists of five items each divided in three levels which can subdivide patients in 243 different health states. The questionnaire also uses a VAS on which patients can score their own health between 0 and 100 [39].
No studies of good methodological quality evaluated the reliability, agreement, content validity, criterion validity, construct validity and responsiveness. One study compared the EQ-5D with the SF-36 [39]. The EQ-5D appears less sensitive when there are lower levels of perceived ill-health, mainly in the first two domains of the questionnaire ''mobility'' and ''self-care''.
A ceiling effect occurs which reduces the EQ-5D to a two-point scale for these two domains [39]. There were also ceiling effects for all other items of the EQ-5D (>15% of the respondents scored 1 on all five items). A floor effect occurred on the ''Pain'' item of the EQ-5D (17.64% of the respondents scored 3) [39].

The World Health Organization quality of life assessment instrument
The World Health Organization quality of life assessment instrument (WHOQOL-100) encompasses 100 items and evaluates 24 facets of QOL within six domains and also has a general component: ''Global quality of life and general health''. Each facet comprises

of four items answered on a five-point Likert-type scale [51]. No studies of good methodological quality were found that evaluated the internal consistency, reliability, agreement, criterion validity and responsiveness.
The development of the measurement instrument started with the development of a definition of QOL. Subsequently, discussion groups evaluated the definition and searched for facets that they thought that belonged to it. Then, focus groups consisting of health professionals, lay persons and persons suffering from a chronic illness evaluated and developed the facets further and finally suggested items for the facets. The pilot instrument was completed by healthy and unhealthy persons. The method of development and evaluation suggests that, according to the COSMIN checklist, the measurement instrument has a good **content validity** [51].
The study has moderate methodological quality for the evaluation of the **convergent validity** between the WHOQOL-100 and the sickness impact profile (SIP), fatigue impact scale (FIS) and social support scales ''Practical support'', ''Emotional support'' and ''Understanding''. The correlations between the WHOQOL-100 and the SIP varied from 0.00 to 0.71, but only three subscales correlated higher than 0.50. Three domains of the WHOQOL-100 correlated significant with the dimension ''Psychosocial functioning'' of the SIP (-0.53, -0.60 and -0.55). Some social support scales were significantly correlated with Domain IV ''social relations'', the facet ''social support'', ''personal relations'' and ''sexual activity'' of the WHOQOL-100 with correlations from 0.50 to 0.84. The WHOQOL-100 was capable to distinguish patients with CFS from healthy persons, which supports its discrimination capability [51].

Work and social adjustment scale
The work and social adjustment scale (WSAS) is a five-item scale that evaluates a person's ability to perform ADL [35,36]. Each item is scored on a nine-point scale (range 0–8; range total score 0–40). A higher score indicates more limitations [36].
One study used the WSAS, but mentioned its psychometric properties merely vague [35].
One study evaluated its psychometric properties, but did not evaluate the reliability, agreement, construct validity, criterion validity and responsiveness according to a good methodological quality.
It does have an excellent methodological quality for the evaluation of the *internal consistency* of the WSAS. The principal component analysis supports the unidimensionality of the WSAS (range of the explained variance in the solutions: 59.1–67.6%). Cronbach's alpha was 0.79 for cohort 1 and 0.89 for cohort 2 at initial administration and 0.93 for cohort 2 after treatment and 0.94 after both 6 and 12 months. Analysis of variance (ANOVA) that classified groups per WSAS quartile indicated that persons who have a high disability rate according to the WSAS also had a high disability score on other measurement instruments [36].

Discussion

The literature search identified 38 different measurement instruments used in scientific research to evaluate activity limitations and participation restrictions in persons with CFS.
The most frequently used measurement instruments are: SF-36 (n=33), SIP (n=11), CFS-APQ (n=9) and Karnofsky Performance Scale (n=4). Based on the lack of information about the psychometric properties of most measurement instruments, more research is needed to determine whether these instruments have acceptable psychometric properties to be used in future studies.
Most measurement instruments that were evaluated in this study are generic, except for the CFS-APQ, which is disease specific [25,60,65]. Most generic measurement instruments do not encompass all activity limitations and participation restrictions experienced by patients with CFS, have limited content validity for this population, are difficult to interpret and time-consuming [64,92]. All this restricts their clinical usability [64]. Disease-specific measurements focus on the domains of quality of life that are related to a specific disease or a group of similar disorders. These measurement instruments are therefore more sensitive to detect significant clinical changes such as the increase or decrease of symptoms and/or functional status [92].
The literature search revealed eight psychometric studies of measurement instruments evaluating activity limitations and participation restrictions in a population with CFS [36,39,51,64,65,67–69]. The Dutch version of the CFS-APQ and WHOQOL-100 and the English version of the SF-36, EQ-5D and WSAS were studied [36,39,51,64,65,67–69]. The CFS-APQ and SF-36 were the only instruments that were evaluated by at least two studies [39,64,65,67–69].
Due to the lack of evidence and the limited information about the psychometric properties, the results of this literature research should be treated with caution. The different studies showed similar methodological shortcomings.
First, none of the studies performed, referred to a factor analysis to evaluate the internal consistency, except for the study of the WSAS [51,64,65,68]. The confirmation of the dimensionality of the other measurement instruments is therefore unknown. Second, most studies did not mention the hypothesis about the expected correlations to evaluate the psychometric property ‘‘construct validity’’ [36,39,51,65]. Finally, the content and psychometric properties of the comparison measurement instrument to evaluate the convergent validity were not always mentioned sufficiently [36,39,51,65].
In addition, there are other aspects that need to be considered when choosing a measurement instrument. First of all, the application method is a point of interest. The CFS-APQ, SF-36, EQ-5D, WHOQOL-100 and WSAS are self-reported measurement instruments [36,39,51,64,65]. According to Myers et al. self-reported instruments have limited value for patients with CFS, because they are prone to hypochondria and often score their performance worse than it actually is [39]. On the other hand, the application of objective measurement instruments is often expensive, time consuming and constitutes a greater burden for the participants than self-reported instruments [77]. Therefore, Myers et al. suggest that the use of self-reported measurement instruments,

which evaluate the health status of a patient, may be a useful addition to detailed assessment and observations of a health care worker during intake.
This systematic review shows that the psychometric properties of measurement instruments used in scientific research with patients with CFS are insufficiently evaluated within this population. This leads to scientific and clinical limitations. The measurement instruments are mostly used in scientific research for discriminative and evaluative purposes, for example to measure the effect of a treatment. The results of these measurement instruments cannot be judged objectively, as there is a chance that these results are not reliable or valid. This also has a large influence on clinical practice. First of all, professional caregivers consult scientific literature to ascertain their approach is evidence-based [91]. Professional caregivers therefore need reliable and valid measurement instruments. This systematic review shows that it is still unclear which measurement instruments are suitable to use in clinical practice with patients with CFS. The reliability and validity of the instruments cannot be guaranteed as long as the psychometric properties are not sufficiently evaluated according to an appropriate methodology.
If professional caregivers or researchers should be in need of a measurement instrument to evaluate activity limitations and participation restrictions, the CFS-APQ currently seems the most appropriate measurement instrument. Although it is a self-reported instrument, it is easy to administer, disease-specific and has moderate content and construct validity. However, the results obtained with the CFS-APQ still need to be used with caution because of its limited psychometric information.
The SF-36 is the most used measurement instrument in scientific research, but the quality of its psychometric properties is unknown due to the use of inadequate research methodologies. It is recommended to evaluate its psychometric properties in a population with CFS, because it could be a valuable measurement instrument for research and clinical practice given its broad content.
Future research should be focused on evaluating the remaining unknown psychometric properties. The studies of poor methodological quality should be repeated with sound methodology to provide strong evidence of the quality of a psychometric property. It seems appropriate to wait with the development of new measurement instruments until studies of high methodological quality indicate that there are significant shortcomings in the current ones, and new measurement instruments are warranted.

Conclusion

The psychometric properties of measurement instruments that evaluate activity limitations and participation restrictions are currently insufficiently evaluated in patients with CFS. At the moment, it is recommended to use the CFS-APQ. It is a disease-specific and self-reported instrument with a moderate content and construct validity. However, a lot of information is still missing about its psychometric properties, so further research is needed.
These findings do not suggest that the current measurement instruments are inadequate, but indicate that there is still a lot of high quality research needed to

evaluate the psychometric properties. It is recommended to use the COSMIN checklist while performing these studies.
On the other hand, this systematic research indicates that there are enough measurement instruments available to evaluate activity limitations and participation restrictions.
One can conclude that the development of new measurement instruments seems unnecessary. However, adequate evaluation of the current measurement instruments constitutes a priority.

[Supplementary material]

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Supplement: General information of all measurement instruments found measuring activity limitations and activity restrictions

Measurement instrument		Information
19-Item Medical Outcome Study Short-Form General Health Survey (MOS-19) *(n = 2)*	Authors	Katon et al. 1992; Morriss et al. 1997
	Population	CFS [37,38]
	Content	It consists of six subscales [38] and 19 items that measure physical, role and social functioning, mental health, health perception [37] and disability [38].
	Psychometric properties	*Reliability:* reliability coefficients for multi-item health scales: range 0.81-0.88 in an ambulatory population [37]. Correlations between subscales are found to be statistically significant [37]. Percentages of persons with poor health ratings were significantly higher on MOS subscales in a patient sample than a general population sample [37].
20-Item Medical Outcome Study Short-Form General Health Survey (MOS-20) *(n = 1)*	Authors	Clapp et al. 1999
	Population	CFS [22]
	Content	Survey-instrument consisting of 20 items that measure general health (physical and social functioning, mental health, health perception and pain) over the previous three months.
	Psychometric properties	*Validity:* Pearson product-moment correlation coefficient: r=-0.73 between MOS-20 and Wood Mental Fatigue Inventory scores.
Activity and symptom diary *(n = 1)*	Authors	Rahman et al. 2011
	Population	CFS [21]
	Content	Structured diary used for the monitoring of activities, intensity of fatigue, mood and pain and questions about sleep quality and timing over a period of five days.
	Psychometric properties	None mentioned.
Activity Restriction Index (ARI) *(n = 1)*	Authors	Clapp et al. 1999
	Population	CFS [22]
	Content	Measures a person's current ability to engage in seven activities: exercise and sports; housework and family responsibilities; shopping; work, career, or school; social activities; outdoor work; and favorite recreational activities on a seven point scale from 0 (not applicable or do not normally engage in this activity) to six (severely limited).
	Psychometric properties	*Reliability:* Intraclass correlation coefficient = 0.84
Assessment of functional status *(n = 1)*	Authors	Solomon et al. 2003
	Population	CFS [24]
	Content	Detailed interview asking the hours currently spend on work, household chores and other activities. The total hours spend on meaningful activities were calculated according to a variable. Time spend on activities before the onset of fatigue, current employment status and energy, wellness and ability to complete ADL on a scale from 1 to 100 were also asked.
	Psychometric properties	None mentioned

Supplement (continued)

Measurement instrument		Information
Baecke Physical Activity Questionnaire (BPAQ) *(n = 2)*	Authors	Clapp et al. 1999; Nijs et al. 2004
	Population	CFS [22,25]
	Content	Self-administered questionnaire consisting of three sections (work, sport and non-sport activity) assessing habitual leisure and occupational physical activities [25]. Higher scores indicate more habitual physical activity [25].
	Psychometric properties	Psychometric properties in both healthy and unhealthy subjects have been published [25]. *Reliability:* Test-retest reliability coefficient of the total index score in healthy persons using a one moth interval: Spearman's ρ= 0.93 [25]. Reliability coefficients range from 0.86 to 0.92 in persons without functional limitations [22]. Associations between total index and maximal oxygen consumption (ρ = 0.54, P < 0.05), percentage of body fat (ρ = 0.49, P < 0.05) and the four week activity history (ρ = 0.37, P < 0.05) by use of Spearman correlations [25].
Barthel Activities of Daily Living Index *(n = 1)*	Authors	Allanson et al. 2002
	Population	CFS, motor conversion disorder and diverse somatoform disorders [26]
	Content	Scores range from 0-20 with 20 indicating full independence.
	Psychometric properties	None mentioned.
Brief Disability Questionnaire (BDQ) *(n = 1)*	Authors	Rahman et al. 2011
	Population	CFS [21]
	Content	Measures functional impairment: number of days over the past month ADL could not be performed fully.
	Psychometric properties	None mentioned.
Canadian Occupational Performance Measure (COPM) *(n = 1)*	Authors	Nijs et al. 2009
	Population	CFS [27]
	Content	A semi-structured interview assessing the ability to perform ADL within three domains: self-care, productivity and leisure time with the focus on personal problems while performing ADL. Two subscale scores can be calculated: the 'performance score' indicates the ability to perform ADL and the 'satisfaction score' indicates a person's satisfaction with ADL.
	Psychometric properties	The psychometric properties of the COPM are well established.

Supplement (continued)

Measurement instrument		Information
Chronic Fatigue Syndrome Activities and Participation Questionnaire (CFS-APQ) *(n = 11)*	Authors	Meeus et al. 2012; Nijs et al. 2003; Nijs et al. 2004; Nijs et al. 2004a; Nijs et al. 2004b; Nijs et al. 2004c; Nijs et al. 2005; Nijs et al. 2008; Nijs et al. 2008a; Nijs et al. 2008b; Nijs et al. 2009
	Population	CFS [25,27,33,58–65]
	Content	Self-administered[27,58,59], disease [25,60,65] and time-specific [65] questionnaire consisting of 26 items [63] measuring activity limitations and participation restrictions with persons with CFS [25,27,33,58–61,63,65]. Two overall scores can be calculated: ▪ Total score 1/Quality of Life Index: importance verification (range 1 to 16) [27,33,58,61,63–65] ▪ Total score 2: no importance verification (range 1 to 4) [25,33,58,61,63–65] Application time ranged from four to fourteen minutes in 25 persons (mean score ± SD 7.9 ± 2.7) [73].
	Psychometric properties	***Dutch version with a study sample of 47 adults with CFS:*** Cronbach's alpha coefficient total item scores: 0.94 [33,61,65]. *Reliability:* Test-retest reliability for the overall scores (total score 1 and 2) using intraclass correlation coefficient were ≥0.95 (99%) [33,61,63]. ICC total scores > 0.80 except for question 6, 9 and 18 [65]. *Validity:* Convergent validity: correlation between overall scores (total score 1 and 2) and VASscores for pain (Spearman rho = 0.51 (99%) / 0.44 (95%)) and fatigue (Spearman rho = 0.50 (99%) / 0.47 (98%)) [61,63,65]. Correlation of total score 2 with VAS ability to concentrate (Spearman rho = 0.41 (92%)) [65]. Content validity was reported [61,63]. Items of the CFS-APQ were checked against the ICIDH and only activity limitations and participation restrictions were measured [61,65]; 85.8% matched the content of the CFS-APQ [65]. *Internal consistency:* Cronbach's alpha with 88 adults with CFS = 0.87 [64]. *Validity:* Convergent validity: both CFS-APQ scores correlated significantly with 6 SF-36 dimensions with Pearson correlation coefficients ranging from -0.34 to -0.78. Discriminant validity: no correlation was found between the two CFS-APQ scores and the 'emotional role functioning' and 'mental health' dimension of the SF-36. All correlation coefficients are mentioned in Table 3 of the article [64]. Criterion validity: statistically significant correlations were found between the main variables during exercise testing and both scores of the CFS-APQ [61].

Supplement (continued)

Measurement instrument		Information
Danish CFS Questionnaire Repeated Measure *(n = 1)*	Authors	Andersen et al. 2004
	Population	CFS [29]
	Content	QOL questionnaire that measures coping with daily living. It consists of three sections with questions regarding (1) social life, work situation, etc. (2) cognitive abilities, memory, etc. (3) neuropsychological problems, allergies, etc. Constructed in Danish.
	Psychometric properties	None mentioned.
Euroqol Questionnaire (EQ-5D) *(n = 1)*	Authors	Myers et al. 1999
	Population	CFS [39]
	Content	It consists of five domains with each three levels which classifies a person into 243 health states and a VAS on which a person can rate its own health between 0 and 100.
	Psychometric properties	It has been validated in normal populations and used in persons with other chronic conditions. It seems less useful at lower levels of perceived ill-health. ***EQ-5D and SF-36:*** SF-36 dimensions and Euroqol-5D health value and VAS correlated well, except for the 'physical limitation of role' dimension. Lowest correlations were with the 'emotional limitation of role' and 'mental health' dimension. All correlations are mentioned in Table 3 of the article. Significant and appropriate differences were found when comparing SF-36 dimensions and individual EQ-5D items which address similar concepts with exception of the comparisons with the 'physical limitation of role' dimension. All comparisons are mentioned in Table 1 of the article. Duration of ill-health was significantly negatively correlated with the EQ health score and VAS score.
Frenchay Activities Index *(n = 1)*	Authors	Allanson et al. 2002
	Population	CFS, motor conversion disorder and diverse somatoform disorders [26]
	Content	Scores range from 0 to 45 with 45 indicating full involvement in domestic tasks, social events, hobbies, and employment.
	Psychometric properties	None mentioned.
Functional Status Questionnaire (FSQ) *(n = 1)*	Authors	Christodoulou et al. 1998
	Population	CFS [40]
	Content	Examines three aspects of functional disability (activities of daily living, social activities and general inactivity) by measuring activity over the previous month.
	Psychometric properties	None mentioned.

Supplement (continued)

Measurement instrument		Information
General questions regarding daily functioning *(n = 1)*	Authors	Vercoulen et al. 1994
	Population	CFS [23]
	Content	Measures the interference of complaints with daily activities, problems and satisfaction in housekeeping activities and work.
	Psychometric properties	None mentioned
Human Activity Profile (HAP) *(n = 1)*	Authors	Weinstein et al. 2009
	Population	CFS [30]
	Content	Self-reported instrument containing 94 items representing common activities that require a known amount of average energy expenditure (MET). The higher the number of the activity, the greater the MET value. The activities can range up to 10 MET. Two scores can be calculated: Maximum Activity Score (MAS) and the Adjusted Activity Score (AAS)
	Psychometric properties	None mentioned.
Karnofsky Performance scale *(n = 4)*	Authors	Clapp et al. 1999; Sharpe et al. 1996; Thomas et al. 2008; Wiborg et al. 2010
	Population	CFS [22,28,41,42]
	Content	A descriptive, ordinal scale [42] that measures the degree of disability on a scale from 1 to 100 [22,41,42]with a ten-point interval [42]
	Psychometric properties	It was found reliable and valid in several patient populations [28]. Good agreement was found when allocating patients to specified outcome categories (Cohen's K greater than 0.8 at every time point) [28]. Limited sensitivity and ability to detect change for persons with CFS due to its limited range of scores for the majority of persons with CFS [22].
Manchester Short Assessment of Quality of Life (MANSA) *(n = 1)*	Authors	Priebe et al. 2008
	Population	CFS [66]
	Content	Measures generic QOL, consists of 16 questions of which four are objective and the twelve measure satisfaction with life as a whole and specific life domains (leisure activities, financial situation, living situation, personal safety, social relations, mental health and family relationship)
	Psychometric properties	*Validity:* Results of the MANSA have high concordance with the Lancashire Quality of Life Profile.

Supplement (continued)

Measurement instrument		Information
Medical Outcome Study Short-Form General Health Survey (SF-36) *(n = 37)*	Authors	Buchwald et al. 1996; Ciccone et al. 2003; Ciccone et al. 2003a; Ciccone et al. 2010; Collin et al. 2011; Fulcher et al. 1997; Heins et al. 2011; Herrell et al. 2002; Jason et al. 2003; Jason 2008; Jason et al. 2009; Jason et al. 2011; Kempke et al. 2010; Kennedy et al. 2004; Knoop et al. 2007; Komaroff et al. 1996; Kop et al. 2005; Meeus et al. 2012; Mos-Morris et al. 2003; Myers et al. 1999; Nijs et al. 2004c; Nijs et al. 2005; Nijs et al. 2008; Nijs et al. 2008a; Nijs et al. 2009; Núñez et al. 2011; O'Dowd et al. 2006; Pardaens et al. 2006; Powell et al. 2001; Priebe et al. 2008; Schmaling et al. 2000; Schoofs et al. 2004; Tummers et al. 2010; Tummers et al. 2012; VanNess et al. 2010; Ware et al. 1992; White et al. 2011
	Population	CFS [27,32–34,39,52–54,58–60,64,66,68,69,71,72,74,75,79–81,85–87,89,90] CFS en/of FM [82,88] CFS en RA [83] CFS/ME [73,76–78,84] CFS, FM, MCS [70]
	Content	Generic [81,84] self-reported measure [34,39,66,76,78–80] consisting of eight subscales [33,34,39,58,64,67–69,72,75,76,78,80,81,83–85,87] (physical functioning, role limitation due to physical health problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health) [33,39,64,66–69,75–77,80–82,85,87,89] and 36 items [34,67,68,70,74–76,78,84] measuring functional status [27,33,39,58–60,64,68,70,75,76,79,83,84,87] and QOL [27,33,34,58–60,64,68,70,71,75,82,84,87] in medically ill persons [70–72,82,83]. Subscale scores range from 0 to 100 [32–34,39,52–54,58,64,69,71,72,75,80,87] with a higher score indicating less disability [33,34,52,58,68,69,71,72,75–77,79,82,85,87]. Physical and mental summery scores can be calculated [66,75].Application time < 10 minutes [68,75,81]. Each subscale has acceptable reliability and validity [27,32,58,59,64,68,69,71,75–77,79,88,89] in different patient populations [27,58–60,64,68,75,89] and is able to discriminate between gradations of disability [69,77]. Adequate internal consistency, discriminant validity among subscales and important differences between patient and nonpatient populations in the pattern of scores were found [69,77,78,84]. It has sufficient psychometric properties to measure functional status in patients with CFS/ME [76]. General scores of the US population have been calculated [75].
	Psychometric properties	ROC analysis: the 'vitality', 'physical limitation of role' and 'social functioning' dimensions have an AUC of 0.86 or higher in both the community sample and the tertiary care CFS sample. A cut-off score of ≤ 35 or less for 'vitality', ≤ 62.5 for 'social functioning' and ≤ 50 for 'physical limitation of role' dimension were calculated and should be used to designate substantial reductions in functional status [69].

Supplement (continued)

Measurement instrument		Information
Medical Outcome Study Short-Form General Health Survey (SF-36) *(n = 37)* *(continued)*	Psychometric properties	*Internal consistency:* Cronbach's alpha physical functioning scale (Dutch Version) = 0.92 [52]. Cronbach's alpha 'physical functioning scale' with persons with CFS = 0.86 [79] / 0.90 [68]. Cronbach's alpha overall = 0.852 [88]. Cronbach's alpha coefficients range from 0.78 to 0.93 [64]. Cronbach's alpha coefficients range from 0.74 to 0.90 [68]. *Reliability:* Reliability coefficients for physical functioning scale > 0.90 [33]. Median of the reliability coefficients for each subscale ≥ 0.80, except for the social functioning scale [33]. Test-retest reliability coefficients for SF-36 scales range from 0.60 to 0.81 [64]. *Sensitivity:* It is a sensitive indicator of change in health status [80]. Sensitive to treatment change [76,84].
Multidimensional Assessment of Fatigue (MAF) *(n = 2)*	Authors	Schmaling et al. 2000; Weinstein et al. 2009
	Population	CFS [87] CFS, RA en PM [30]
	Content	Self-reported scale [30] consisting of 16 items [30,87] that measure 4 dimensions of fatigue: severity, distress, degree of interference in activities of daily living, and timing [30]. It can generate two scores: fatigue severity and fatigue-related disability [87]. Scores range from 1 to 10 [87].
	Psychometric properties	*Internal consistency:* Cronbach's α = 0.92 [30]. *Validity:* it has concurrent validity [30].
Subsidiary measures of functioning *(n = 1)*	Authors	Sharpe et al. 1996
	Population	CFS [28]
	Content	Patient rating of interference with ADL, improvement in employment status, number of days spend in bed/week.
	Psychometric properties	None mentioned.
One-Time Measure *(n = 1)*	Authors	Andersen et al. 2004
	Population	CFS [29]
	Content	Retrospective questionnaire with a rating of symptoms and functional changes over the past five years. Constructed in Danish.
	Psychometric properties	None mentioned.

Supplement (continued)

Measurement instrument		Information
Patient-Reported Outcomes Measurement Information System, Health Assessment Questionnaire (PROMIS HAQ) *(n = 1)*	Authors	Costigan et al. 2010
	Population	CFS [31]
	Content	It measures the functional impact of CFS on persons. It is derived from the HAQ, consists of eight domains of physical function (dressing, arising, eating, walking, hygiene, reach, grip and activity) and 20 questions that ask about the ability to carry out ADL. Higher scores indicate greater functional impairment.
	Psychometric properties	None mentioned.
Physical Activity Questionnaire (PAQ) *(n = 1)*	Authors	Tummers et al. 2012
	Population	CFS [32]
	Content	The PAQ measures functional patterns.
	Psychometric properties	None mentioned.
Quality Of Life Scale *(n = 1)*	Authors	Jason 2008
	Population	ME/CVS [76]
	Content	Consists of six conceptual domains (material and physical well-being, relationships with other people, social, community and civic activities, personal development and fulfillment, and recreation, and independence) and 16 items measuring the degree of satisfaction with different life activities for persons with various chronic illnesses. Higher scores indicate more overall life satisfaction.
	Psychometric properties	*Reliability:* high test-retest reliability. *Validity:* high convergent and discriminate construct validity in groups with persons who suffer from various stable chronic illnesses.
Quality of Life Questionnaire *(n = 1)*	Authors	Schoofs et al. 2004
	Population	CVS/FM [88]
	Content	Consists of 192 questions divided into 15 categories that measure QOL and other behaviors related to physical health, psychological health, and substance abuse Range scores from 0 to 80 with 50 representing an average score
	Psychometric properties	*Internal consistency:* (Cronbach's alpha) = 0.851 (n = 16 adults with CFS).
Questionnaire *(n = 1)*	Authors	Assefi et al. 2003
	Population	CFS, MED, FM, CF [2]
	Content	Interview consisting of 22 items measuring a person's financial, occupational and social status.
	Psychometric properties	None mentioned.
Questionnaire *(n = 1)*	Authors	Nijs et al. 2008a
	Population	CFS [33]
	Content	Consists of five items (illness duration, disability compensation, activity status, employment status, and premorbid versus current employment rate in percentage) measuring employment status.
	Psychometric properties	None mentioned.

Supplement (continued)

Measurement instrument		Information
Questionnaire *(n = 2)*	Authors	Gadalla 2008, Gadalla 2008a
	Population	Chronic physical illness [43,44]
	Content	Two variables were used to measure short-term disability: number of disability days two weeks prior to the interview; help needed when performing ADL [43,44].
	Psychometric properties	None mentioned.
Questionnaire *(n = 1)*	Authors	Perruccio et al. 2007
	Population	13 chronic conditions [45]
	Content	Difficulty to perform activities or reduction of activities due to a disease or illness were assessed.
	Psychometric properties	None mentioned.
Questionnaire *(n = 1)*	Authors	Wilson et al. 2001
	Population	CFS [46]
	Content	Self-reported questionnaire consisting of 119 items divided in six sections: (1) personal information (2) information about illness (3) rating the presence of 48 specific symptoms either physical, cognitive or neuropsychiatric and ten questions asking about non-specific symptoms (4) medical antecedents (5) family history of psychiatric disorders (6) functional impairment (work participation and social activity).
	Psychometric properties	None mentioned.
Self-assessment of functional impairment *(n = 1)*	Authors	Butler et al. 1991
	Population	CFS [47]
	Content	Consists of four VASs about ability to work, home management, social and private leisure activities.
	Psychometric properties	None mentioned.
Sickness Impact Profile (SIP) 8 *(n = 6)*	Authors	Goedendorp et al. 2009; Heins et al. 2011; Knoop et al. 2007; Tummers et al. 2010; van der Werf et al. 2000; Vercoulen et al. 1994
	Population	CFS [23,52–56]
	Content	Consists of eight subscales [52,53] (home management; mobility; alertness behavior; sleep/rest; ambulation; social interactions; work; recreation and pastimes) [23,53–56] measuring limitations in ADL as well as overall impairment [52,54,55]. Total scores range from 0 to 5799 [56] with higher scores indicating more impairment [52,56].
	Psychometric properties	Mean SIP8 total score of a healthy group of 78 women is 65.5 (SD ± 137.8) [53]. *Internal consistency:* overall Cronbach's α of the Dutch version = 0.91 [52].
Sickness impact profile (SIP) *(n = 4)*	Authors	De Vries et al. 1997; Hadlandsmyth et al. 2009; Lutgendorf et al. 1995; Petrie et al. 1995; Wiborg et al. 2010
	Population	CFS [42,48–51]

Supplement (continued)

Measurement instrument		Information
Sickness impact profile (SIP) *(n = 4)* *(continued)*	Content	Self-reported measure consisting of 136 items [48,49] measuring disability/functional limitations associated with health problems [42,48–51]. It has 12 subscales [49,50]: sleep and rest, body care and movement, emotional behavior, home management, mobility, social interaction, ambulation, alertness behavior, communication, work, recreation/pastimes, and eating [49]. Three domain scores can be calculated: physical, psychosocial and independence/total impairment score [48,49]. Higher score indicates more impairment [42,49].
	Psychometric properties	It has been found reliable [71,88] and valid [70-71,88] for a variety of patient groups, is able to detect subtle changes in functional abilities in medical patients [70-71].
Sickness Impact Profile (SIP) Short version *(n = 1)*	Authors	Van Damme et al. 2006
	Population	CFS [57]
	Content	It consists of 68 items and assesses the impact of an illness on ADL (functional impairment). It has 6 subscales: somatic autonomy, mobility control, psychic autonomy and communication, social behavior, emotional stability, mobility range. Higher scores indicate more impairment.
	Psychometric properties	It is found to be reliable and valid.
Stanford Health Assessment Questionnaire (HAQ) *(n = 1)*	Authors	Núñez et al. 2011
	Population	CFS [34]
	Content	Self-administered measurement consisting of 20 items that include 8 functional categories which measure the functional capacity to perform ADL. It also includes a general evaluation of a person's health status from his own perspective and a measurement of pain intensity by use of two VASs. Scores range from 0 to 3 with a higher score indicating more disability.
	Psychometric properties	None mentioned.
The World Health Organization Quality Of Life Assessment Instrument (WHOQOL-100) *(n = 1)*	Authors	De Vries et al. 1997
	Population	CFS and healthy persons [51]
	Content	It consists of 100 items assessing 24 facets of QOL within six domains (physical health, psychological health, level of independence, social relationships, environment, and spirituality/religion/personal beliefs) and a general evaluative facet: overall quality of life and general health.
	Psychometric properties for CFS group	*Internal consistency* Cronbach's alpha for the facets ranged from 0.43 (physical environment) to 0.96 (activities of daily living) Cronbach's alpha for the domains ranged from 0.71 (social relationships) to 0.93 (level of independence) All reliability coefficients can be found in table 3 of the article.

Supplement (continued)

Measurement instrument		Information
The World Health Organization Quality Of Life Assessment Instrument (WHOQOL-100) *(n = 1)* *(continued)*	Psychometric properties for CFS group	*Construct validity* WHOQOL-100 and SIP = high correlation between scales that measure more or less the same construct. All correlations can be found in table 4 of the article. WHOQOL-100 and Fatigue Impact Scale = significant correlation between WHOQOL-100-Energy and Fatigue and FIS-Social Dimension (r = -0.31). WHOQOL-100 and Social support scales = correlations can be found in table 6 of the article. *Discriminatory capacity* = all healthy persons were distinguished from the CFS group based on their scores on the WHOQOL-100
Work and Social Adjustment Scale (WSAS) *(n = 2)*	Authors	Cella et al. 2011; Cella et al. 2011a
	Population	CFS [35,36]
	Content	Consists of 5 items measuring a person's ability to work, engage in household management and participate in social and private leisure activities and relationships [35,36]. Scores range from 1 to 40 [35]. Higher scores indicate higher levels of disability [36]. Reliable and valid measure of impaired functioning [35]. Good internal consistency (Cronbach's alpha ranging from 0.70 to 0.90) [36]. Sensitive to patient differences in disorder severity and treatment-related change [35,36].
	Psychometric properties	***Psychometric properties with a population with CFS*** It has a monofactorial structure [36]. *Internal consistency:* Cronbach's alpha = 0.79 (cohort 1) and 0.89 (cohort 2) at initial assessments; 0.93 (cohort 2) posttreatment and 0.94 (cohort 2) at 6 and 12 months [36]. *Split-half reliability:* Spearman-Brown split-half reliability 0.73 (cohort 1) and 0.85 (cohort 2) at initial assessment; Cohort 2 = 0.90 posttreatment, 0.93 6-month follow-up and 0.94 12-month follow-up [36]. *Construct validity:* correlations between the WSAS and nine other measurement instruments were calculated. Correlations ranged from -0.381 to 0.411. All correlations are mentioned in table 1 of the article [36]. *Sensitivity to change:* repeated-measure ANOVA showed a significant reduction of WSAS scores across four WSAS assessments (initial assessment, posttreatment, 6-month interval, 12-month interval) [36].

ADL = Activities Of Daily Living; QOL = Quality of Life; PM = Polymyositis; FM = Fibromyalgia; CF = Chronic Fatigue; MED = chronically fatiguing but unrelated medical condition; COPD = Chronic Obstructive Pulmonary Disease; ROC analysis = Receiver Operating Characteristics; AUC = Area Under the Curve

n = number of articles that used the mentioned measurement instrument

CHAPTER 3

Measuring the physical activity level and pattern in daily life in persons with chronic fatigue syndrome/myalgic encephalomyelitis: a systematic review

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Abstract

Background: A lower activity level and imbalanced activity pattern are frequently observed in persons with chronic fatigue syndrome (CFS)/myalgic encephalomyelitis (ME) due to debilitating fatigue and post-exertional malaise (PEM). To provide an optimal treatment strategy, insight into a patient's current physical activity level and pattern is necessary and identification of reliable and valid measures or scales measuring physical activity level and pattern in this population is warranted.

Objective: To identify measures or scales used to evaluate activity level and/or pattern in patients with CFS/ME and review their psychometric properties.
Methods: A systematic literature search was performed in the electronic databases PubMed and Web of Science until 12 October 2016. First, articles including relevant measures were identified. Secondly, psychometric properties of relevant measurement instruments were extracted and rated based on the COSMIN checklist.

Results: The review was performed and reported according to PRISMA statement. A total of 51 articles and 15 unique measurement instruments were found, but only three instruments have been evaluated in patients with CFS: the Chronic Fatigue Syndrome-Activity Questionnaire (CFS-AQ), Activity Pattern Interview (API) and International Physical Activity Questionnaire-Short Form (IPAQ-SF), all self-report instruments measuring physical activity level.

Conclusions: The IPAQ-SF, CFS-AQ and API are all equally capable of evaluating the physical activity level, but none of these are optimal to use. Although often used as gold standard to capture physical activity patterns, activity monitors have not yet been evaluated in these patients. More research is needed to evaluate the psychometric properties of existing instruments, including activity monitors.

Introduction

Chronic fatigue syndrome (CFS)/myalgic encephalomyelitis (ME) comprises a complex of symptoms characterized by clinically defined debilitating fatigue that cannot be explained by other medical or psychiatric conditions and is not sufficiently reduced by resting [1,2]. The experience of fatigue causes substantial reductions in previous levels of occupational, educational, social or personal activities, resulting in limitations in meaningful areas of life [1,2]. Scientific evidence indeed shows that the activity levels of patients with CFS/ME are significantly lower than those of healthy subjects and a large variation exists in activity levels between patients [3–9]. Additionally, the performance of mild physical or mental activities can lead to the exacerbation of symptoms, also known as PEM.

PEM is one of the primary characteristics of CFS/ME and a main reason why patients with CFS/ME are unable to continue their daily routine [4,8,10,11]. The presence of these exacerbations may result in avoidance of activities and prolonged periods of rest, expecting that this strategy will cause improvement [11–13]. In contrast to this perception, this strategy instead results in decreased exercise tolerance and reduced ability to perform activities of daily living (ADL) [3,9,11–14].
Additionally, although most patients perform fewer, and mostly sedentary activities, bursts of exertion are sometimes observed in periods in which patients try to perform at pre-morbid level [6,13,15]. This deviant activity pattern observed in some patients with CFS/ME may cause a negative feedback cycle where PEM, an overall lower activity level and imbalanced activity pattern are often observed [3,6,15,16].

Therefore, the focus of rehabilitation treatment lies in enabling patients to participate in meaningful life activities, depending on a patient's physical, social, cultural and spiritual context and beliefs that promotes or maintains their health, well-being, participation and autonomy [17–19]. Treatment strategies for CFS/ME are focused on activity self-management preventing both PEM and avoidance behaviour [3,12–14,20,21]. Frequently used therapeutic interventions are activity pacing, graded exercise therapy and cognitive behavioural therapy [15,21–26].

To maintain an optimal activity level and balanced pattern over a longer period of time, insight into daily activity performance of a patient is necessary [6,9,20]. Thus, the activity level and pattern need to be established using reliable and valid measures or scales before a clinical practitioner can assess and evaluate a patient's health status, provide information, a suitable treatment strategy and evaluate a patient's course of recovery after treatment [3–5,9,27].

The aim of the review was twofold. The first aim was to systematically review the literature for measures or scales capable of evaluating the activity level and/or pattern that were used in patients with CFS/ME; second, to critically appraise the psychometric properties of identified measures or scales in patients with CFS/ME.

Method

PRISMA guidelines (Preferred Reporting Items for Systematic reviews and Meta-Analyses) were used to structure the review methods [28] and the eligibility criteria, search strategy, methods for study selection, data-extraction and rating were specified in advance.

Eligibility criteria

To be included in the first part of the present systematic review, studies had to report the use of measures or scales evaluating (physical) activity level or pattern and the study had to be undertaken with adult patients with CFS/ME. The second part of the systematic review only included studies that evaluated the psychometric properties of identified measures or scales during the literature search.

Information sources and search strategy

The electronic databases PubMed and Web of Science were used to execute the literature search (Table 1). Both databases were searched until 12 October 2016 for relevant articles. No limits were set for the date of publication.

Study selection

Study selection was based on two screening phases. Both screening phases were performed by two independent reviewers. The initial literature search was performed until February 2014 and studies were screened by two of the authors (JVR and AD). An update of the systematic literature search was performed from March 2014 until 12 October 2016 and the studies were screened by two other authors (IH and KV). During both literature searches, a third reviewer (MM) was only involved in the screening process if consensus could not be reached between the two reviewers.

The first selection was based on title and abstract. Articles that met the first two inclusion criteria and could not be excluded based on the criteria mentioned below were included for full text reading. The third inclusion criterion was only applied during full-text reading, because not all articles mentioned the used measure or scale in their abstract. All articles that used a relevant measure or scale evaluating the activity level or activity pattern were included, unless exclusion criteria were identified during full-text reading. References of all included articles were checked to identify other articles measuring the psychometric properties of relevant measures or scales.

Inclusion criteria:

- The study included adult humans with CFS/ME;
- was written in Dutch or English;
- included a measure or scale that evaluates (physical) activity level or pattern.

Exclusion criteria:

- Studies regarding measures or scales evaluating limitations in activities, quality of life or any other construct than the activity level or pattern;
- studies measuring body functions including biomarkers, sleep, spirometry or participation;

- laboratory research or *in vitro* research;
- use of a model or theory as intervention;
- random non-further specified or dichotomous questions or instrument measuring fatigue;
- abstract, guideline, congress report, review, meta-analyses, study protocol or case study.

Data extraction and rating

First, all relevant measures or scales evaluating the physical activity level and/or pattern in patients with CFS/ME were extracted from the articles and compiled (Table 2).

Second, as recommended by Mokkink et al., the research methodologies of articles evaluating the psychometric properties of measures or scales assessing the physical activity level or pattern of patients with CFS/ME were rated using the COSMIN checklist (Consensus-based Standards for the selection of health Measurement Instruments) [29]. The COSMIN checklist was developed in 2010 according to a Delphi study by international experts in health-related measurement instruments. The COSMIN checklist evaluates ten psychometric properties and consists of four possible answers: 'excellent', 'good', 'fair' and 'poor'. The 'Interpretability' box was filled in for every article and scored based on the number of questions that could be answered with 'yes' (1 or 2 = poor; 3 or 4 = fair; 5 or 6 = good; 7 = excellent). A general score for the methodological quality was provided for every individual psychometric property for every measure or scale by taking the lowest score from every box (Table 4) [30]. General information for every study and measure or scale was extracted with the help of the 'Generalizability' box of the COSMIN checklist and compiled in Table 3 [30].

Table 1: Search strategy

Population	Intervention		Outcome	Exclusion
chronic fatigue syndrome (MeSH)	measurement(s)	activities of daily living [MeSH]	activity	depression [MeSH]
(benign) myalgic encephalo(mye)litis (ME)	outcome / health impact / outcome and process / risk / process / symptom / self-assessment(s) [MeSH]	activity level	exercise [MeSH]	(depressive / mental) disorder(s) [MeSH]
CFS/ME	self-reporting questionnaire(s)	activity pattern(s)	(leisure / human) activities [MeSH]	psychiatric status rating scales [MeSH]
post-viral/infectious fatigue syndrome	interview [MeSH]	(treatment) outcome(s)	physical endurance [MeSH]	neurasthenia
yuppie flu	evaluation(s)	metabolic equivalent [MeSH]	(physical) movement	
chronic Epstein-Barr virus syndrome	health surveys [MeSH]		(an)aerobic,	
myalgia syndrome	accelerometry [MeSH]		daily functionality	
myalgic encephalopathy	actigraphy [MeSH]		psychological adaptation [MeSH]	
	exercise test [MeSH]		activities of daily living [MeSH]	
	monitoring		physical / mental exertion(s)	
	data collection [MeSH]		physical exertion [MeSH]	
	evaluation studies as topic [MeSH]		motor activity [MeSH]	
	instrument(s)		movement [MeSH]	
	self-evaluation programs [MeSH]			
	diagnostic self-evaluation [MeSH]			
	health care evaluation mechanisms [MeSH]			
	psychometric characteristics			
	clinimetric proprties			
	treatment outcome [MeSH]			
	test			
	interview as topic [MeSH]			
	assessment(s)			
	questionnaires [MeSH]			
	outcome(s)			

Table 2: Information regarding all included measurement instruments

Measurement instrument	Goal	Ref.
Activity Record (ACTRE)	To measure physical activity	[31,32]
Activity Pattern Inventory (API)	To measure the usual activities performed on a typical day	[33]
Atherosclerosis Risk in Communities (ARIC) Baecke Physical Activity Questionnaire	To assess habitual leisure and occupational physical activities	[34–37]
Activity monitor	To measure physical activity	[6,15,16,31,38–64]
Checklist Individual Strength (CIS)	To measure physical activity	[6,38–40,42,43,46,47,49–51,57,61–63,65–67]
Chronic Fatigue Syndrome-Activities Questionnaire (CFS-AQ)	To measure physical activity	[33]
Dartmouth Primary Care Cooperative Research Network functional health assessment charts/World Organization of General Practice/Family Physicians (COOP/WONCA Charts)	To measure physical activity	[68]
Diary and Self Observation List	To measure physical activity	[31,33,53,64,69–72]
Godin Leisure-Time Exercise Questionnaire	To measure physical activity	[73]
Intelligent Device for Energy Expenditure and Activity	To measure physical activity	[69]
International Physical Activity Questionnaire-Short Form (IPAQ-SF)	To measure physical activity	[33,64,74]
Older Adult Exercise Status Inventory (OA-ESI)	To measure physical activity	[75]
Paffenbarger Physical Activity Questionnaire	To measure physical activity	[76]
Physical Activity Index of College Alumnus Health Questionnaire	To measure physical activity	[77]
Visual Analogue Scale (VAS) Daily Physical Activity Level	To measure physical activity	[6,60]

Results

Identification of measures or scales evaluating the physical activity level or activity pattern

The systematic literature search identified 919 articles. After exclusion of 717 articles based on the criteria mentioned above, 202 articles were included for full text reading. Full-text reading led to the exclusion of another 151 articles (Figure 1).

During full-text reading, 15 unique, relevant measures or scales evaluating the physical activity level or activity pattern of patients with CFS/ME were identified (Table 2), but the psychometric properties of only three instruments were evaluated (Tables 3 and 4).

Critical appraisal of psychometric properties of included measures or scales

Chronic fatigue syndrome – activity questionnaire

The Chronic fatigue syndrome – activity questionnaire (CFS-AQ) was used by Scheeres et al. to measure activities performed in the previous two weeks by patients with CFS [33]. The measure consists of four subscales: physical activity (four items), rest (four items), using aids (one item) and social activity (one item). The 10 items are scored on a four-point Likert scale. The time to complete the questionnaire ranged from five to seven minutes. Scheeres et al. described that this newly developed questionnaire has good *internal consistency* (Cronbach's alpha = 0.73) and *test–retest reliability* (Spearman's rho = 0.72). Although the internal consistency and test–retest reliability appear to be adequate, insufficient information about the research methodology was provided. Methodological quality of the study by Scheeres et al. for evaluating the internal consistency and test–retest reliability is therefore rated as poor by the COSMIN checklist [33].

Criterion validity was evaluated by calculating the correlations between the three measures or scales CFS-AQ, Activity Pattern Interview (API) and International Physical Activity Questionnaire – Short Form (IPAQ-SF), and continuous scores of the activity monitor, a frequently used measure to objectively evaluate daily physical activity [6,15,16,31,39–46,48–62,64,78].

The mean daily physical activity score of CFS patients was calculated based on 12 days actography to define an activity monitor typology (passive/fluctuating active). Patients scoring zero or one days of the 12 measured days above a reference score were defined as 'passive'. Patients scoring two or more days above a reference score were defined as 'fluctuating active'.

Logistic regression analyses were performed with the CFS-AQ and IPAQ-SF and activity monitor typology as dependent variable to predict the probability that a person with CFS is active, according to the activity monitor typology. The obtained predicted probability scores led to the development of a dichotomous outcome scale of activity level (active/passive) for the CFS-AQ and IPAQ-SF.

Receiver operating characteristics (ROC) curve was calculated to identify the CFS-AQ's sensitivity and specificity.

Sensitivity is the number of passive patients identified as being passive, while *specificity* is the number of active patients identified as being active. The best cut-off point for the CFS-AQ is 0.73 with a sensitivity of 64.6% and specificity of 65.2%. Area under the curve

(AUC) calculated the CFS-AQ's validity. The AUC was 0.710, which means that the validity of the CFS-AQ is higher than the API, but lower than the IPAQ-SF. The CFS-AQ correlated moderately with the continuous scores of the activity monitor (Spearman's rho = 0.41) [33].

Methodological quality of the study for evaluating the criterion validity was found to be fair by the COSMIN checklist [33]. Scheeres et al. concluded that the CFS-AQ has no added value compared to the IPAQ-SF or the API [33]. No other studies evaluating the CFS-AQ were found.

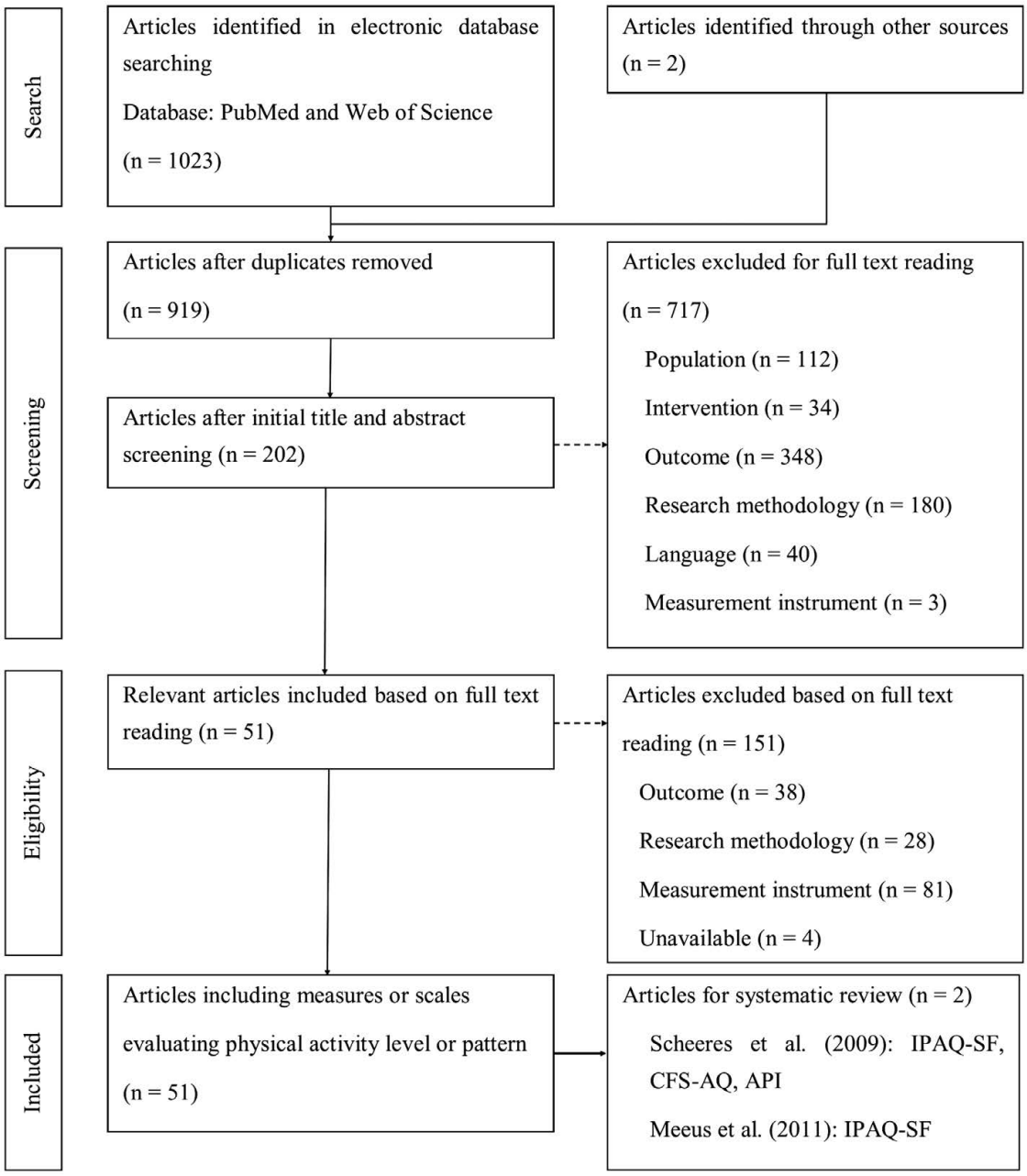

Figure 1: Flowchart of search strategy
CFS-AQ = Chronic Fatigue Syndrome – Activity Questionnaire
API = Activity Pattern Interview
IPAQ-SF = International Physical Activity Questionnaire – Short Form

Activity pattern interview

The API is an interview which identifies the usual activities performed on a typical day. During the interview, three relevant topics are questioned: routine pattern of activities, amount of time laying or sitting the day before, the number of times leaving the house during a day and practicing an (un)paid job or not. Based on the answers on these three topics, the interviewer classified the person as 'active' or 'passive'. The routine pattern was investigated by questioning the day of yesterday as detailed as possible. When the day of yesterday was not a typical day, another day of the past week was used to minimize recall bias. The average time to complete the interview was 10 minutes. To produce valid results, experience in CFS and training in using the interview is recommended [33].

The psychometric properties of the API were evaluated by Scheeres et al. and, as described earlier, the instrument was compared to the CFS-AQ and IPAQ-SF to identify the most suited measure or scale to evaluate the daily physical activity level of patients with CFS. More specifically, all instruments were evaluated on their capability to correctly classify a patient as (fluctuating) active based on activity monitor typology [33].

Criterion validity was evaluated by calculating correlations between the API and continuous activity monitor scores, but only weak correlations were found (Spearman's rho = 0.27). ROC curve was calculated to identify the API's sensitivity and specificity. The sensitivity of the API was 52.3% and specificity was 75.8%. The API had an AUC of 0.643, which was smaller than the validity of the CFS-AQ (0.710) and the IPAQ-SF (0.711). Methodological quality of the study by Scheeres et al. for evaluating the criterion validity was found to be fair by the COSMIN checklist [33]. No other studies evaluating the API in patients with CFS/ ME were found.

International physical activity questionnaire-short form

The International Physical Activity Questionnaire-Short Form (IPAQ-SF) is a self- or telephone-administered measure which evaluates health-related physical activity. The instrument was developed in 1996 by the 'International Consensus Group of Physical Activity Management' and validated in twelve countries by Craig et al. [79]. Four long and four short versions of the instrument are available. The use of a short self-administered version with persons with CFS was suggested, because these patients often experience cognitive impairments [64].

The IPAQ-SF consists of nine items and gathers information on the time spent walking, the performance of moderate and vigorous physical activity and the minutes spent sitting on weekdays during the past seven days [33,64]. Patients also have to rate how many days and how many minutes they spent per specific activity category. The amount of Metabolic Equivalents (METs)-minutes is calculated for all categories by multiplying the amount of minutes with 1.3 (sitting), 3.3 (walking), 4 (moderate physical activity) or 8 (vigorous physical activity) [64]. Four subscale scores and one total score can be calculated by adding the METs minutes of the last three categories together [33,64]. The time to complete the questionnaire ranged from five to seven minutes [33].

The *internal consistency* was evaluated in a study of Meeus et al. in a population of patients with CFS. Cronbach's alpha was calculated for the categories walking, moderate

and vigorous activities and was 0.337 [64]. Methodological quality of this study was found to be fair by the COSMIN checklist [64].

The *criterion validity* was evaluated by two studies. Scheeres et al. calculated correlations between the CFS-AQ, API and IPAQ-SF and the continuous activity monitor scores, as mentioned earlier [33]. The logistic regression analysis and calculation of predicted probability scores were also performed with the IPAQ-SF. ROC calculated the sensitivity and specificity. The best cut-off point for the IPAQ-SF is 0.67 with a sensitivity of 70.1% and specificity of 62.7%. The AUC was 0.711 and the IPAQ-SF had a greater validity than the API and CFS-AQ. The IPAQ-SF and continuous activity monitor scores had a weak correlation (Spearman's rho = 0.33) [33]. Methodological quality of the study by Scheeres et al. for evaluating the criterion validity was found to be fair by the COSMIN checklist [33].

Meeus et al. evaluated the *criterion validity* by comparing the IPAQ-SF with an activity monitor and an activity diary [64]. METs-minutes spent per activity category (sedentary, moderate and vigorous activity) were the outcomes that were compared between the three measures. Spearman's rho varied between 0.282 and 0.426 (p = 0.05) indicating only weak correlations. Furthermore, the weak significant correlations were especially found in the moderate and vigorous activities. These were found to be irrelevant, because CFS patients rarely perform such activities. No correlations were found in the sedentary activities, which are the ones CFS patients perform the most [64]. Methodological quality of the study by Meeus et al. for evaluating the criterion validity was found to be good by the COSMIN checklist [64].

Table 3: General information per study

Study	Population and pathology	Measurement instrument	Psychometric qualities and methodological quality	
Meeus et al. (2011)	**CFS (n = 56)** 41.09 years SD 9.51 range 20-62 years ♀: n = 56 (100%) *Disease duration* 93.61 months SD 78.41 months range 6-360 months	IPAQ-SF	Internal consistency	fair
			Criterion validity	good
Scheeres et al. (2009)	**CFS (n = 226)** 37 years SD 11.3 range 15-68 years ♀: 167 (74%) *Disease duration* 5 years range 2-32 years	CFS-AQ	Internal consistency	poor
			Test-retest reliability	poor
			Criterion validity	fair
		API	Criterion validity	fair
		IPAQ-SF	Criterion validity	fair

Table 4: Methodological quality per psychometric property of included articles based on COSMIN checklist

Measurement instrument	Internal consistency	Reliability: relative measures	Measurement error: absolute measures	Content validity	Structural validity	Hypotheses testing	Cross-cultural validity	Criterion validity *(including AUC, sensitivity and specificity)*	Responsiveness	Interpretability
CFS-AQ										
Meeus et al. (2011)	poor	poor						fair		poor
API										
Meeus et al. (2011)								fair		poor
IPAQ-SF										
Scheeres et al. (2009)								fair		poor
Meeus et al. (2011)	fair							good		poor

Discussion

The aim of this review was twofold. First, scientific literature was systematically reviewed for currently used measures or scales evaluating the physical activity level or pattern in patients with CFS/ME. The systematic literature search identified 51 studies and a total of 15 different unique measures or scales. Second, the methodologies of studies evaluating the psychometric properties of identified measures or scales in a population with CFS/ME were critically appraised by use of the COSMIN checklist [29,30]. It was remarkable that, despite the high number of available instruments, only two studies evaluated the psychometric properties of three different measures in patients with CFS: the CFS-AQ, API and IPAQ-SF [33,64]. When listing all measures or scales identified by the literature search, activity monitors were found to be the most frequently used (n = 29) and are often seen as the gold standard to compare other measures or scales evaluating the perceived physical activity level or activity pattern to, such as self-report measurements [6,15,16,31,39–46,48–62,64,78].

Based on the critical appraisal of the two studies evaluating the psychometric properties of the CFS-AQ, IPAQ-SF and API, both studies used an activity monitor to evaluate the criterion validity of the CFS-AQ, API and IPAQ-SF [33,64]. The research methodologies of the studies of Scheeres et al. and Meeus et al. were rated 'fair' and 'good', respectively, on the COSMIN checklist for evaluating the criterion validity and it can be concluded that these three measures are equally valid or equally invalid, given the lack of studies evaluating the psychometric properties of these activity monitors in patients with CFS/ME.

All three instruments can be used to measure the perceived physical activity level in daily life in CFS patients but have a low correlation with the actual activity level measured by an activity monitor [33]. The validity, tested with the area under the curve, of the CFS-AQ and IPAQ-SF (0.710 and 0.711) was slightly higher than the API (0.643). Some experience with CFS and training in performing the interview is enough to produce

equally valid results to the self-reporting questionnaires IPAQ-SF and CFS-AQ [33]. If a patient's activity pattern needs to be determined, the API could be more practical to use in the work field, because it has a dichotomous outcome (active/passive). The CFS-AQ and IPAQ-SF on the other hand, solely measure the activity level and the results have to be transformed to a dichotomous outcome by use of complicated formulas. However, a high number of false predictions by all three measures were found when compared to an activity monitor. If patients are incorrectly identified as being active (scoring two or more days above a reference score) or passive (scoring zero or one days of the twelve measured days above a reference score) according to an activity monitor typology in clinical practice, they could receive inappropriate treatment which could lead to more functional and participation restrictions [38]. Future research addressing this problem is recommended.

Considerations

The CFS-AQ, API and IPAQ-SF are all self-reported measures and consequently assess a patient's perception of daily performed physical activities [4]. Self-reports might not be highly related to the actual, objectively measured, daily life activity level as measured with activity monitors [4,9,46,64,80]. A previous study by Vos-Vromans et al. found discrepancies between perceived daily activities and objectively measured daily activities in patients with CFS; however, the cause of this discrepancy in patients with CFS needs to be further investigated [47]. In patients with chronic low back pain (CLBP), this discrepancy was associated with the presence of depressive symptoms influencing a patient's perception of their activity level [81], that could lead to the assumption that mood changes in patients with chronic conditions influence the perceived activity level.

Activity monitors on the other hand are known to be reliable and valid measures or scales to objectively evaluate a patient's activity level in the general population [82], but their psychometric properties have not yet been evaluated with patients with CFS/ME [4,8,46,47,64,82]. The reliability and validity depend on the device, population and the studied activity behaviour [64,83,84]. First of all, the optimal place of attachment has not been established. The place of an activity monitor on the body influences its output and activity monitors worn on the lower body tend to underestimate activities of the upper body and vice versa [46,82,84]. Since patients with CFS/ME perform mostly sedentary activities, the place of attachment that provides the most accurate results of their performed physical activities needs to be determined [48]. Secondly, it is unknown when and for how long the activity monitor needs to be worn to obtain sufficient valid information for an accurate representation of a patient's activity level. In patients with chronic pain, it is recommended to include more than three days, because they have large between-day variations in physical activity and need periods of rest between activities [85]. Patients with CFS/ME also often have a fluctuating activity level, therefore inclusion of more than three assessment days and at least one weekend day can be useful to have an accurate representation of a patient's activity level. Third, the influence of an activity monitor on the behaviour of CFS/ME patients is also unknown. Some patients engage in reactive behaviour, which means changing their normal physical activity pattern when consciously wearing an activity monitor [48]. Because information about the actual daily activity level in patients with CFS/ME is useful, evaluation of the

psychometric properties of activity monitors and development of a protocol encompassing clear instructions on the place of attachment, duration of measurement etc. are necessary in order to obtain high quality results.
The discrepancy between the objective measurement and subjective perception of a patient's performed physical activities is an important topic for further investigation. Patients with CFS/ME, classified as active based on self-report measurement, may have a tendency to overestimate themselves due to the presence of PEM after performing many or intensive activities. On the other hand, patients classified as being passive are hypothesized to have a tendency for underestimation. They avoid most activities causing PEM, but the performance of other sedentary or light activities, such as cleaning, cooking, walking during household activities, washing and doing laundry [85,86], will be performed, resulting in a similar activity level as active patients [15], as found by Huijnen et al. [87]. Measurement of the objectively measured physical activity level indicated that there were no significant differences between the avoidant group and persistent group with CLBP [87]. Vos-Vromans et al. also found no discrepancies between the actual activity level of passive and relatively active patients with CFS established by an activity monitor, but discrepancies were found between the perceived and actual physical activity level [47] and clinical practice should take this discrepancy into account when working with patients with CFS/ME.

Implications
Based on the evaluation of all measures or scales, their psychometric properties and further remarks, none of the three measures or scales should be used in isolation and training in performing the API is necessary to evaluate the activity level and pattern of activity in a population with CFS.
Future research is needed to further evaluate the reliability and validity of the IPAQ-SF, CFS-AQ and API and activity monitors. The systematic literature search identified fifteen unique measures evaluating physical activity in patients with CFS/ME of which the psychometric properties are not or insufficiently known. It is therefore recommended to first evaluate the psychometric properties of these measures, because they could potentially be appropriate for patients with CFS/ME. If psychometric properties are insufficiently robust, then perhaps new measures or scales to assess the activity level in a population with CFS/ME should be developed. Such measurements would need to have good psychometric properties, be short and easy to administer. Recall over a long period of time should be avoided, due to the possible presence of cognitive impairments. The questions and answers ought to be simple without the possibility of subjective interpretation. Since patients with CFS/ME mostly perform sedentary and light activities, these should be the instrument's focus [64]. Because ambulatory monitoring assesses the physical activity pattern more accurately than a measure using retrospective self-report, Meeus et al. suggest the development of a kind of activity diary with daily registration, which minimizes recall bias as previously discussed [16,64]. According to Wickel et al., self-report measures where the type, amount and intensity of physical activity can be recorded are the most used to measure physical activity levels [46]. The more details available on performed daily activities, the more accurate the physical activity level or pattern can be determined and false predictions can be prevented.

Moreover, Jason et al. state that solely looking at the total daily activity might not be enough to differentiate between patients with CFS/ME and healthy controls, but examination of the variability of their activity pattern over time is necessary [22]. The ability to map activity patterns would be a useful improvement for clinical practice, because patients with CFS/ME often have an imbalance between rest and activity and do not spread their activities equally during the day [4,6,15]. Mapping of a patient's activity pattern could lead to better understanding their problems and origin of their complaints, which would ultimately lead to better management and rehabilitation [64].

Limitations

This systematic review has several limitations. First, although the research methodology was specified in advance, the protocol was not published.

econd, both screening phases of the systematic literature search were performed by two independent reviewers and a third if consensus could not be reached between the first two. However, an update of the systematic literature search was performed from March 2014 until October 2016 by two different reviewers than the initial literature search, which could have led to a slightly different selection. Nevertheless, the final supervision was continuously performed by the last author.

The literature search was performed in two electronic databases. Searches in additional databases could have generated additional relevant studies. Restricting the inclusion criteria to English- and Dutch-language publications could also have limited the results.

The quality of the research methodology of the studies varied. One patient population was smaller than 100 participants which, according to the COSMIN-checklist, is insufficient for evaluating the psychometric properties of measures or scales. The other publication provided insufficient information about its research methodology and is therefore automatically assigned with the lowest score. However, if the research methodology was performed accurately but reported poorly, this could have led to the underestimation of the measurement's qualities.

Conclusion

This systematic review identified 15 unique and relevant measures or scales used in patients with CFS/ME to evaluate the physical activity level and pattern, but the psychometric properties of only three measures or scales were evaluated in patients with CFS/ME: the CFS-AQ, API and IPAQ-SF. Based on the critical appraisal of their psychometric properties, it can be concluded that none of the three unique measures or scales are optimal to evaluate the activity level or pattern in patients with CFS/ME.

Their psychometric properties have been insufficiently evaluated; therefore, their results should be interpreted with caution when used. The results of this systematic review clearly indicate that more research is necessary to further evaluate the psychometric properties of existing measures or scales and it is recommended to evaluate the validity and use of activity monitors for the population of patients with CFS/ME.

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CHAPTER 4

An exploratory study of discrepancies between objective and subjective measurement of the physical activity level in female patients with chronic fatigue syndrome

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Abstract

Objective: To explore the ability of a self-report activity diary to measure the physical activity level (PAL) in female patients with chronic fatigue syndrome (CFS) and whether illness-related complaints, health-related quality of life domains (HRQOL) or demographic factors are associated with discrepancies between self-reported and objectively measured PAL.

Methods: Sixty-six patients with CFS, recruited from the chronic fatigue clinic of a university hospital, and twenty matched healthy controls wore an accelerometer (Actical) for six consecutive days and registered their activities in an activity diary in the same period. Participants' demographic data was collected and all subjects completed the CFS Symptom List (illness-related complaints) daily and Short-Form-36 (HRQOL domains) during the first and second appointment.

Results: A significant, but weak association between the activity diary and Actical was present in patients with CFS ($r_s = 0.376$ and $r_s = 0.352$; $p < 0.001$) and a moderately strong association in healthy controls ($r_s = 0.605$; and $r_s = 0.644$; $p < 0.001$) between week and weekend days, respectively. A linear mixed model identified a negative association between age and the discrepancy between the self-reported and actual measure of PA in both patients with CFS and healthy controls.

Conclusion: The activity diary showed limited ability to register the actual PAL in female patients with CFS. The discrepancy between measures was not explained by illness-related complaints, HRQOL domains or demographic factors. The activity diary cannot replace actual activity monitoring measured with an accelerometer, but may provide additional information about the perceived activity.

Introduction

In chronic fatigue syndrome (CFS), a condition characterized by persistent or relapsing debilitating fatigue lasting more than six months which is not alleviated by rest [1,2], both objectively measured (i.e. with accelerometry) [3] and self-reported [3,4] lower physical activity levels (PAL) have been found in comparison to healthy controls. Subjects with CFS mostly perform activities of mostly sedentary and light intensity [5,6] , which is similar to healthy adults [4,5] , but they perform less activities of moderate and high-intensity [5,6]. Additionally, large individual differences have been identified and suggested to be the result of two different coping strategies applied by patients with CFS, the pervasively passive and relatively active strategy, respectively [7]. The pervasively passive patients show avoidance behavior towards physical activity (PA) and become inactive, while the relatively active patients try to perform at pre-illness levels despite their complaints, which leads to an irregular activity pattern with an imbalance between activity and rest [7,8]. Because both subgroups show such different activity patterns, activity management programs that aim at improving patients' PAL need to be tailored to their individual coping strategy [7–9] by accurately estimating patients' PAL and pattern.

Use of objective activity monitor systems (i.e. accelerometers) is recommended [7,8], but their psychometric properties depend on the device, how it is used, the studied population and type of activity [10–13]. Also, different calibration methods and cut-points for defining and categorizing physical activity intensities are often used [11,13–15]. Their psychometric properties are mostly investigated at group-level in healthy non-sedentary individuals [10,13,16] , but it is unclear if they are able to detect the amount and intensity of performed activities accurately in patients with CFS at an individual level [10,17]. Also, they do not provide detailed information about the type and context of the performed PA and give no insight into a patient's perceived PAL [11,13].

Self-report measures are capable of registering this additional information and therefore offer complementary information on a patient's PAL not captured by an objective activity monitor system. Various studies suggest using multiple assessment methods simultaneously when measuring PAL, depending on the assessment goal(s) [11,13]. However, some considerations must be made when using self-report measures in patients with CFS. Previous research has established a weak relationship between objective and subjective PA measures [11,12,18] and, even though no clear trends regarding over- or underestimation have been identified [11], various factors have been hypothesized to potentially influence self-report. In self-report measures relying on recall, incorrect remembering could induce false reporting [11,13], especially in patients with CFS often suffering from cognitive problems such as impairments in working memory, information processing speed, immediate and delayed recall [19]. Moreover, measures using general subjective interpretations about PA in CFS seem to reflect a patients' view about PA and may be biased by their cognitions about illness and disability causing them to estimate their own activity level inaccurately [7,18]. Unrealistic thoughts about their premorbid activity level and misjudgment of the activity level of healthy

controls contribute to these incorrect cognitions and patients' tendency to report being inactive most of the time [7,8]. Results of previous studies [18,20] also suggested fatigue to be related to discrepancies between self-report and objective measures. PAL and health-related quality of life (HRQOL), mainly physical domains, have been found to be significantly associated in healthy controls [21,22] with objective measures having a slightly higher association than self-report measures [22]. Results indicate a discrepancy between self-reported and objectively reported PAL, but it has not been identified if perceived HRQOL itself is associated with the discrepancy between both measures. Finally, in healthy individuals reporting discrepancies exist between genders with, on average, females having a higher overestimation than males [11]. Associations with other sociodemographic factors have not been identified. Overall, studies investigating factors associated with discrepancies between both measures, and more specifically in patients with CFS, are scarce.

Because subjective activity measures are relevant for clinical practice, identification of a format that is capable of measuring the PAL similar to an objective activity monitor would be a significant asset. Because the relationship between self-report measures consisting of subjective and general interpretations of PA and relying on recall and objective activity measures are low, self-report measures encompassing detailed information about a patient's daily activities including the type, amount and intensity of the activity are recommended [8,23]. According to Terwee et al. (2010), the total activity counts generated by an accelerometer as outcome measure is the most optimal comparison to validate a measurement instrument that aims to measure total PA, due to lack of a 'gold' standard for PA [24].

This exploratory study primarily aims to evaluate the ability of a detailed self-report activity diary based on an instantaneous registration of activities to measure the PAL in female patients with CFS by comparing it to an accelerometer, and to compare potential discrepancies between subjective and objective measures in patients with CFS versus healthy controls.
The correlation coefficient between both measures should be ≥ 0.50 for an acceptable convergent validity [24].
In case of discrepancies between both measures, it will be investigated whether and which illness-related complaints, HRQOL domains or demographic factors are associated with these discrepancies.

Method

Participants

Patients were recruited through the chronic fatigue clinic of the department of Human Physiology and Rehabilitation Sciences of the Vrije Universiteit Brussel in Brussels, Belgium.
Patients had to be (1) Dutch speaking, (2) female, (3) aged between 18 and 65 years, (4) diagnosed with CFS according to the international criteria [2].

All patients were diagnosed with CFS by the same physician of internal medicine and underwent an extensive medical evaluation including a clinical examination, analyses of the medical history, exercise tolerance test and routine laboratory assessment. If judged necessary by the physician, additional psychiatric, neurological, gynaecological, endocrinological, cardiac and/or gastrointestinal examinations were performed. A positive result on any of the examinations led to the exclusion of patients according to the diagnostic criteria [2]. If all inclusion criteria were met, patients were contacted by telephone by a researcher to inform them on the present study and invite them for participation. If they consented, two appointments were made, always on a Monday or Tuesday, with one week between both consultations. Patients also received an information brochure by mail or e-mail.

CFS patients were age-matched to healthy controls to evaluate whether the association between the self-reported and objective PAL established in this study is CFS-specific. They were recruited from hospital personnel, personnel from the College University of Antwerp (Department of Healthcare) and social network of researchers. Selection was based on following criteria: Dutch speaking, female, aged between 18 and 65 years, sedentary.
A sedentary lifestyle was defined as having a predominant sitting or standing job and performing moderate or intensive physical activity less than three hours per week [25].

Procedure
During first consultation, both patients with CFS and healthy controls were informed again about all aspects of the study, received an information brochure and were asked to sign an informed consent in case of agreement. This study was approved by the Medical Ethics Commission of the Academic Hospital of the Vrije Universiteit Brussel (University Hospital Vrije Universiteit Brussel; O.G. 016).
Participants' demographic data were collected during the first appointment and all participants were asked to complete a test battery (standardized test order) with the CFS Symptom List and the Short Form Health Survey-36 (SF-36). After completion, the accelerometer (Actical) and activity diary were explained and provided.
At the second appointment one week later participants handed in the Actical and activity diary and completed the test battery a second time.

Measures
Patient characteristics
Age and disease duration were collected during the first appointment.

Objectively measured physical activity
Objective measurement of PA was measured with the Actical (Mini Mitter, Bend, OR), an omnidirectional accelerometer. The device weighs 17 g and measures 28 mm x 27 mm x 10 mm. The Actical has an output called 'activity counts' (AC), which is a result of voltage generated by the sensor and produced by a change in amplitude and frequency of movements [16]. In this study, AC are calculated in 1-minute intervals. Total AC per day were calculated and then divided by 1440 to obtain AC/min.

At the start, gender, age, height and weight of the participant and start date and time were entered into the Actical. Measurement started after attachment of the Actical on the non-dominant wrist of the participant.
Participants were instructed to wear the Actical 24 h/day for six consecutive days until their second consultation, even when sleeping or bathing. The Actical is waterproof and resistant to normal water exposure up to 1-m depth for 30 min. The Actical is validated for measuring activity energy expenditure in healthy persons [16,26].
In patients with CFS, three activity patterns can be distinguished: pervasively passive [7,8,27], pervasively active [7,8,27] and moderately active [7,8]. Both patients with CFS and healthy controls were categorized into one of the aforementioned activity patterns based on the mean total AC of the CFS sample (mean = 242.80 AC/min) and the following criteria:
Pervasively passive (PP): Total AC of all five measured days are below mean total AC of the CFS sample [7,27].
Pervasively active: Total AC of all five measured days are above the mean total AC of the CFS sample [7,27].
Moderately active (MA): There is no PP or PA pattern [7].

Self-reported physical activity
The activity diary consists of a paper version template in which performed activities per day should be registered. For each activity the kind of activity, starting time, end time and total duration need to be recorded. Participants were instructed to start recording their activities the morning after their first consultation until the evening before the second appointment to have data of six full days, including week and weekend days. Activities had to be registered at the beginning of each activity to avoid inaccurate registration due to recall. During the second consultation, the researcher manually checked all activities registered in the activity diary to correct errors when the diary was not completed according to the instructions and to minimize missing data by filling in gaps if possible (based on recall).
Researchers calculated the Metabolic Equivalent of Task-value (MET), an expression of the intensity of PA relative to an individual's resting energy expenditure, for each activity reported in the activity diary using the Compendium of Physical Activities Tracking Guide [28]. Microsoft Excel was used to calculate the total MET per day, which were then divided by 1440 to obtain MET/min.

CFS symptom list
Self-reported symptom severity was measured daily with the CFS Symptom List. It refers to the past 24 h [29] and includes 19 symptoms most frequently reported by patients with CFS. The measure assesses symptom severity with a 100-mm visual analogue scale (VAS) per symptom and total symptom severity can be calculated [29,30]. These symptom severity scores were used for this study. The VAS has acceptable psychometric properties in various chronic disease populations [31–33].

Health related quality of life

The SF-36 (version 1) was used to measure HRQOL. It contains 36 items on eight subscales: physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy/fatigue, emotional wellbeing, social functioning, pain, general health and measures health change. Scores range from 0 to 100 and a higher score indicates a higher HRQOL [34]. The Dutch language version is reliable and valid [35].

Statistical analysis

Data were analyzed in SPSS version 27 and R. Non-parametric statistics were used due to non-normal distributions of both groups. Sample descriptive characteristics and PAL outcomes of both measures (AC and MET) for week and weekend days were compared using Mann-Whitney U tests.

The strength of the association between the Actical (AC) and activity diary (MET) was studied using Spearman correlation coefficients for week- and weekend days separately, because of frequently observed differences between performed activities during week- and weekend days [36]. Correlation coefficients between AC and MET were calculated for both the total case and control group separately and per activity pattern (PP, MA, pervasively active).

To evaluate which factors are associated with the potential overestimation or underestimation of the actual PAL by self-report (discrepancy) in patients with CFS relative to healthy controls, first linear regression was carried out with AC as dependent variable and MET as independent variable for both cases and controls. Second, the residuals after regression, an indication of the relative margin of error in the ability of the activity diary to predict the PAL in this sample, were entered as dependent variable in the linear mixed model to identify factors associated with the discrepancy between self-reported and objective activity monitoring. Daily measured symptom severity per symptom and total symptom severity (CFS Symptom List), HRQOL at baseline (SF-36 subscale scores), age and disease duration were entered as independent variables in the linear mixed model.

For each linear mixed model, the significance of the fixed effect was tested using a likelihood ratio test. Due to the multitude of variables tested, that could lead to an increased type 1 error, a false discovery rate (FDR) analysis was carried out [37]. Finally, case–control status was included in the final model to identify whether the associated factor(s) were influenced by differences in the factor(s) between patients with CFS and healthy controls and/or an interaction effect between the associated factor(s) and case-control status that could (partially) account for the difference in the strength of the association between both measures for cases and controls. Significance level for all analyses was set at $p \leq 0.05$.

Results

Participants

A total of 66 female patients with CFS and 20 female healthy controls participated. Table 1 presents descriptive statistics for age, disease duration, AC and MET for weekdays and weekend days.

Both groups did not differ for age ($median_{CFS}$ = 42; $median_{controls}$ = 43; p = 0.91).
Patients with CFS had a significantly lower PAL compared to healthy controls for MET for weekdays ($median_{CFS}$ = 1.42; $median_{controls}$ = 1.50; *U* = 3925.5, p = 0.003) and weekend days ($median_{CFS}$ = 1.35; $median_{controls}$ = 1.41; *U* = 1940.5, p = 0.02), and for AC for weekdays only ($median_{CFS}$ = 231.27; $median_{controls}$ = 264.9; *U* = 4850, p = 0.03) (Table 1).
A significantly higher PAL for weekdays in comparison to weekend days in patients with CFS ($median_{week}$ = 1.42; $median_{weekend}$ = 1.35; *U* = 10,142, p = 0.001) and in healthy controls ($median_{week}$ = 1.50; $median_{weekend}$ = 1.41; *U* = 914.5, p = 0.04) was identified for registered MET, but not for AC (Table 2).

Comparison of self-reported and objectively measured PA

Table 3 presents Spearman correlation coefficients between the activity diary and Actical. A significant, but weak association was found for patients with CFS for both weekdays (r_S = 0.376, p < 0.001) and weekend days (r_S = 0.352, p < 0.001). In the healthy control group, however, there was a significant and moderately strong association for both weekdays (r_S = 0.605; p < 0.001) and weekend days (r_S = 0.644; p < 0.001). The association between both measures was highest for CFS patients for the MA group (45%) (r_S = 0.333, p = 0.001) followed by the PP group (35%) (r_S = 0.254, p = 0.04) both for weekdays only. In healthy controls, the highest association was for the PP group (25%) for both weekdays (r_S = 0.886, p < 0.001) and weekend days (r_S = 0.806, p = 0.005), followed by the MA group (50%) for weekdays only (r_S = 0.503, p = 0.005). There was no significant association between both measures for the pervasively active group in both CFS patients (20%) and healthy controls (25%).

Table 2: Mann-Whitney U test comparing AC and MET between weekdays and weekend days for patients with CFS and healthy controls

		N[b]	Median	IQR	M[c]	U[c]	Z[c]	p
CFS (n = 66)[a]								
AC	weekday	198	231.3	177.2-308.7	170.92	11,994	-1.265	0.20
	weekend day	132	213.1	170-287.1	157.36			
MET	week day	198	1.42	1.31-1.52	179.28	10,142	-3.348	0.001
	weekend day	131	1.35	1.26-1.46	143.42			
Healthy controls (n = 20)[a]								
AC	week day	60	264.9	188.1-372.4	53.75	1005	-1.372	0.17
	weekend day	40	218.9	168.8-336.3	45.63			
MET	week day	60	1.50	1.41-1.68	55.26	914.5	-2.009	0.04
	weekend day	40	1.41	1.32-1.67	43.36			

CFS = chronic fatigue syndrome; AC = activity counts; MET = metabolic equivalent of task; IQR = interquartile range.

[a] number of participants.

[b] number of measurements (five measurements per participant for AC and MET; three weekdays and two weekend days).

[c] Mann-Whitney U test comparing age, AC and MET between weekdays and weekend days for patients with CFS and healthy controls; M = mean rank.

Table 3: Spearman correlation coefficients between subjectively measured MET and objectively measured AC for weekdays and weekend days

			Actical					
			CFS			HC		
			n	AC (week)	AC (weekend)	n	AC (week)	AC (weekend)
Diary	**Total group**	**MET (week)**	66	.376**		20	.605**	
		MET (weekend)	66[a]		.352**	20		.644**
	PP	**MET (week)**	23	.254*		5	.886**	
		MET (weekend)	23		.279	5		.806**
	PA	**MET(week)**	13	.206		5	.266	
		MET (weekend)	13		.149	5		.042
	MA	**MET (week)**	30	.333**		10	.503**	
		MET (weekend)	30[a]		.249	10		.293

CFS = chronic fatigue syndrome; HC = healthy controls; MET = metabolic equivalent of task for week days / weekend days; AC = activity counts for weekdays / weekend days; PP = pervasively passive; PA = pervasively active; MA = moderately active.

[a]MET = n-1

*p<0.05, **p<0.01

Factors associated with discrepancies between self-reported and objectively measured PA

Age was negatively associated with discrepancies between the activity diary and Actical (unstandardized residual) in both patients with CFS and healthy controls (Table 4). This result indicates that younger persons tend to underestimate their PAL and older persons tend to overestimate their PAL with an activity diary. The association remained significant after controlling for case-control status ($p = 0.005$). There was no interaction between age and case-control status ($p = 0.82$) indicating that the association between age and the discrepancy did not differ between patients with CFS and healthy controls. Individual symptom severity and total symptom severity (CFS Symptom List), HRQOL at baseline (SF-36 subscale scores) and disease duration were not significantly associated with discrepancies between the activity diary and Actical.

Table 4: Linear mixed model summary of associations with the relative margin of error (unstandardized residual) between AC and MET in patients with CFS and healthy controls

Variable	B	95% CI	p-value	q
Age	-2.8	-4.75; -0.86	0.005	0.08

B = unstandardized beta coefficient; CI = confidence interval; q = adjusted p-values using false discovery rate approach

Discussion

Patients with CFS had a lower PAL in comparison to healthy controls according to the activity diary for both weekdays and weekend days, and the Actical for weekdays only. In healthy controls, the association between the activity diary and Actical was significant and moderately strong. In patients with CFS the association was also significant, but weak, suggesting that female patients with CFS are less capable than healthy persons of accurately registering their PAL. Linear mixed model analysis only identified a significant and negative association between age and discrepancies between both measures in patients with CFS and healthy controls and the association did not differ for both groups. This indicates that younger persons tend to underestimate their PAL and older persons tend to overestimate their PAL with an activity diary. The influence of age is only 2.8 AC/min per year increase in age.

When comparing the association between both measures based on the three subgroups of activity patterns identified in previous research, a significant association between both measures was present for the PP and MA group in both patients with CFS and healthy controls, but not for the pervasively active subgroup. These results indicate that there are additional factors that influence the association between both measures in the pervasively active group. These subgroups could not be analyzed further due to the small number of participants per subgroup, but this finding provides an additional point of attention for future research. A recent study proposed two criteria to identify an additional activity pattern in patients with CFS, i.e. boom and bust pattern [27]. In our patient sample, only one of the participants (2%) who was not already classified into the PP or PA group could be identified with a boom and bust pattern based on the proposed criteria, in contrast to 30% of the participants of the study of King et al. (2020) [27]. Even though our patient group (n = 66) is significantly smaller than this study (n = 579), it could be that the proposed criteria are not completely applicable to the total CFS

population. It could also be that our period for activity recording, which was 5 days (although including week and weekend days), was too short to correctly identify all different activity patterns adopted by patients with CFS, as discussed by King et al. (2020) who had an average recording period of 3 to 7 days [27]. Since the correct identification of a patient's activity pattern is important to tailor the activity management program to their individual coping strategy, these concerns require further attention in future studies.

The above findings suggest that the activity diary and Actical do not measure the same parameters of PA and cannot replace one another. These results are in accordance with previous studies comparing self-report to direct measures indicating that PA measured by self-report measures should be interpreted with caution, because it does not seem to be an accurate reflection of actual behavior [7,11]. Additionally, self-reported improvements, e.g. decrease in fatigue, are not always reflected by objective improvements, e.g. increase in PAL [38,39]. Therefore, objective measures, i.e. accelerometers, seem most suitable to use in clinical practice and research when the aim is to identify patients' PAL and activity pattern and objectively measure improvements in PAL [7,9]. Prevention of post-exertional malaise (PEM), the exacerbation of symptoms after exertion, is also important in patients with CFS, because PEM causes longer resting periods after exertion [7,40,41] and avoidance of activities which leads to a passive activity pattern [42]. Objective assessment of patients' activity level and pattern is therefore important to tailor activity management programs to the patient's individual coping strategy aimed at attaining and maintaining a regular, balanced activity pattern allowing the patient to perform meaningful activities of daily living, enable participation and prevent PEM [9,42,43]. The significant and moderately strong associations between both measures in healthy controls indicate that, when used complementary, a more comprehensive view of a person's PAL could be obtained. The Actical could capture more incidental activities and those of lower intensity, while the activity diary offers more specific information on the type and context of the performed activity [11,13,23] A person's perceived difficulty of the performed activity was currently not a part of the activity diary, but could provide even more information to the researcher [11]. Therefore, self-report measures can be used in addition to objective measures to gain more insight into a patient's daily routine and gather contextual factors about the performed activities facilitating the formulation of an individualized activity management program including patients' meaningful activities of daily living [9].

Whether patients registered each activity according to the instructions to exclude inaccurate reporting based on recall and feasibility of the activity diary from a patient's perspective were both not examined. It was also not examined whether patients (previously) underwent any treatment focusing on PA or experienced illness-related cognitions that influenced their perception of PA [39,42] and consequently their self-reported PA. Future research should therefore investigate patients' reporting behavior and feasibility of the activity diary, and take PA related treatment and illness-related cognitions into account when exploring factors associated with the discrepancy between objective and self-report PAL. A digitalized activity diary based on experience sampling that yields regular reminders during the day requiring registration of the current performed activity could be of additional value [44].

None of the included factors could explain the discrepancy between both measures in patients with CFS relative to healthy controls, suggesting that there are other factors associated with the discrepancy that have not been investigated in this study. One possible factor could be mood. In patients with chronic low back pain, a lower PAL was reported by patients with a higher depression score and depression was significantly associated with the discrepancy found between self-report and objectively measured PA [45]. In patients with major depressive disorder (MDD), discrepancies between self-report questionnaires and objective measures of PA have been identified, suggesting that self-report measures do not reflect actual PAL [46]. The proportion of patients with comorbid non-psychotic or non-melancholic MDD in our sample was not measured. This is a significant limitation considering it is an accepted comorbidity according to the CDC-94 criteria that could (partly) explain the found discrepancy between measures. In addition, patients with non-psychotic, non-melancholic MDD or anxiety engage in high levels of sedentary behavior and have a lower PAL compared to healthy controls [46,47], which could explain the different activity patterns in patients with CFS. The association between comorbid psychiatric disorders and discrepancies between objective and subjective measures of PA should be investigated further in patients with CFS.

This study has several additional limitations. First, different output variables were used to compare the activity diary to the Actical. Ideally, the output variable MET would have been used for both measures to allow direct comparison, but this included some limitations. The algorithm behind the calculation of MET-values and cut-points for the intensity categories of the Actical is unknown and these differ across devices and populations [13–15]. This causes ambiguity on how to analyze the collected data appropriately [13,14]. In addition, individual estimations of physical activity energy expenditure are often associated with large errors. Comparing MET-values across measurement instruments could therefore lead to misinterpretation of the results. The large errors also prevent the use of accelerometers to estimate changes in PA in response to activity management programs [14], which is an important goal of CFS rehabilitation. It is recommended that raw acceleration signals are collected and saved to prevent errors due to conversion into alternative variables (i.e. AC, MET) and allow comparison across populations and measures [48]. Additionally, the Compendium of Physical Activity used to calculate MET values is developed based on the energy expenditure of healthy individuals [28], but these values could be different for patients with CFS due to altered physiological capacities [13,49,50]. Previous research in healthy persons also found more discrepancies between self-report and direct measures in categories of higher intensity with self-report overestimating activities performed of vigorous intensity [11], suggesting self-report is less capable of accurately registering these activities. In contrast, accelerometers have been found to miss or misclassify certain activities depending on their placement and they do not take environmental and contextual factors, such as the terrain or added strain of carrying objects, into account when measuring activity intensities [11,13,16].
Second, sleep time was not differentiated from awake time for total AC. MET during sleep time was included in the activity diary by multiplying sleep time with 0.9 MET/min. in accordance with the Compendium of Physical Activities Tracking Guide [28], but this

calculation assumes a constant sleep pattern. A disturbed sleep pattern is common in patients with CFS [51], which could (partially) account for the lower correlation between both measures, since higher AC would be registered by the Actical during sleep time, but not in the activity diary. Future research should therefore investigate whether a disturbed sleep pattern influences the relationship between the self-reported and objectively measured PAL or differentiate between awake and sleep time to control for this possible influence [7,8,27].

Because this study is a secondary analysis of previously gathered data, the sample size was not determined based on an a priori power analysis for the current analysis. Therefore, the power of this study cannot be reported.

The generalizability of the current research findings to the overall CFS population is also limited. Because of the statistical methods used, systematic bias of the activity diary cannot be excluded and the lack of associations with the discrepancy only applies to this sample and not necessarily to male patients. Additional research using the same output variable for the self-report and objective measure with consideration of mentioned points of attention and recommendations should be performed to allow direct comparison between both measures, explore their level of agreement and investigate systematic bias of the activity diary [11,50]. Additionally, a higher accuracy for self-report for males than females was identified in healthy controls [11], which should be further investigated in patients with CFS.

Conclusion

The activity diary used in this study showed limited ability to register the PAL in female patients with CFS. Discrepancies between self-report and objective activity monitoring in patients with CFS relative to healthy controls could not be explained by illness-related complaints, health related quality of life or demographic factors. The activity diary cannot replace actual activity monitoring measured with a motion sensor, but may provide additional information about the perceived activity. Future research should explore the discrepancy between self-report and direct measures of PA and associated factors further and identify a self-report measure that encompasses detailed information about patients' perceived PAL complementary to a direct measure.

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PART 2

Health-related quality of life and physical activity in chronic fatigue syndrome and multiple osteochondromas

CHAPTER 5

Physical activity level and health-related quality of life in adults with multiple osteochondromas: A Dutch cross-sectional study

This chapter is submitted as:
Vergauwen K & Amajjar I, Willigenburg NW, de Groot C, Huijnen IPJ, Smeets RJEM, Ham SJ. Physical activity level and health-related quality of life in adults with multiple osteochondromas: A Dutch cross-sectional study.

CHAPTER 6

Associations between health-related quality of life and fatigue, pain, depression, pain catastrophizing and physical activity level in chronic fatigue syndrome and multiple osteochondromas: an exploratory study

This chapter is submitted as:
Vergauwen K, Amajjar I, Meeus M, Huijnen IPJ, Willigenburg NW, de Groot C, Ham SJ, Smeets RJEM. Associations between health-related quality of life and fatigue, pain, depression, pain catastrophizing and physical activity level in chronic fatigue syndrome and multiple osteochondromas: an exploratory study.

CHAPTER 7

General discussion

General discussion

Chronic fatigue and chronic pain are common symptoms in the general population with an estimated prevalence >20% [1–3]. Both can present themselves as a solitary health condition or as a secondary symptom related to other disorders [1,2,4], and both often co-occur [1]. Given that pain and fatigue complaints often occur together, it seems warranted to include both symptoms in fatigue-related research.

Chronic fatigue and pain can have a negative impact on a person's health-related quality of life (HRQOL) [5–8]. Achieving optimal HRQOL should be considered a main outcome of healthcare. Both disease-specific and transdiagnostic factors, either unmodifiable or modifiable, can be determining for HRQOL [8,9]. Understanding the factors that positively or negatively influence HRQOL is therefore necessary to tailor and optimize interventions accordingly. Insight into determinants of HRQOL, and whether they are transdiagnostic or disease specific, in patients with chronic fatigue and pain, was lacking. The comparison of two distinct patient populations sharing both symptoms could increase our knowledge; this dissertation therefore included patients with chronic fatigue syndrome (CFS) and patients with multiple osteochondromas (MO).

Physical activity was a specific factor of interest due to the negative effect of physical inactivity on the development of non-communicable diseases [10] and the positive effect of regular physical activity on HRQOL [11].

The aims of this thesis were:

1. to provide an overview of reliable and valid measures that are suited to assess activity limitations and participation restrictions as part of HRQOL in patients with CFS.
2. to provide an overview of reliable and valid measures that are suited to assess physical activity levels (PAL) and patterns in patients with CFS. Additionally, knowledge on the ability of a self-reported measure to assess the actual PAL in patients with CFS is extended. Self-reported measures have the ability to provide more environmental and contextual information, and also give insight into the type of activities that are performed. The concurrent validity of an activity diary with an actometer was evaluated and factors associated with the observed discrepancy between the activity diary and actometer were explored.
3. to explore HRQOL, the PAL and associated biopsychosocial factors herewith in patients with MO.
4. to compare HRQOL between patients with CFS and MO and explore whether associated biopsychosocial factors with HRQOL could be considered transdiagnostic or disease-specific in patients experiencing chronic fatigue and specific and/or non-specific chronic pain complaints.

This general discussion will first provide a summary of the main results for each aim. Knowledge gained will be integrated and discussed in relation to current scientific evidence, and clinical implications are formulated. Strengths and limitations of this thesis are then addressed, followed by suggestions for future research and valorisation.

Interpretation of main findings

Measures to assess activity limitations, participation and HRQOL

In *chapter 2* results of a systematic review on the psychometric properties of measurement instruments to evaluate activity limitations and participation restrictions in persons with CFS are described. Meaningful activities and participation are inextricably linked to HRQOL. Fekete et al. (2019) reported that engagement in productive activities including both paid and unpaid work, despite a chronic condition, was positively related to mental health and quality of life [12]. Additionally, social participation is associated with physical HRQOL in both directions [13].

Because chronic fatigue is the primary focus of this thesis, we focused on the psychometric properties of measurement instruments evaluated in patients with CFS, since chronic fatigue is its primary diagnostic criterium.
Although a total of 71 relevant articles and 38 different measurement tools were identified, the psychometric properties of only five measurement tools were (partially) evaluated in patients with CFS. Since the systematic review dated back to 2012, an update was performed with the same search strategy until April 2, 2023. After title and abstract screening, 276 articles were included for full-text reading. A total of 132 additional articles mentioned a measurement instrument including some part of activity limitations or participation restrictions. Appendix 1 presents an overview of mentioned measurement instruments.

The high number of articles published in the last decennium that use a measurement instrument to evaluate limitations in activities and/or participation restrictions clearly shows the increased interest for these outcome measures, which can only be considered positive. The shift from a biomedical view, focusing on the presence and absence of disease, to a biopsychosocial view, which recognizes the complex interplay between biological, psychological and social factors, has a positive effect at the individual level as it takes into account all factors that can influence HRQOL. Addressing all factors that enable or impede participation will better help patients to remain (more) involved in social life. Consequently, the biopsychosocial view can also have a positive effect at the societal level [14]. Keeping patients involved in social life can result in lower burden on the social system through less utilization of healthcare services, less need for formal and informal support (e.g., paid household help) and higher employment rates, less absenteeism and presenteeism [15–17].

Unfortunately, only one additional study was conducted in patients with CFS on the psychometric properties of measurement instruments evaluating activity limitations or participation restrictions [18].
Nevertheless, resulting from our updated search, the SF-36 is still the most frequently used instrument in scientific research (n = 97), followed by WSAS (n = 24), SIP 8 (n = 13) and EQ-5D (n=9). A notable observation was that often only the physical functioning subscale of the SF-36 was used, which gives the impression that there is still more

attention for physical aspects in comparison to other aspects of HRQOL. In this thesis, the SF-36 was also chosen to assess HRQOL. Norm scores exist from the Dutch general population [19] and, because of its wide use, it is an interesting measurement tool to use in research as it allows comparison of different patient populations in terms of HRQOL.

The only study identified during the updated search that was conducted with patients with CFS reported to have evaluated the psychometric properties of the RAND-36, but references used rather give the impression that it concerns the (MOS) SF-36 [18]. In scientific literature, it is sometimes unclear whether the RAND-36 or the (MOS) SF-36, further referred to as SF-36, was used. The designations seem to be used interchangeably, creating ambiguity about the differences between the two measurement instruments. Even though both measurement instruments evaluate the same construct, consist of the same subscales and items, minor differences are reported. For instance, the SF-36 scores the second item of bodily pain conditionally dependent on the response to the first item, which the RAND-36 does not. In addition, the SF-36 has an uneven distribution between the response categories on bodily pain, while the RAND-36 has an even distribution. Finally, the SF-36 uses other scale scores for the different response options on general health compared to the RAND-36 [20]. Despite these minor differences, a longitudinal study reported a correlation coefficient of 0.99 between bodily pain and general health of the SF-36 and RAND-36 [20,21]. In the Dutch version, differences between wording have been described but the level of accordance between both versions has not yet been investigated. Since both versions use the same scoring algorithm as their original (English) version, it could be assumed that the Dutch versions have similar agreement [19]. However, differences in terms of interpretation of wording can have an unprecedented influence which makes such an assumption precarious. Whether comparing subscale scores between the Dutch MOS SF-36 and RAND-36 is possible or methodologically flawed is as yet unclear. Due to lack of correct reporting of the measurement instrument used, it is not always clear which measurement instrument is involved and an unintended comparison of different measurement instruments could occur. This emphasizes the need for correct reporting of used measurement instruments in scientific research.

Even though it is unclear which one of the two measurement instruments was evaluated by Murdock et al. (2017), they suggest important limitations [18]. A *floor effect* on role in physical functioning in patients with CFS was identified, with 89% reporting the lowest score possible. The authors refer to the floor effect as a ceiling effect, because they used reverse scoring in their study. Because in this thesis a lower score refers to a lower HRQOL, the results of Murdock et al. (2017) will be interpreted/reported as such[18]. The *internal consistency* was insufficient for general health (α = .56), and within questionable range for vitality (α = .68). All other subscales had an acceptable to excellent internal consistency (α = .71 – .91). Other psychometric properties were not evaluated. The floor effect implies that the effectiveness of interventions targeting improvements in this domain may be underrated due to the inability of the measurement instrument to adequately detect clinically important differences. Patients may not be able

to rate their limitations on role in physical functioning adequately at baseline due to the inability to score low enough. So even though they might experience clinically significant improvements the instrument will not be able to pick up this change after a targeted intervention, as they could not rate themselves below the minimum before receiving treatment [18]. Therefore, caution is recommended when using the measurement instrument as an outcome measure to evaluate the effectiveness of treatment strategies targeting improvement in performing physical roles.

Studies regarding the responsiveness of SF-36 subscales are ambiguous. On the one hand, Angst et al. (2008) found a large effect size for the subscale vitality, moderate effect sizes for role in physical functioning, bodily pain, social functioning, mental health and Mental Component Summary (MCS), and small effect sizes for physical functioning, general health, emotional functioning and Physical Component Summary (PCS) in patients with chronic pain [22]. On the other hand, Wittink et al. (2004) found only a moderate effect size for bodily pain and small effect sizes for physical and social functioning after a multidisciplinary pain treatment [23]. The responsiveness of the SF-36, including the minimal clinical important difference (MCID), varies depending on the population under study, meaning that not every subscale seems suitable for observing change for every purpose and population [22–25].

Floor and ceiling effects can largely be avoided by using the PCS and MCS. It is argued that summary scores also produce smaller confidence intervals and reduce the number of analyses from eight to two [20]. On the other hand, summary scores are also criticized because of their scoring algorithm. First, summary scores can only be calculated using norm scores, which are available for different populations, for example United States, Wales, Sweden, Norway and the Netherlands [19,26–29]. Not every country, such as Belgium, has these norm scores, so calculation of summary scores is not possible or is performed using norm scores from a different population. Whether the use of norm scores from another population generates summary scores that can be considered an accurate representation of the measured HRQOL domains in the assessed population is open to debate.

An important assumption of the summary scores is that they are uncorrelated (orthogonal) and each represent a different health outcome, that is physical and mental health. A point of discussion raised by Taft et al. (2001) is that in the calculation of summary scores all eight subscales are used, but with different weights depending on the calculated summary score. Specifically, when calculating the PCS, five subscales are positively weighted and three subscales - social functioning, emotional functioning and mental health - are negatively weighted. In the MCS, four subscales are positively weighted and four subscales - physical functioning, role in physical functioning - bodily pain and general health, are negatively weighted. This scoring algorithm is defended by Ware et al. (2001) who discuss the overlap between the PCS and MCS when negative coefficients are not used, because then some subscales would be counted twice as they measure content that is not unique to either orthogonal component [30]. By using this algorithm, confounding is kept to a minimum. However, Taft et al. (2001) express concerns about this scoring algorithm by discussing that summary scores are influenced by the negative weighted subscales in an unwanted way. According to them, the 'expected' range of summary scores is 20-58 for the PCS and 17-62 for the MCS [30,31].

They argue that a patient can only score below 20 (PCS) or 17 (MCS) when they report zero on all positively weighted subscales and score higher on the negatively weighted subscales primarily related to the opposite health component. They use the same reasoning for scores higher than 58 (PCS) or 62 (MCS), stating that these scores can only be obtained if individuals report the maximum score on all positively weighted subscales and lower scores on the negatively weighted subscales. According to their reasoning, a score outside the 'expected' range for the PCS would thus reflect a change in mental health rather than physical health and vice versa for the MCS [31]. Due to the presence of chronic fatigue, pain, as well as psychological factors, such as depression and catastrophizing, in patients with CFS and MO, the interaction between mental and physical aspects of HRQOL should not be underestimated. Consequently, the question arises whether the summary scores calculated according to the MOS SF-36 scoring algorithm compromise an accurate representation of the two distinct health components in these patient populations. Ware et al. (2001) examined the hypothesis raised by Taft et al. (2001) stating that an extremely low or high PCS or MCS outside the 'expected' range is mainly due changes in the opposite health domain and does do not reflect an actual change in the respective health domain. Although they found that a small percentage of persons (<15%) reported the minimum or maximum score on all positively weighted subscales of the respective summary score, the majority of persons scoring outside the 'expected' range did not. Ware et al. (2001) identified that for the majority of persons scoring at the 'ceiling' for PCS or MCS, this score was due to variation in the positively weighted subscales of the respective component score. Consequently, Ware et al. (2001) could not confirm the hypothesis of Taft et al. (2001) on the relationship between summary scores beyond their 'expected' range and negatively weighted subscale scores [30,31]. According to Ware et al. (2001), the proposed algorithm assures minimal confounding and maximal validity in measuring only one component of HRQOL, i.e., physical or mental health [30]. They also emphasized that they always recommended to interpret the summary scores parallel to subscale scores to draw accurate conclusions, because subscale variability and thus possible valuable information is lost when calculating summary scores [20,29,30]. To address this criticism, other algorithms have been developed to calculate summary scores that either sum the four physical subscales (physical functioning, role in physical functioning, physical pain and general health) and the four mental subscales (emotional functioning, mental health, vitality and social functioning) or allow correlation between the two factors. Nevertheless, the use of orthogonal factors is apparently still used most often [20]. In conclusion, using only the summary scores does not seem to be an appropriate procedure and, on top of that, the calculation does not always appear possible due to the unavailability of norm scores. This discussion advocates the use of subscale scores that can be calculated regardless of the available norm scores, but the user should be attentive to potential floor and ceiling effects. Whenever possible, summary scores can be calculated, but they should always be interpreted relative to subscale scores.

Based on the results of the systematic review in **chapter 2**, none of the identified measurement tools were considered appropriate for use in patients with CFS due to limited evidence about their psychometric properties. However, if healthcare

professionals or researchers need a measurement tool to evaluate activity limitations or participation restrictions in patients with CFS, the Chronic Fatigue Syndrome-Activities and Participation Questionnaire (CFS-APQ) is recommended. Nevertheless, healthcare professionals should use this questionnaire with caution due to the limited available evidence about its psychometric properties. It is important to note that the questionnaire was developed specifically for patients with CFS and may therefore be less appropriate for use with other patient populations experiencing chronic fatigue not due to CFS. In that case, the SF-36 seems to be the best option at the moment.

Measures to assess the physical activity level and activity pattern

In *chapter 3* results of a systematic review on the psychometric properties of measurement instruments to evaluate the PAL and pattern in persons with CFS are described. Even though substantial reductions in previous levels of occupational, educational, social or personal activities is part of the CDC-1994 CFS criteria [32], limitations in meaningful activities do not necessarily correspond to a disrupted PAL or activity pattern. But vice versa, these disruptions can lead to a reduced ability to perform meaningful activities [33], for example through increased symptom severity when physical activity limits are not respected [34]. Patients with chronic fatigue or chronic pain also display different coping strategies towards physical activity. Patients may avoid any activity thought to exacerbate fatigue or pain symptoms, or they stay active despite symptom severity or they have a variable pattern depending on how they feel [33–36]. In order to make an accurate assessment of patients' PAL and activity pattern to tailor treatment interventions, valid and reliable measures are necessary.

A systematic review on the PAL of patients with CFS concluded that all included studies reported lower habitual physical activity in patients with CFS compared to healthy individuals [37]. Band et al. (2016) found indications that symptom severity, i.e., fatigue and pain, and affect drive the physical activity pattern (all-or-nothing behavior or activity limitation) of patients with CFS, both in and beyond the immediate context [38]. In patients with fibromyalgia, lower sedentary time en higher levels of light physical activity were associated with lower fatigue and pain intensity [39]. Additionally, in healthy individuals both positive and negative associations between the PAL and HRQOL have been reported. Higher sedentary time is associated with a lower HRQOL [40], while higher PALs are associated with a higher HRQOL [11,40–42]. Individuals who meet the daily amount of exercise recommended by the WHO are also at lower risk of developing non-communicable diseases [10].

The systematic review performed until 2016 included 51 articles and 15 unique measurement instruments to assess the PAL or activity pattern in CFS were identified.
An updated search until April 2, 2023 with the same search strategy yielded 90 articles for full-text reading. A total of 22 articles mentioned a measurement instrument that assesses the PAL or activity pattern; Appendix 2 presents an overview. Unfortunately, no additional studies were conducted on the psychometric properties of identified measurement instruments in patients with CFS either, except for our own study evaluating the ability of a self-reported activity diary to measure the actual PAL

(concurrent validity with an actometer) [43], described in *chapter 4*. Identified measurement instruments can be categorized in two groups, objective measures or self-reported, each with its own strengths and limitations [44].

Activity monitors, categorized as objective measures, were most frequently used in scientific research (n = 38). Activity monitors are especially useful to measure frequency, duration and intensity of physical activity [45,46].
One way to process the raw acceleration data (acceleration signals) generated by activity monitors, is to calibrate activity monitors in a laboratory setting [45,47]. During calibration, raw acceleration data (acceleration signals) generated by the activity monitor are converted to activity counts per unit time (an epoch) [45,46]. How acceleration signals are converted to activity counts depends on the device-dependent algorithm, which is not always made accessible or clearly reported by researchers [45,47]. An activity count in itself has no meaning and has to be transformed to an alternative unit to quantify the intensity of an activity [46]. Consequently, during calibration in a laboratory setting, activity counts are often simultaneously recorded with a physiological variable such as indirect calorimetry (VO_2-VCO_2), which is later converted (considering age, gender, height and weight of the individual) to Metabolic Equivalent of Task (MET), a measure of energy expenditure defined as light (<3 METs), moderate (3-5.99 METs), vigorous (≥6 METs) and sometimes very vigorous intensity (≥9 METs) [45]. Regression equations are used to estimate the relationship between activity counts and METs and to predict point estimates of energy expenditure, expressed in activity counts, that reflect the duration and intensity of the performed activity. In research, numerous different regression equations used during calibration have been reported, each generating slightly different cut-off points for similar energy expenditures [46,48]. However, lack of consensus on these cut-off points makes comparisons between studies difficult. On the other hand, uniform cut-off points do not seem an appropriate solution, because it is likely that differences exist between individuals and patient populations in terms of energy expenditure and experienced activity intensity [46]. This is shown by the multiple studies on the estimation of cut-off points for specific patient populations, for example rheumatoid arthritis, Parkinson's disease and breast cancer [49–51], which all report cut-off points that differ from non-patient specific cut-off points. In addition, the accuracy of the energy expenditure estimates is, among others, influenced by the type and attachment of the activity monitor, and the type of activity [46]. Since researchers use different protocols in terms of location of the monitor (e.g., wrist, ankle, hip) and duration of the measurement (amount of consecutive days, inclusion of weekdays and/or weekend days), and apply varying cut-off points, it remains unclear how to obtain the most accurate and valid result using these monitors [48,52–55].
Following the discussion on cut-off points, it is important to note that, to date, no cut-off points (for categorizing PAL according to intensity) have been developed specifically for patients with CFS. It is discussed that fatigue is the consequence of complex interactions between multiple systemic and central pathways that may lead to physiological changes, which makes it plausible to expect that the cut-off points in individuals with CFS would differ from healthy individuals [56]. As no CFS-specific cut-off points exist, only general cut-off points or cut-off points based on other patient

populations can be used. This may lead to misinterpretation of data for individuals with CFS, i.e., over- or underestimation of energy expenditure and time spent in activities of different intensities, as e.g., patients with CFS seem to spend more energy during walking compared to healthy individuals [57]. Researchers and clinicians should therefore be careful when interpreting results using these general cut-off points.

Because the use of cut-off points based on processed data (activity counts) instead of raw acceleration data (acceleration signals) generates such limitations, Freedson et al. (2012) already suggested 10 years ago to invest in the development of pattern recognition using raw acceleration data [47]. This could reduce the chance of over- and underestimation of energy expenditure [47]. A systematic review on machine learning approaches to analyze accelerometer output reported opportunities to improve accuracy of data interpretation with machine learning instead of traditional statistical methods such as linear regression calibration and cut-off points. However, current models are developed in laboratory settings and more research is needed to develop models that provide similar accuracy in free-living settings and independent populations [58]. So, despite that activity monitors could add great value to the evaluation of physical activity, more research is necessary to accurately interpret data derived from activity monitors.

The second group of physical activity measures consists of self-reported measures. Although self-reported measures are often questionnaires on (habitual) physical activity with closed questions, activity diaries are also used and have the main advantage of being able to gather information on the type and context of the performed physical activity [44,46]. Self-reported measures of physical activity have important limitations to consider. Low correlations have been found between objective and subjective measures, especially if the self-reported measure relies on recall [44,46]. An unclear definition of physical activity and distorted cognitions on e.g., their condition or on pre-morbid levels of physical activity can also contribute to observed discrepancies [59,60].

The complete systematic literature search identified a total of 22 different self-reported measurement instruments to assess physical activity. Only three articles examined limited psychometric properties of three self-reported measures, CFS-AQ, API and IPAQ-SF, and none was deemed optimal to use in patients with CFS. This review shows that there is limited evidence on the psychometric properties of measurement instruments that evaluate the PAL level or activity pattern in patients with CFS.
Therefore*, chapter 4* aimed to increase the knowledge on the validity of an activity diary by comparing it to an activity monitor (Actical). The activity diary excludes recall as much as possible by requiring immediate reporting of the activity performed, assuming that this is one of the factors driving the discrepancy between self-reported and objective measurement. The goal was to investigate whether the activity diary is able to capture the PAL accurately in female patients with CFS, and if not, whether factors could be identified that are associated with the discrepancy relative to healthy controls. Patients with CFS did not reach the predetermined correlation coefficient of ≥ 0.50 [61], where healthy controls did so. Female patients with CFS were thus less capable of evaluating their actual PAL with a self-reported activity diary. Unfortunately, none of the included

factors (age, disease duration, CFS self-reported symptoms (CFS Symptom list), HRQOL (SF-36 subscales)) could explain the observed discrepancy relative to healthy controls.

Based on physical activity pattern, King et al. (2020) identified three subgroups in patients with CFS: pervasively active, pervasively passive and moderately active [33]. Further investigation of the data revealed that in the pervasively active group, there was no significant association between the Actical and activity diary. And even though the correlation coefficients in the pervasively passive and moderately active group were statistically significant, no subgroup reached a correlation coefficient ≥ 0.50. It seems that additional, currently unknown factors affect the accordance between both measures which seem to differ depending on the patients' activity pattern [43].

This result confirmed the findings of Troiano et al. (2014), who discussed that self-reported measures and objective measures are not interchangeable, because they measure a different construct [62]. Activity monitors are able to measure continuous bodily motion and accurately reflect time spent on non-continuous physical activities (e.g., lifting and bending), but do not provide contextual and behavioral information on the performed physical activity. Self-reported measures on the other hand, especially activity diaries, can provide contextual and behavioral information on performed daily physical activities which are often non-continuous in nature (e.g., 30 minutes of grocery shopping which implies short-term carrying of loads, walking and bending over). Self-reported instruments can also measure physical activities that are difficult to capture by an activity monitor due to its attachment, e.g., cycling with a wrist worn accelerometer.

Based on our and previous results, ideally, a self-reported measure and an objective measure are used together because of their complementarity [44,62]. Use of both measurement instruments together provides a comprehensive idea of the adopted movement pattern and coping behavior (e.g., all-or-nothing or avoidance behavior), accurately reflects the time spent per activity and its intensity level, and provides the necessary contextual information on physical activities performed. Based on this information, among other things, the practitioner can choose the most appropriate treatment strategy and adapt it to the patient's needs, for example pacing, graded activity or exercise.
An activity diary is most valuable to provide contextual information related to activities recorded with the activity monitor and to select personally relevant physical activities to prioritize during treatment. It provides a starting point to create an individualized activity plan. An activity monitor is most helpful to establish a personal baseline and monitor gradual increases in physical activity during graded activity / graded exercise or monitor periods of effort and rest during pacing.
When only a single measurement is possible, it is important to sufficiently define the purpose of the measurement and to keep the capabilities and limitations of each type of measurement instrument in mind. Based on these considerations, the most appropriate type of measurement instrument can then be chosen.

Health-related quality of life and physical activity level in patients with MO

In *chapter 5*, HRQOL and the PAL in Dutch patients with MO were explored. Limited studies investigated HRQOL in patients with MO and none explored the PAL or associated factors with HRQOL or the PAL. MO has a clear etiology and is known as a chronic musculoskeletal condition which causes localized pain. Studies on other pain types are limited, but available results point towards the presence of generalized pain in a subgroup of patients [63]. Bathen et al. (2019) were the first authors who confirmed that fatigue is also a prevalent symptom in patients with MO [64]. The aim of our study was therefore to explore whether, and in which direction, demographic, disease-specific (i.e., pain and fatigue) and psychosocial factors that were identified in previous research in chronic populations, influence the HRQOL and PAL of patients with MO. To fill a current knowledge gap, it was of specific interest to explore whether and which psychological factors (pain catastrophizing, fear-avoidance beliefs, anxiety and depression) are present in patients with MO, and whether they have the same negative impact as in other chronic pain patients.

Taking into account the concerns of Taft et al. (2001) and the responses of Ware et al. (2001) about the use of summary scores versus subscale scores, *chapter 5* favored the use of summary scores. First, it reduces the analyses from eight to two. Second, it provides a more general view of the mental and physical HRQOL. Third, it limits floor and ceiling effects and, finally, it allows comparison of patients' scores with reference scores from the healthy population or from other patient populations. Where appropriate, these summary scores were compared with the subscale scores, as reported by Ware et al. (2001). Using the SF-36 summary scores, only a significantly lower physical HRQOL (PCS) compared to the available norm scores was observed. If the subscale scores are compared instead of the MCS, vitality and mental health (both males and females), and social and emotional functioning (only females) were significantly lower compared to norm scores. This confirms the argument of Ware et al. (2001) that subscale scores should always be taking into account when using summary scores to ensure a correct interpretation [30]. Even though some domains related to mental health are more affected than others, the overall mental health of patients with MO is less negatively affected than their physical HRQOL. The average PCS is well below average for both males and females (<50). Even though the MCID differs between subscales and patient groups in which it was investigated, a general rule of thumb for the SF-36 subscales is that a minimal 5-point difference points towards a clinically significant worse or better state; both males and females with MO reached a negative 5-point difference on all subscales, except for emotional and social functioning (both only females), compared to norm scores suggesting a clinically worse state.

Pain intensity, depressive feelings and BMI were negatively related to the PAL. Previous research showed that engaging in regular physical activity of moderate intensity, among which gardening, household activities and brisk walking were considered, could reduce the risk of depression [65], lower pain and increase physical HRQOL [66]. Therefore, it seems important during treatment to focus on limiting sedentary time and pay more attention to performing physical activities of preferably at least moderate intensity, of

which daily activities constitute an important part. In patients with MO, having a paid job seemed to be an indicator of an overall higher PAL. Even though a cross-sectional study was conducted and no interferences can be made on causality, exploration of current employment status and identification of challenges and opportunities for job reintegration seem worthwhile. Fekete et al. (2019) advocate for vocational rehabilitation to reintegrate persons into paid or unpaid productive activities [12]. Attention should be given to individual needs regarding work, such as workload and functional capacity, but also towards environmental factors such as legislation, financial aspects, access to the regular job market and attitudes towards persons with a chronic disorder [12,67]. Timely involvement of specialized organizations in vocational reintegration can support an employee and employer in coping with and finding solutions to the changed employment status as a result of a chronic condition, so that the person can maintain their desired employment status as much as possible. A preventive approach in which experts can be called upon, if possible, and workplace modifications made before significant work-related limitations develop, can also be valuable.

In MO, there is ambiguity around gender differences. In our PCS model, gender was not retained, indicating that in the light of other factors, gender is not an important contributor to physical HRQOL. Higher pain, fatigue, anxiety and more pain-related disability were reported by females, which in turn were associated with physical HRQOL. Gender thus seems to have an indirect rather than a direct effect.
The PAL was not significantly related to physical HRQOL, but more pain-related disability was negatively associated with physical HRQOL. This result points to a greater relevance for increasing personally relevant activities than for merely increasing the "general" PAL to improve physical HRQOL. However, increasing the PAL could play a significant role due to its established positive association with health [10,11,42,68].
Although the orthopedic surgical treatment of patients with MO is not the focus of this research project, the negative association between more surgical interventions and lower physical HRQOL pleads for a further investigation of necessity and effect of surgical interventions in patients with MO. It could be that the higher amount of surgical interventions is caused by other disease-related problems or related to phenotype differences. Another possibility is that surgical interventions may result in short-term postoperative physical limitations, which depend on the type of surgical procedure and surgical site among other factors, and prevent patients from performing physical activities and fulfilling physical roles. Our study asked only about the amount of surgical interventions, but not whether patients had recently undergone surgery.
Currently, prehabilitation, that is preoperative optimization of predictive factors of recovery to obtain better postoperative outcomes, is receiving more attention from researchers and clinicians. Specifically for patients undergoing orthopedic surgery, prehabilitation includes optimizing muscle strength, function and HRQOL. A recent systematic review identified moderate preoperative improvement after prehabilitation in outcomes such as back pain (lumbar surgery), HRQOL (total hip replacement, lumbar surgery), function (total knee replacement) and muscle strength (total knee replacement). However, evidence regarding postoperative outcomes after prehabilitation compared to usual care was inconsistent and the quality of evidence was low to very low

[69]. Further investigation whether better preparation for surgery has a positive impact on recovery and thus leads to fewer postoperative physical limitations is indicated.
The overall mental HRQOL did not significantly differ from the available Dutch norm scores, and pain catastrophizing, anxiety, depression and fear-avoidance beliefs were all, on average, below clinical cut-off points in our sample of patients with MO. Nevertheless, higher anxiety and depressive symptoms were significantly associated with lower mental HRQOL. None of the psychological factors were significantly associated with physical HRQOL. Comparison of anxiety and depression scores (Hospital Anxiety and Depression Scale) of patients with MO to available norm scores of the general population of the United Kingdom and Germany shows that patients with MO report similar scores [70,71]. Based on these findings, it seems that severe psychological symptoms are less present in patients with MO compared to other patients with chronic pain and fatigue, which could also explain their limited or missing associations with HRQOL in our sample. However, when severe anxiety or depressive symptoms are present, they appear negatively associated with mental HRQOL and thus require attention in patients with MO. No subgroups based on the severity of psychological factors were further analyzed, which could have provided more insight into the percentage of patients who do experience severe psychological strain and its relation with both domains of HRQOL [72].
Most importantly, fatigue was retained in both the physical and mental HRQOL model and, because pain was not part of the mental HRQOL model, confirmed the hypothesis that fatigue is stronger related to mental well-being than pain and should not be overlooked in patients with MO. A causal relationship between pain and fatigue has been established where pain precedes and predicts subsequent fatigue, advocating for the evaluation of both symptoms in patients presenting with chronic pain complaints, such as patients with MO [73].
Finally, some results showed an unexpected directionality. These were all results based on insufficient data or of insufficient magnitude to draw informed conclusions and require further investigation.

One finding worth exploring further is the positive association between higher education level and physical HRQOL. Salaffi et al. (2009) hypothesized that a higher level of education may lead to better self-efficacy, allowing these patients to better adapt to and manage their disease-related symptoms such as fatigue and pain [74]. Whether a treatment intervention that focuses on self-management, addressing goal setting, improvement of personally relevant activities, self-efficacy and development of adequate coping skills yields improvement in HRQOL, seems worth investigating.

Disease-specific and transdiagnostic determinants of HRQOL
Chapter 6 further build on the results of chapter 5 and explored which determinants of HRQOL can be considered disease-specific or transdiagnostic by including patients with CFS and MO who both experience chronic fatigue and chronic pain.

In chapter 6, subscales scores instead of summary scores were used because of the unavailability of Belgian norm scores. Both patient populations reported lower subscale

scores compared to Dutch norm scores for nearly all subscales, except male MO-patients for emotional and social functioning. Eight different HRQOL models were calculated, one for each SF-36 subscale. Only fatigue was negatively associated with each subscale, pain was associated with all subscales except with vitality and mental health. This confirms the hypothesis with which this thesis began: CFS is a rare syndrome in which chronic fatigue is the main symptom, but chronic fatigue is also a common symptom in chronic pain patients, and fatigue has a large association with HRQOL in patients with chronic fatigue and pain. Its association with HRQOL is sometimes even greater than the association between pain and HRQOL and should therefore not be ignored. Although fatigue and pain can be considered transdiagnostic symptoms based on our results, the extent of their association with HRQOL appeared disease-dependent. When controlling for all other factors, the negative association between HRQOL and fatigue was greater in individuals with MO than in those with CFS, except for the subscales physical functioning and vitality. The same applies to the subscales with which pain was associated. Initially, these results seemed rather counterintuitive given the lower mean scores for fatigue and pain in patients with MO compared to patients with CFS and higher SF-36 subscale scores. The hypothesis for this is that in patients with CFS, in general, there is a complex interaction of factors that causes them to experience lower HRQOL than patients with MO where such complex interaction is less common. In patients with CFS, the psychological factors pain catastrophizing and depression are part of the complex interaction. Without this complexity, it is plausible that patients with a long-term chronic condition such as MO have a more negative association between fatigue or pain and their HRQOL.

Pain catastrophizing was negatively associated with more physically oriented subscales, i.e., role physical functioning and pain, but in addition also mental health. Depression was only negatively associated with mental wellbeing, i.e., emotional functioning, social functioning, mental health and vitality. As with fatigue and pain, the models including interaction-effects of pain catastrophizing or depression with diagnosis showed a greater decrease in the respective HRQOL subscale in patients with MO than CFS when controlling for all other factors. Again, this was initially paradoxical given that the mean score on the Pain Catastrophizing Scale is significantly higher for patients with CFS than MO, and more patients with CFS report mild, moderate and severe depressive symptoms. However, the results are consistent with the hypothesis that patients with CFS have a complex interaction of disease-specific (fatigue and pain) and psychological (pain catastrophizing and depression) factors, which is not the case in most patients with MO. What these results clarify is that severe psychological strain is not common in patients with MO, but when present, is associated with lower HRQOL than in patients with CFS.

For healthcare providers, this highlights the importance of asking about and evaluating the presence of psychological symptoms in patients with chronic fatigue or pain in order to identify and treat them in a timely manner.

Mental health literacy has been identified as a significant determinant of mental health and includes knowledge about mental health and mental health disorders, awareness of how to seek help and treatment and reducing stigma [75]. Improving mental health literacy at the individual level, that is the patient and if possible their network, might promote the timely recognition of psychological symptoms. Because the development of

psychological symptoms may be recognized early by the patient or their network, patients are given the opportunity to take control of their cognitions and behaviors and manage their disorder to the best of their ability. By improving patients' self-management, further deterioration can potentially be prevented, which will reduce the demand for professional help for a number of patients. Nevertheless, if necessary, this approach also allows timely consultation of specialized care.
Given the relationship between these factors and HRQOL, it seems warranted to investigate whether a preventive approach consisting of early sharing of information about the comorbidity of psychological symptoms and how to recognize them, along with regular evaluation of psychological symptoms by healthcare professionals in patients with chronic fatigue and pain, can prevent their onset or lead to timely recognition when developing.

A final interesting result was a positive association between the PAL and physical functioning, pain, vitality and general health which turned out to be limited and smaller than expected. Although previous research has shown a positive effect of higher levels of physical activity on HRQOL [10,11], based on the results of chapter 6 it is warranted to question whether solely increasing the PAL is sufficient to achieve clinical improvement in terms of HRQOL. Chapter 5 identified a significant relationship between pain-related disability and physical functioning, contributing to the hypothesis that increasing personally relevant activities may have a more positive relationship with HRQOL than merely increasing the PAL where desired daily activities are not necessarily taken into account. Further investigation of this hypothesis constitutes an interesting future research topic.

Methodological considerations

Each chapter addressed specific limitations of each study. In this section, general considerations are discussed.
Both systematic reviews, chapters 2 and 3, focused on patients with CFS, which in this thesis was considered a representative population for persons experiencing chronic fatigue. It can be debated whether this population is truly a good representation of all patients experiencing chronic fatigue. Possibly a broader inclusion of also other conditions causing chronic fatigue would have generated more generalizable results.
In chapter 4 which evaluated the validity of the activity diary, a prior feasibility study on the activity diary could have provided more information on its usability.
To interpret accelerometer output, activity counts were used instead of METs. This prohibited the interpretation of time spent per activity intensity and it could not be deduced whether patients with CFS were unable to accurately register all activity intensities, or only one or more specific intensity types. The choice to use activity counts was taken thoughtfully, precisely because the algorithm behind the calculation of METs is unknown and most likely not completely correct for patients with CFS. Although activity counts are a less processed output measure than METs, there is also an algorithm behind this calculation that is often unknown to the user. Use of the raw acceleration data (acceleration signals) would have been more appropriate, but was not accessible.

Because only female patients with CFS were included, generalizability of the results to male patients is limited.

In chapters 5 and 6, a large sample of patients with MO was included (n=342) through different recruitment channels. The Dutch patient association 'HME-MO vereniging Nederland' informed their members about the study through its website and other means, OLVG Amsterdam informed patients who came for consultation at the outpatient clinic. Careful follow-up of the study progress by and high involvement of the coordinating investigator ensured this large sample, which increased the reliability of the studies. The large sample size also made inclusion of most variables of interest possible. Literature describes genotype-phenotype differences in individuals with MO [76,77]. While recognizing the possible impact of genotype (EXT1/EXT2), unfortunately genotype could not be included in chapter 5 because it is not known in many participants. This would have greatly reduced the sample size, and consequently the reliability of the overall results. An additional study that includes genotype-phenotype on top of associated factors identified in chapter 5 in a subsample of patients where the genotype is known, could improve current knowledge on the impact of genotype-phenotype on HRQOL in relation to other factors.
In chapter 6, some variables were measured with different, but similar measurement instruments in both populations. This required categorization or transformation of the measured variables, which lead to loss of variability and may have led to a less exact representation of the association between the respective variable and HRQOL subscale.
Additionally, not all variables of interest were measured in both patient populations. For example, fear-avoidance beliefs and anxiety are two variables which are frequently present in patients with chronic pain, but were not included in this study because they were not measured in the sample of patients with CFS.
As mentioned, there is lack of recent Dutch norm scores and complete absence of Belgian norm scores of the SF-36 and the Baecke Physical Activity Questionnaire. Since society has undergone major changes since the norm values were assessed, it is not unrealistic that people’s HRQOL may have changed. Societal changes also led to an increase in sedentary activity, which on average has likely led to an altered PAL compared to 1982.

Directions for future research

The results of this thesis give rise to future research on HRQOL and the PAL in patients with chronic fatigue and pain by identifying important considerations to be made when setting up a study that uses HRQOL and PAL measurement instruments and offering insight into factors associated with HRQOL. The results of this thesis will also guide healthcare professionals in their clinical practice by providing insight into which factors to evaluate and consider when aiming to improve HRQOL in patients with chronic fatigue and pain.

Main conclusions and directions for future research are summarized point by point.

- Even though the SF-36 is the most frequently used measurement instrument to measure HRQOL, evaluation of its psychometric properties in populations that are

assumed to be significantly different from populations in which they were previously evaluated is necessary. The subscale role limitations in physical functioning showed a bottom-effect in a previous study [18] and chapter 6, and the general health subscale also resembled a bottom-effect in chapter 6. This raises the question whether bottom-effects may also be present in other subscales and whether the SF-36 is suited to adequately measure HRQOL in patients with CFS.

- The SF-36 was used in chapter 5 and 6 because of the available Dutch norm scores and ability to compare scores to other patient populations. However, Dutch norm scores were collected before 1998 and Belgian norm scores are not available [19]. Availability of recently collected norm scores for both the Dutch and Belgian population is necessary to accurately interpret patients' HRQOL. It is recommended that researchers intending to use the SF-36 first ensure to have or collect norm scores of their country, or even subgroups if they are expected to be significantly different within one country, making accurate calculations and interpretations possible.
- The same applies for the availability of recently collected norm scores of the Baecke Physical Activity Questionnaire, where Dutch norm scores are outdated and unavailable for Belgium [78].
- Since the algorithm to calculate Physical and Mental Component Summary Scores (PCS and MCS) uses norm scores, they are only recommended to use when norm scores of the included population are available. Additionally, subscale scores should always be taken into account when interpreting summary scores due to the reduction in variability. Researchers should also pay extra attention towards correct referencing the measurement instrument used, i.e., the RAND-36 or SF-36, since small differences exist between both measures, especially in the Dutch version [19]. Finally, clear MCID for patients with chronic fatigue and pain would help researchers and clinical practitioners to identify effective treatment interventions.
- It should be investigated how raw data from activity monitors can be used to evaluate patients' PAL to avoid unnecessary errors when converting this data to another output. In addition, it should be ensured that the output obtained can be interpreted and used by healthcare providers in clinical practice.
- Rather than comparing self-reported and objective measurement tools to evaluate the PAL, it seems more valuable to explore their complementarity in capturing the full picture of a person's PAL, such as time spent by intensity level, type and context of activity and personal relevance/meaningfulness of the activity.
- The HRQOL models defined in chapter 5 and 6 should be further developed. Other research has identified possible additional factors, such as anxiety, fear-avoidance beliefs and self-efficacy, that may be associated with the HRQOL in patients with chronic fatigue and pain, which should be added to the current models to explore their association. Longitudinal research could provide more insight into causal relationships of identified factors.
- Finally, exploring whether increasing self-efficacy and working towards personal goals aimed at engaging in personally relevant activities, such as employment, causes a clinically significant improvement in HRQOL in patients with chronic fatigue and pain may contribute to future (para)medical practice and treatment development. The added value of improving mental health literacy as a preventive approach for the

development of psychological symptoms in treatment interventions should also be explored.

Impact

This thesis provided innovative insights regarding physical activity, HRQOL and associated factors in individuals with chronic fatigue and pain with an impact for future research and clinical practice. This section reflects on the overarching scientific and anticipated social impact of the results found.

Measuring the physical activity level

Chapter 3 and its update identified activity monitors as the most frequently used measurement instruments to evaluate patients' PAL. Although activity monitors have been shown to provide reliable and valid output in populations in which they were validated, ambiguity about the algorithm used to convert the raw output to more easily interpretable output (activity counts or metabolic equivalent of task) makes the translation of results to other (non-validated) populations difficult. Correctly determining the activity level of a person with chronic fatigue is important to establish an appropriate activity program to avoid both over- and underexertion (pacing). In individuals with chronic pain, it is important for graded activity/exercise that baseline levels and graduated increases can be monitored. To achieve this, a healthcare provider needs to be sure that the output obtained through the activity monitor is interpretable and correct, which is unclear at present for certain populations and specific brands of activity monitors that have not been validated in the population of interest. The use of open-source software would allow the algorithms behind the outcome measure to be checked and, if necessary, adapted to the population of interest. Companies are therefore asked to be more open about their activity monitor software and algorithms used to benefit scientific research and clinical practice. Until then, vigilance is required.

Measuring health-related quality of life

Health-related quality of life (HRQOL) is a reflection of a person's quality of life that is influenced by their health status and can be changed by treatment. HRQOL as a concept is thus not only applicable to individuals coping with a chronic disorder, but to all people as the valuation of health is constantly changing throughout a person's life.

Chapter 2 and its update, reported in the general discussion of chapter 7, showed increased attention towards HRQOL in scientific research. Evaluating the impact of interventions, whatever they may be, on HRQOL is an important patient-reported outcome, because it defines whether a person values the result obtained as contributing to a "better quality of life".

It is not only the cost and effectiveness of an intervention on the target parameter that are important, but also in the longer term whether a person sees significant added value from it themselves, especially when it comes to invasive interventions.

Both our studied populations, CFS and MO, reported lower HRQOL than norm scores, confirming the importance of measuring HRQOL and identifying factors associated with

or causing the lower ratings of HRQOL, and more importantly, interventions to address modifiable factors.
Chapter 6 contributed to this knowledge by providing insight into factors associated with a better or worse HRQOL across disorders which cause chronic fatigue and pain. The next step would be to further elaborate on these models and design appropriate treatment interventions.

Healthcare professionals are encouraged to question patients' HRQOL and discuss their personal goals. Setting goals in dialogue with the patient helps healthcare professionals to choose the most appropriate treatment intervention to improve a patient's HRQOL, because HRQOL implies an individual's perception about their own situation, which cannot be judged by anyone else.

Opportunities for a preventive approach
Persons with chronic fatigue or pain are at risk of experiencing activity limitations or participation restrictions, which are more objective measurable subitems of HRQOL. More limitations and restrictions can in turn contribute to the perpetuation of these complaints, causing a vicious circle that is not easily broken. A preventive approach could add value to avoid such vicious circle, but for this, health professionals in clinical practice need an understanding of what factors could potentially lead to its emergence. Factors associated with HRQOL were identified in chapters 5 and 6.
Healthcare professionals are urged to do a thorough evaluation of a person’s fatigue and pain intensity, symptoms of depression and anxiety, pain catastrophizing thoughts, the PAL and activity limitations. Assessing mentioned factors should be done in a timely and consistent manner for early detection of additional and increasing symptoms and disability. Even age, which in chapter 6 was found to be associated with physical functioning, and gender, associated with vitality, could provide more insight into patients’ perceived HRQOL. Healthcare professionals should be alert to limitations in physical functioning in older individuals and decreased energy in women.
In our studied population, a preventive approach could include educating patients and their network about the possible concomitant consequences of chronic fatigue and pain. It may include questioning about and sharing information on depressive symptoms and catastrophizing thoughts and how to recognize them. With this approach, patients are given the opportunity to self-manage their chronic disorder and associated symptoms, cognitions and behaviors. Additionally, patients should be encouraged to seek timely specialized help when self-management appears to be insufficient of impossible, with the healthcare provider having an important signaling function. Patients should be given information about the guidelines on physical activity and on the positive (preventive) impact of physical activity on their health. The difference between physical activity and exercise should also be explained.
By sharing information with patients early on about their condition and possible associated symptoms and behaviors, rehabilitation is made more accessible to the general population. Patients are given the necessary knowledge and tools to best manage their disorder, but also to recognize their rehabilitation needs in a timely manner and seek professional help to optimize their functioning and minimize disability. This is

in line with the WHO Rehabilitation 2023 Initiative aimed at strengthening health systems worldwide to provide rehabilitation to optimize functioning of the population [79].

Discussing patients' current employment status, their satisfaction with the current situation and options for work resumption, if applicable, should also be part of a consultation or therapeutic session. Good follow-up on this may lead to work retention, reduced absences from work, increased job satisfaction and also higher HRQOL by allowing a person to fulfil their physical and social roles. In chapter 5, having a paid job seemed to contribute to higher levels of physical activity, which in turn also contributes to better overall health. Therefore, we dare to hypothesize that improving the ability to perform personally relevant activities may have a greater positive impact on HRQOL than increasing the PAL alone, of which employment is only one aspect. A higher PAL does not guarantee that a person is able to perform their personally relevant and desired activities and is able to participate, thus experiencing a sense of engagement and meaningfulness. Therefore, in the context of increasing physical activity, we suggest starting from the patient's personal goals and focusing on improving the performance of personally relevant activities rather than just exercise.

Given the multiplicity and diversity of factors involved, a monodisciplinary approach does not seem appropriate even in the early stages, but rather requires a multidisciplinary approach.

Expanding primary care

Because this thesis only examined associations and not causal relationships, it is not possible to determine with certainty whether lower HRQOL is the result of a complex interaction of identified (chapter 6), and as yet unidentified, factors, or whether lower HRQOL contributes to the development of modifiable factors. However, according to our hypotheses based on a predefined ICF-model, HRQOL would result from the complex interaction of identified factors and not the other way around. As mentioned, this argues in favor of exploring the added value of a preventive approach. Primary care plays an important role in prevention. Primary care providers are directly accessible and therefore most often consulted. This gives them the most opportunity to screen and question patients about their impairments, limitations and restrictions, and provide early information and guidance to avoid their (further) development. They also have an important signaling function to refer a patient to specialized care if they are unable to help the person themselves. A timely referral most often leads to a better outcome.

We discussed employment and the potential added value of focusing on personally relevant activities to improve HRQOL, which are areas of expertise of the occupational therapist. Ideally, these are guided from primary care, but a major gap in Belgium is the lack of a legal framework for directly accessible occupational therapy. In the Netherlands, every person is entitled to ten hours of therapy annually from an occupational therapist with reimbursement without a medical prescription. This allows people who experience limitations in activities of daily living or are unable to participate to call on the expertise of an occupational therapist when necessary. Occupational therapists can help them

rehabilitate by working towards recovery, teaching compensatory strategies or the use of assistive devices if needed. This also applies to people with chronic fatigue or pain, who can experience limitations at work, at home or during leisure time and can seek therapeutic treatment or guidance in a timely manner. If the situation worsens, the current situation can be re-evaluated and a new plan of action drawn up. In Belgium, the nomenclature for occupational therapy interventions in primary care is limited to people who have completed a full rehabilitation program for locomotor or neurological rehabilitation. This excludes individuals with chronic fatigue or pain which is not the results of a locomotor or neurological disorder. Even though there are multidisciplinary pain centers organized in general or university hospitals, they do not allow brief monodisciplinary interventions by occupational therapists with reimbursement when necessary, such as in case of temporary limitations in performing activities of daily living or participation restrictions. Enabling directly accessible occupational therapy and expanding the nomenclature for occupational therapy in primary care in Belgium is urgently needed to provide appropriate support not only to individuals with chronic fatigue and pain, but to all individuals experiencing limitations in activities of daily living. Evaluating resource allocation and implementing appropriate financing for rehabilitation, making rehabilitation accessible to all individuals, is also part of the WHO Rehabilitation 2030 Initiative [79]. Given the limitations that individuals with chronic fatigue and pain may experience, the occupational therapist is an important partner of the multidisciplinary (primary care) rehabilitation team.

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Appendix 1: Update literature search on measurement instruments to evaluate activity limitations and participation restrictions in patients with chronic fatigue syndrome

Measurement instrument	Article
Barthel Index	Strassheim et al. (2018)
Bell score	Jäkel et al. (2021)
EuroQol-5D (EQ-5D) (n = 9)	Antcliff et al. (2021), Clark et al. (2017), Collin et al. (2016), Heald et al. (2019), Jonsjo et al. (2019), McCrone et al. (2012), Richardson et al. (2013), Vyas et al. (2022), Wiborg et al. (2015)
EuroQol-6D (EQ-6D)	Janse et al. (2018)
Fibromyalgia Impact Questionnaire (FIQ) physical impairment subscale	Thompson et al. (2018)
Karnofsky performance status (n = 6)	Castro-Marrero et al. (2018), Chang et al. (2021), Flores et al. (2013), Friedberg et al. (2013), Gleason et al. (2018), Rowe et al. (2018)
London Handicap Scale	Fenouillet et al. (2016)
Quality of Life Scale	Schafer et al. (2015)
RAND-36	Bernhoff et al. (2022), Murdock et al. (2017)
Self-developed questionnaire: assess patient disability on six themes (household tasks, socializing, leisure activities, leaving the house, work, and general activity). Question: 'Since the last beep I was able to'	Band et al. (2016)
Self-reported questionnaire assessing work participation: "Which situation applies to you?" (answer categories: working, retired; early retired; unemployed/ looking for work; disabled for work; welfare; homemaker; study)	Joustra et al. (2015)
Self-developed questionnaire: 15 questions about the frequency of performing selected activities, including social activities, personal hygiene, eating, and cooking.	Sommerfelt et al. (2023)
Sheehan Disability Inventory (SDI)	Sáez-Francàs et al. (2015)
Short Form-12 (SF-12) (n = 6)	Antcliff et al. (2015), Antcliff et al. (2021), Antcliff et al. (2017), Dansie et al. (2012), De Gucht et al. (2017), Strauss et al. (2012)

Appendix 1 (continued)

Measurement instrument	Article
Short Form- 36 (SF-36) (n = 97)	Adamson et al. (2020), Ali et al. (2017), Band et al. (2014), Bileviciute-Ljungar et al. (2020), Bloot et al. (2015), Brooks et al. (2013), Brown et al. (2013), Brown et al. (2012), Burgess et al. (2012), Carr et al. (2021), Cambras et al. (2018), Castro-Marrero et al. (2017), Castro-Marrero et al. (2018), Castro-Marrero et al. (2019), Chalder et al. (2015), Chang et al. (2021), Cheshire et al. (2020) Clark et al. (2017), Cockshell et al. (2013), Collin et al. (2015), Collin et al. (2016), Collin et al. (2017), Collin et al. (2017a), Crawley et al. (2013), Cvejic et al. (2016), Daniels et al. (2017), De Venter et al. (2017), Dougall et al. (2014), Eykens et al. (2019), Fernie et al. (2015), Fernie et al. (2016), Fjorback et al. (2013), Flo et al. (2014), Goedendorp et al. (2013), Goldsmith et al. (2015), Gotaas et al. (2023), Heins et al. (2013), Hodges et al. (2018), Huber et al. (2018), Ickmans et al. (2013), Ickmans et al. (2015), Ingman et al. (2016), Jakel et al. (2021), Janse et al. (2018), Jason et al. (2013), Johnston et al. (2014), Jones et al. (2023), Jonsjo et al. (2019), Joustra et al. (2015), King et al. (2020), Kingdon et al. (2018), Lewis et al. (2013), Lewith et al. (2016), McBride et al. (2017), McCrone et al. (2012), McKay et al. (2021), Meeus et al. (2016), Nacul et al. (2018), Naess et al. (2012), Natelson et al. (2019), Nijs et al. (2012), O'Connor et al. (2019), Pendergrast et al. (2016), Pinxsterhuis et al. (2017), Rajeevan et al. (2018), Rekeland et al. (2022), Rimes et al. (2013), Roor et al. (2022), Rowe et al. (2018), Schafer et al. (2015), Schmaling et al. (2016), Sharpe et al. (2015), Smakowski et al. (2022), Stevelink et al. (2019), Stevelink et al. (2022), Strand et al. (2018), Tummers et al. (2012), Tummers et al. (2013), Unger et al. (2017), van Campen et al. (2020) Van Den Houte et al. (2019), Van Oosterwijck et al. (2017), Vermeulen et al. (2014), Vos-vromans et al. (2013), Vos-vromans et al. (2016), Vos-vromans et al. (2016a), Wearden et al. (2013), Wiborg et al. (2012), Wiborg et al. (2014), Williams et al. (2017), Worm-Smeitink et al. (2016), Worm-Smeitink et al. (2017), Worm-Smeitink et al. (2019), Worm-Smeitink et al. (2019a), Yang et al. (2019), Yang et al. (2022)
Sickness Impact Profile 8 (SIP8) (n = 13)	Bloot et al. (2015), Braamse et al. (2020), Collin et al. (2016), Densham et al. (2016), Goedendorp et al. (2013), Heins et al. (2013), Roor et al. (2020), Roor et al. (2022), Verspaandonk et al. (2015), Vos-vromans et al. (2016), Vos-vromans et al. (2013), Wiborg et al. (2012), Worm-Smeitink et al. (2019)
WHO DAS 2.0	Johnston et al. (2014)
WHOQOL- BREF	Brittain et al. (2021)
Work ability index (WAI)	Bernhoff et al. (2022)
Work and Social Adjustment Scale (WSAS) (n = 24)	Adamson et al. (2020), Ali et al. (2017), Ali et al. (2017), Band et al. (2016), Burgess et al. (2012), Cella et al. (2013), Clark et al. (2017), Collin et al. (2017), Flo et al. (2014), Hughes et al. (2017), Hughes et al. (2018), Ingman et al. (2016), Janse et al. (2018), Jones et al. (2023), Nyland et al. (2014), Rimes et al. (2013), Sharpe et al. (2015), Smakowski et al. (2022), Stahl et al. (2014), Stevelink et al. (2022), Stevelink et al. (2019), Williams et al. (2017), Worm-Smeitink et al. (2016), Worm-Smeitink et al. (2019)

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Appendix 2: Update literature search on measurement instruments to evaluate the physical activity level and pattern in patients with chronic fatigue syndrome

Measurement instrument	Article
Activity diary Activity diary (VAS: in the past hours I was physically / socially / mentally active 0-100; 3 separate questions)	Vergauwen et al. (2021) Worm-Smeitink et al. (2021)
Actometer (Actiwatch) Actometer (Actical)	King et al. (2020) Vergauwen et al. (2021)
Android smartphone with a modified CFS-specific version of the Clintouch app **Measures** Question: "Before the beep went off I was . . ." or "Right now I am . . .")	Band et al. (2016), Band et al. (2017)
Checklist Individual Strength	De Venter et al. (2017), Eyskens et al. (2019), Worm-Smeitink et al. (2019), Worm-Smeitink et al. (2021)
Hours of upright activity (HUA) The amount of time spent with feet on the floor over a 24-hour period, including seated with feet on floor and standing, walking or running.	Lee et al. (2020)
International Physical Activity Questionnaire (IPAQ)	Clark et al. (2017)
International Physical Activity Questionnaire (IPAQ), short version	Chapman et al. (2019), Maclachlan et al. (2017)
Self-developed questionnaire to specify the total time spent on activity during a normal week [1]time spent on high intensity activity, [2] time spent on moderate intensity, [3] time spent practicing everyday physical activity Outcome = "activity minutes"	Bernhoff et al. (2022)
Sensewear armband	Rekeland et al. (2022), Van Campen et al. (2020), Van Campen et al. (2020a)
Short Questionnaire to Assess Health-Enhancing Physical Activity (SQUASH)	De Gucht et al. (2017)
The Cognitive and Behavioural Responses Questionnaire Behavioral responses: avoidance/resting behavior and all-or-nothing behavior	Ingman et al. (2016), Lewith et al. (2016)
Tri-axial accelerometery Tri-axial actigraphy (actilog) Tri-axial accelerometery (Equivital system)	Cvejic et al. (2017) Worm-smeitink et al. (2021) Sandler et al. (2016)
UpTime calculation—IMU sensor fusion The Shimmer (accelerometer, gyroscope, and magnetometer)	Palombo et al. (2020)

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SUMMARY

Summary

Chronic fatigue and pain are prevalent symptoms in the adult general population (approximately >20%), debilitating in nature and often co-occurring in various chronic conditions. Both symptoms have been found to negatively affect health-related quality of life (HRQOL), one of the primary outcomes of healthcare and rehabilitation. HRQOL is seen as a comprehensive concept that can be influenced by biological factors, such as fatigue and pain, psychological as well as social factors. Despite the established high prevalence and negative effects of fatigue, it is not always taken into account in clinical research on chronic pain, and its importance is frequently overlooked in clinical practice. This thesis is therefore interested in the impact of chronic fatigue in patients who also experience chronic pain.
Fatigue is proposed as a transdiagnostic rather than a disease-specific symptom. To explore this hypothesis, two distinct patient populations experiencing chronic fatigue and pain were included in this doctoral thesis, patients with chronic fatigue syndrome (CFS) and patients with multiple osteochondromas (MO). Because HRQOL is an important health care outcome, this doctoral thesis is centered around the exploration of disease-specific and transdiagnostic bio-, psycho-, social determinants of HRQOL in patients with chronic fatigue and pain, and specifically taking the physical activity level into account due to its established positive relationship with health in the general population.

This thesis consists of three general aims:
1. To explore HRQOL in patients with CFS and MO;
2. To explore the physical activity level in patients with CFS and MO;
3. To identify transdiagnostic and disease-specific determinants of HRQOL.

The first part focuses on measurement instruments to evaluate activity limitations and participation restrictions, which are considered more objectively measured subitems of HRQOL, and the physical activity level and pattern in patients with CFS.

Chapter 2 describes the results of a systematic review on measurement instruments to evaluate activity limitations and participation restrictions in patients with CFS. The main objectives of this study were to (1) explore which measurement instruments are currently used to evaluate activity limitations and participation restrictions in patients with CFS, (2) gather information on the psychometric properties of these measurement instruments in patients with CFS, and (3) determine which of these measurement instruments are suited to use in patients with CFS.
A total of 71 studies and 38 unique measurement instruments were identified, but only eight studies evaluated the psychometric properties of five measurement instrument. Psychometric studies of the Chronic Fatigue Syndrome-Activities and Participation Questionnaire (CFS-APQ), Work and Social Adjustment Scale (WSAS), Euroqol Questionnaire (EQ-5D), World Health Organization quality of life assessment instrument (WHOQOL-100) and Short-Form 36 (SF-36) were critically appraised. Based on available evidence, it could only be concluded that the psychometric properties of measurement instruments used in scientific research with patients with CFS are insufficiently evaluated

within this population. Development of new measurement instruments is strongly discouraged, given the high number of measurement instruments found (n = 38). Instead, it is recommended that future research evaluates the unknown psychometric properties and repeats the studies of poor methodological quality with sound methodology to provide strong evidence of the quality of a psychometric property. An interesting observation is that all identified measurement instruments are self-reported, which have been found to have limited value in patients with CFS because they tend to rate their functioning worse than it actually is. Even though subjective reporting of one's functioning reflects important information for healthcare professionals, it is suggested that it be supplemented by more objective measures such as detailed assessment and observations performed by healthcare professionals.

Chapter 3 describes the results of a systematic review on measurement instruments to evaluate the physical activity level and pattern in patients with CFS/ME. The main objectives of this study were to (1) systematically review the literature for measures or scales capable of evaluating the activity level and/or pattern that were used in patients with CFS/ME, and (2) critically appraise the psychometric properties of identified measures or scales in patients with CFS/ME. A total of 50 articles and 15 unique measurement instruments were identified, but only two studies examined the psychometric properties of three measurement instruments: the Chronic Fatigue Syndrome–Activity Questionnaire (CFS-AQ), Activity Pattern Interview (API) and International Physical Activity Questionnaire-Short-Form (IPAQ-SF). Based on these results, all three measurement instruments are considered equally (in)valid and further research is recommended to evaluate the psychometric properties of existing measures or scales.
Even though activity monitors were most frequently used in research (n = 29), there is lack of studies investigating their psychometric properties in patients with CFS/ME. In addition, the CFS-AQ, API and IPAQ-SF are all self-reported measurement instruments reflecting patients' perception of their performed physical activity, rather than providing an accurate representation of their actual physical activity level. Activity monitors have been found capable of objectively capturing the physical activity level in the general population, but to date it is unclear whether they are reliable and valid to use in patients with CFS/ME. Given the added value of activity monitors to accurately measure patients' physical activity levels, evaluation of their psychometric properties in patients with CFS/ME is recommended.

Self-reported measures, more specifically activity diaries, are capable of capturing more information on patients' physical activity level, such as type, context and meaningfulness of an activity. Therefore, in addition to objective measures, they provide useful information for healthcare professionals to select appropriate treatment interventions. However, the systematic review of **chapter 3** did not identify a self-reported measurement instrument suitable for use in patients with CFS/ME. Therefore, the aim of **chapter 4** was to evaluate the ability of a detailed self-reported activity diary based on an instantaneous registration of activities to measure the PAL in female patients with CFS by comparing it to an activity monitor (Actical). Additional objectives were to

compare potential discrepancies between subjective (activity diary) and objective (Actical) measurement instruments in patients with CFS versus healthy controls and, in case of discrepancies between both measurement instruments, to investigate whether and which illness-related complaints, HRQOL domains or demographic factors are associated with these discrepancies. The results showed that female patients with CFS are less able to record their physical activity level with an activity diary in comparison to healthy controls. In both patients with CFS and healthy controls, younger persons tended to underestimate their physical activity level, while older persons tended to overestimate their physical activity level with an activity diary. No other factors were significantly associated with the discrepancies found between the two measurement instruments. In conclusion, the proposed detailed self-reported activity diary cannot replace activity monitoring to assess the physical activity level in patients with CFS, but may provide additional information about the perceived activity. Further exploration of factors associated with the discrepancy between self-reported and objective measurement instruments could facilitate the development or adaptation of a self-reported measurement that can be used complementary to an objective measurement instrument by encompassing more detailed information about patients' perceived activities.

The second part of this thesis focuses on the physical activity level and HRQOL in patients with MO, and transdiagnostic and disease-specific determinants of HRQOL.

Chapter 5 describes the results of an explorative study on HRQOL and the PAL of patients with MO. The aims of the study were to (1) identify the physical activity level and HRQOL of patients with MO and compare them to reference scores of the healthy population, and (2) determine which illness-related symptoms, sociodemographic or psychological factors are associated with patients' physical activity level, and physical and mental HRQOL. A significantly lower physical activity level and physical HRQOL in patients with MO compared to reference scores of healthy controls was confirmed, but mental HRQOL did not differ. Surprisingly, the physical activity level was not associated with physical HRQOL, opening the debate on whether increasing the physical activity level is important when it comes to physical HRQOL or whether more emphasis should be placed on enabling personally relevant activities. Additionally, a higher educational level was positively related to physical HRQOL which fits the hypothesis that a higher educational level may be related to higher self-efficacy, which in turn is positively related to HRQOL. The negative association of fatigue with both physical and mental HRQOL confirms the hypothesis that fatigue is a prevalent symptom in patients with chronic pain and sometimes even more debilitating than pain. An interesting result was that having a paid job was associated with a higher physical activity level and mental HRQOL and seems to call for increased attention towards employment and vocational rehabilitation.

Chapter 6 builds further on findings of **chapter 5** to identify transdiagnostic and disease-specific determinants of HRQOL. **Chapter 6** included age, gender, disease duration, pain, fatigue, depression, pain catastrophizing and the physical activity level as possible determinants of HRQOL. Based on the results, fatigue, pain, pain catastrophizing, depressive feelings and the physical activity level can be considered

transdiagnostic determinants of HRQOL, but the magnitude of their association with HRQOL appears to differ depending on the underlying disease. Per unit increase in the physical activity level, the general health subscale increased by 2.4 more in patients with MO compared with patients with CFS. This contributes to the question whether merely increasing the physical activity level leads to a clinically relevant change in HRQOL or whether enabling personally relevant activities might have a more direct positive relationship with HRQOL, especially in patients with CFS. The identified transdiagnostic determinants, i.e. fatigue, pain, pain catastrophizing and depressive feelings, were less severe in patients with MO than in patients with CFS. However, results showed that when patients with MO do experience severe fatigue, pain, pain catastrophizing or depressive feelings, these symptoms are significantly and negatively related to various domains of HRQOL. This advocates for a timely and systematic evaluation of these determinants in clinical practice in patients with chronic fatigue or pain. In addition, exploring whether increasing personally relevant activities improves patients' HRQOL is recommended.

Chapter 7 contains the general discussion in which the findings are summarized and discussed. Based on the results of this thesis, it has become clear that fatigue and pain are co-occurring symptoms that may not be overlooked in patients presenting with either chronic fatigue or chronic pain. Patients may report significant reductions in their physical activity level, mental and physical HRQOL and several determinants negatively related herewith were identified. With respect to clinical practice, the importance of investigating fatigue, pain, depression, pain catastrophizing and the physical activity level in patients presenting with chronic fatigue or pain is discussed. It is proposed that timely and systematic evaluation of psychological factors may lead to early recognition of developing symptoms, which allows for timely treatment, referral to specialized help and may prevent exacerbation. Also, improvement of mental health literacy may contribute to prevention and early recognition of developing symptoms, which may also lead to better self-management. To improve HRQOL, it is recommended to focus on increasing personally relevant activities and self-efficacy rather than solely on increasing the physical activity level. Implications for research include that psychometric properties of measurement instruments to evaluate activity limitations, participation restrictions or the physical activity level or pattern in patients with CFS are currently considered insufficient and should be examined further. Especially examination of activity monitors in patients with CFS requires urgent attention, because complementary use of a self-reported and objective measurement instrument is recommended but requires reliable and valid measurement instruments. Until then, results should be interpreted and used with caution. The concluding paragraph provides directions for future impact: measuring the physical activity level and HRQOL in clinical practice and related future research needs; opportunities for a preventive approach to prevent psychological symptoms, activity limitations and participation restrictions; and needs regarding the expansion of occupational therapy in primary care to provide appropriate treatment to patients with chronic fatigue and pain.

SAMENVATTING

Samenvatting

Chronische vermoeidheid en pijn kennen een hoge prevalentie bij de volwassen algemene bevolking (ongeveer >20%). Beide symptomen zijn slopend van aard en komen vaak voor bij verschillende chronische aandoeningen. Daarnaast blijken ze een negatieve invloed te hebben op de gezondheidsgerelateerde levenskwaliteit (HRQOL; Health-Related Quality Of Life), één van de belangrijkste uitkomsten van onze gezondheidszorg en zeker van de revalidatiegeneeskundige zorg. HRQOL wordt gezien als een veelomvattend concept dat kan worden beïnvloed door biologische factoren, zoals vermoeidheid en pijn, psychologische en sociale factoren. Ondanks de hoge prevalentie en negatieve effecten van vermoeidheid, wordt er in klinisch onderzoek naar chronische pijn niet altijd rekening mee gehouden en wordt het belang ervan in de klinische praktijk vaak over het hoofd gezien. Dit proefschrift focust daarom op de impact van chronische vermoeidheid bij patiënten die ook chronische pijn ervaren.
Er zijn studies die suggereren dat vermoeidheid een transdiagnostisch in plaats van een ziektespecifiek symptoom is. Om deze hypothese te onderzoeken, werden in dit proefschrift twee verschillende patiëntenpopulaties betrokken die chronische vermoeidheid en pijn ervaren, namelijk patiënten met het chronisch vermoeidheidssyndroom (CVS) en patiënten met multipele osteochondromen (MO). Aangezien HRQOL een belangrijke uitkomst is van onze gezondheidszorg, staat in dit proefschrift de verkenning van ziektespecifieke en transdiagnostische bio-, psycho- en sociale determinanten van HRQOL bij patiënten met chronische vermoeidheid en pijn centraal, waarbij expliciet het fysieke activiteitenniveau wordt meegenomen vanwege de positieve relatie tussen fysieke activiteit en gezondheid bij de algemene populatie.

Dit proefschrift bestaat uit drie algemene doelstellingen:
1. Het onderzoeken van HRQOL bij patiënten met CVS en MO;
2. Het onderzoeken van het fysieke activiteitenniveau bij patiënten met CVS en MO;
3. Het identificeren van transdiagnostische en ziektespecifieke determinanten van HRQOL.

Het eerste deel richt zich op meetinstrumenten om beperkingen in activiteiten en participatie te evalueren, dewelke worden beschouwd als meer objectief te meten subitems van HRQOL, en het fysieke activiteitenniveau en -patroon bij patiënten met CVS.

Hoofdstuk 2 beschrijft de resultaten van een systematische review naar meetinstrumenten om beperkingen in activiteiten en participatie bij patiënten met CVS te evalueren. De belangrijkste doelstellingen van deze studie waren (1) onderzoeken welke meetinstrumenten momenteel worden gebruikt om beperkingen in activiteiten en participatie bij patiënten met CVS te evalueren, (2) informatie verzamelen over de psychometrische eigenschappen van deze meetinstrumenten bij patiënten met CVS, en (3) bepalen welke van deze meetinstrumenten geschikt zijn voor gebruik bij patiënten met CVS.
In totaal werden 71 studies en 38 unieke meetinstrumenten geïdentificeerd, maar slechts

acht studies evalueerden de psychometrische eigenschappen van vijf meetinstrumenten. Psychometrische studies van de Chronic Fatigue Syndrome-Activities and Participation Questionnaire (CFS-APQ), Work and Social Adjustment Scale (WSAS), Euroqol Questionnaire (EQ-5D), World Health Organization Quality Of Life assessment instrument (WHOQOL-100) en Short-Form 36 (SF-36) werden kritisch beoordeeld. Op basis van het beschikbare bewijs kon alleen worden geconcludeerd dat de psychometrische eigenschappen van meetinstrumenten die worden gebruikt in wetenschappelijk onderzoek met patiënten met CVS onvoldoende zijn geëvalueerd binnen deze populatie. Gezien het grote aantal gevonden meetinstrumenten (n = 38) wordt de ontwikkeling van nieuwe meetinstrumenten sterk afgeraden. Toekomstig onderzoek dient de onbekende psychometrische eigenschappen te evalueren en de onderzoeken van slechte methodologische kwaliteit te herhalen met een degelijke methodologie om sterk bewijs te leveren voor de kwaliteit van een psychometrische eigenschap. Een interessante observatie is dat alle gevonden meetinstrumenten zelfrapportage meetinstrumenten zijn. Eerder werd vastgesteld dat zelfrapportage meetinstrumenten een beperkte waarde hebben bij patiënten met CVS, omdat gebleken is dat patiënten hun functioneren zelf slechter beoordelen dan in werkelijkheid vaak het geval is. Hoewel subjectieve rapportage van iemands functioneren belangrijke informatie bevat voor hulpverleners in de gezondheidszorg, wordt aanbevolen deze informatie aan te vullen met meer objectieve metingen zoals gedetailleerde evaluaties en observaties uitgevoerd door professionals in de gezondheidszorg.

Hoofdstuk 3 beschrijft de resultaten van een systematische review naar meetinstrumenten om het fysieke activiteitenniveau en -patroon bij patiënten met CVS/ME te evalueren. De belangrijkste doelstellingen van deze studie waren (1) het systematisch onderzoeken van de literatuur op meetinstrumenten of schalen die het activiteitenniveau en/of -patroon kunnen evalueren bij patiënten met CVS/ME, en (2) het kritisch beoordelen van de psychometrische eigenschappen van geïdentificeerde meetinstrumenten of schalen bij patiënten met CVS/ME. In totaal werden 50 artikels en 15 unieke meetinstrumenten geïdentificeerd, maar slechts twee studies onderzochten de psychometrische eigenschappen van drie meetinstrumenten: de Chronic Fatigue Syndrome-Activity Questionnaire (CFS-AQ), Activity Pattern Interview (API) en International Physical Activity Questionnaire-Short-Form (IPAQ-SF). Op basis van deze resultaten worden alle drie de meetinstrumenten als even (niet-)valide beschouwd en wordt verder onderzoek aanbevolen om de psychometrische eigenschappen van bestaande meetinstrumenten te evalueren.
Hoewel activiteitenmonitors het meest werden gebruikt in wetenschappelijk onderzoek (n = 29), is er een gebrek aan studies die de psychometrische eigenschappen ervan onderzoeken bij patiënten met CVS/ME. Bovendien zijn de CFS-AQ, API en IPAQ-SF allen zelfrapportage meetinstrumenten die de perceptie van patiënten over hun fysieke activiteit weergeven in plaats van hun werkelijke fysieke activiteitenniveau. In de algemene bevolking bleken activiteitenmonitors in staat te zijn om het fysieke activiteitsniveau objectief te meten, maar tot op heden is het onduidelijk of ze betrouwbaar en valide zijn bij patiënten met CVS/ME. Gezien activiteitenmonitors een toegevoegde waarde hebben bij het objectief en nauwkeurig meten van het fysieke

activiteitenniveau van patiënten, wordt het aanbevolen om hun psychometrische eigenschappen te evalueren bij patiënten met CVS/ME.

Zelfrapportage meetinstrumenten, en meer specifiek activiteitendagboeken, zijn in staat om meer informatie over het fysieke activiteitenniveau van patiënten vast te leggen, zoals het type, de context en de betekenisvolheid van een activiteit. Daarom bieden ze, naast objectieve metingen, waardevolle informatie voor professionals in de gezondheidszorg om geschikte behandelinterventies te selecteren. Uit de systematische review van **hoofdstuk 3** kwam echter geen zelfrapportage meetinstrument naar voren dat geschikt is voor gebruik bij patiënten met CVS/ME. Daarom was het doel van **hoofdstuk 4** om te evalueren of een gedetailleerd zelfrapportage activiteitendagboek, gebaseerd op een onmiddellijke registratie van activiteiten, in staat is om het fysieke activiteitenniveau te meten bij vrouwelijke patiënten met CVS. Om dit na te gaan, werd het activiteitendagboek vergeleken met een activiteitenmonitor (Actical). Aanvullende doelstellingen waren enerzijds het vergelijken van potentiële discrepanties tussen het subjectieve (activiteitendagboek) en objectieve (Actical) meetinstrument bij patiënten met CVS versus gezonde controles. Anderzijds, in het geval van discrepanties tussen beide meetinstrumenten, het onderzoeken of en welke ziektegerelateerde klachten, HRQOL-domeinen of demografische factoren geassocieerd zijn met deze discrepanties. De resultaten toonden aan dat vrouwelijke CVS-patiënten minder goed in staat zijn om hun fysieke activiteitenniveau vast te leggen met een activiteitendagboek in vergelijking met gezonde controles. Bij zowel CVS-patiënten als gezonde controles onderschatten jongere personen hun fysieke activiteitenniveau, terwijl oudere personen hun fysieke activiteitenniveau overschatten met een activiteitendagboek. Er waren geen andere factoren significant geassocieerd met de gevonden discrepanties tussen de twee meetinstrumenten. Het voorgestelde gedetailleerde zelfrapportage activiteitendagboek kan de activiteitenmonitoring dus niet vervangen om het fysieke activiteitenniveau bij patiënten met CVS in kaart te brengen, maar het kan wel aanvullende informatie geven over de uitgevoerde activiteit(en). Verder onderzoek naar factoren die samenhangen met de discrepantie tussen zelfrapportage en objectieve meetinstrumenten kan de ontwikkeling of aanpassing van een zelfrapportage meetinstrument dat meer gedetailleerde informatie bevat over de uitgevoerde activiteiten van patiënten vergemakkelijken, zodoende dat het als aanvulling op een objectief meetinstrument gebruikt kan worden.

Het tweede deel van dit proefschrift richt zich op het fysieke activiteitenniveau en de HRQOL bij patiënten met MO en op transdiagnostische en ziektespecifieke determinanten van HRQOL.

Hoofdstuk 5 beschrijft de resultaten van een exploratief onderzoek naar HRQOL en het fysieke activiteitenniveau van patiënten met MO. De doelen van het onderzoek waren (1) het bepalen van het fysieke activiteitenniveau en de HRQOL van patiënten met MO en deze vergelijken met referentiescores van de gezonde populatie, en (2) vaststellen welke ziektegerelateerde symptomen, sociodemografische of psychologische factoren samenhangen met het fysieke activiteitenniveau en de fysieke en mentale HRQOL van

patiënten. Het werd bevestigd dat patiënten met MO een significant lager fysiek activiteitenniveau en lagere fysieke HRQOL hebben in vergelijking met referentiescores van gezonde controles, maar de mentale HRQOL verschilde niet. Verrassend genoeg was het fysieke activiteitenniveau niet geassocieerd met fysieke HRQOL, wat het debat opent over de vraag of het verhogen van het fysieke activiteitenniveau belangrijk is als het gaat om fysieke HRQOL of dat er meer nadruk moet worden gelegd op het mogelijk maken van persoonlijk relevante activiteiten. Daarnaast was een hoger opleidingsniveau positief gerelateerd aan fysieke HRQOL, wat past bij de hypothese dat een hoger opleidingsniveau gerelateerd kan zijn aan een hogere zelfeffectiviteit, die op zijn beurt weer positief gerelateerd is aan de HRQOL. De negatieve associatie van vermoeidheid met zowel fysieke als mentale HRQOL bevestigt de hypothese dat vermoeidheid een veelvoorkomend symptoom is bij patiënten met chronische pijn en soms zelfs meer impact heeft dan pijn. Een interessant resultaat was dat het hebben van betaald werk geassocieerd was met een hoger fysiek activiteitenniveau en een hogere mentale HRQOL en lijkt te pleiten voor het behouden of hervatten van werk en arbeidsreïntegratie.

Hoofdstuk 6 bouwt verder op de bevindingen van hoofdstuk 5 om transdiagnostische en ziektespecifieke determinanten van HRQOL te identificeren. In dit onderzoek werden leeftijd, geslacht, ziekteduur, pijn, vermoeidheid, depressie, pijncatastroferen en het fysieke activiteitenniveau meegenomen als mogelijke determinanten van HRQOL. Op basis van de resultaten kunnen vermoeidheid, pijn, pijncatastroferen, depressieve gevoelens en het niveau van fysieke activiteit worden beschouwd als transdiagnostische determinanten van HRQOL, maar de grootte van hun associatie met HRQOL lijkt te verschillen afhankelijk van de onderliggende ziekte. Per eenheid dat het fysieke activiteitenniveau toenam, nam de subschaal 'algemene gezondheid' met 2.4 meer toe bij patiënten met MO in vergelijking met patiënten met CVS. Dit draagt bij tot de vraag of alleen het verhogen van het fysieke activiteitenniveau leidt tot een klinisch relevante verandering in HRQOL of dat het mogelijk maken van persoonlijk relevante activiteiten een meer directe positieve relatie heeft met HRQOL, vooral bij patiënten met CVS. De geïdentificeerde transdiagnostische determinanten, namelijk vermoeidheid, pijn, pijncatastroferen en depressieve gevoelens, waren minder ernstig bij patiënten met MO dan bij patiënten met CVS. De resultaten toonden echter aan dat wanneer patiënten met MO ernstige vermoeidheid, pijn, depressieve gevoelens ervaren of ernstig pijncatastroferen, deze symptomen significant en negatief gerelateerd zijn aan verschillende domeinen van HRQOL. Dit pleit voor een tijdige en systematische evaluatie van deze determinanten in de klinische praktijk bij patiënten met chronische vermoeidheid of pijn. Daarnaast wordt aanbevolen om te onderzoeken of het verhogen van persoonlijk relevante activiteiten de HRQOL van patiënten verbetert.

Hoofdstuk 7 bevat de algemene discussie waarin de bevindingen van dit proefschrift worden samengevat en besproken. Op basis van de resultaten van dit proefschrift is het duidelijk geworden dat vermoeidheid en pijn symptomen zijn die vaak samen voorkomen en niet over het hoofd gezien mogen worden bij patiënten die zich presenteren met chronische vermoeidheid of chronische pijn. Patiënten kunnen aanzienlijke

verminderingen van hun fysieke activiteitenniveau, mentale en fysieke HRQOL rapporteren en er werden verschillende determinanten geïdentificeerd die hier negatief mee samenhangen. Met betrekking tot de klinische praktijk wordt het belang besproken van het onderzoeken van vermoeidheid, pijn, depressie, pijncatastroferen en het fysieke activiteitenniveau bij patiënten die zich presenteren met chronische vermoeidheid of pijn. Er wordt gesuggereerd dat een tijdige en systematische evaluatie van psychologische factoren kan leiden tot een vroegtijdige herkenning van zich ontwikkelende symptomen, waardoor een tijdige behandeling of doorverwijzing naar gespecialiseerde hulp mogelijk is en verergering kan worden voorkomen. Verbetering van de mentale gezondheidsvaardigheden kan ook bijdragen aan preventie en vroegtijdige herkenning van symptomen, wat dan weer positief kan bijdragen aan het zelfmanagement van de patiënt. Om HRQOL te verbeteren, wordt aanbevolen om te focussen op het verhogen van persoonlijk relevante activiteiten en de zelfeffectiviteit in plaats van alleen op het verhogen van het fysieke activiteitenniveau. Een belangrijke implicatie voor onderzoek is dat psychometrische eigenschappen van meetinstrumenten voor het evalueren van beperkingen in activiteiten en participatie, maar ook het fysieke activiteitenniveau of -patroon bij patiënten met CVS op dit moment onvoldoende worden beschouwd. Het wordt dan ook aanbevolen om deze verder te onderzoeken. Vooral onderzoek naar activiteitenmonitors bij patiënten met CVS vereist dringend aandacht, omdat complementair gebruik van een zelfrapportage en een objectief meetinstrument wordt aanbevolen, maar hiervoor betrouwbare en valide meetinstrumenten vereist zijn. Tot die tijd moeten de resultaten van deze activiteitenmonitors met voorzichtigheid worden geïnterpreteerd en gebruikt. Ten slotte beschrijft de afsluitende paragraaf de toekomstige verwachte impact op wetenschappelijk, maatschappelijk en klinisch vlak: het meten van het fysieke activiteitenniveau en HRQOL in de klinische praktijk en gerelateerde toekomstige onderzoeksbehoeften; mogelijkheden voor een preventieve aanpak om psychologische symptomen, beperkingen in activiteiten en participatie te voorkomen; en behoeften met betrekking tot de uitbreiding van ergotherapie in de eerstelijnszorg om patiënten met chronische vermoeidheid en pijn de juiste behandeling te bieden.

DANKWOORD

Dankwoord

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ABOUT THE AUTHOR

Curriculum Vitae

Kuni Vergauwen was born on May 30, 1990, Belgium. She attended secondary school at the Sint-Agnesinstituut in Hoboken, Belgium. After obtaining her diploma in the Latin-Sciences track, she pursued her studies as an occupational therapist at Artesis Hogeschool Antwerpen, Belgium. Upon completing her bachelor degree in 2011, she furthered her studies with a Master of Science in Occupational Therapy at Ghent University, following a preparatory program at Catholic University Leuven. She received her master degree in 2013.

During and after her master studies, Kuni worked at the rehabilitation hospital Revarte until 2015. From 2015 to 2016, she worked as an occupational therapist at Zorgbedrijf Antwerpen in primary care, and from 2016 to 2019 at Functioneel Aanbod Meerderjarigen De Storming, residential care for individuals with acquired brain injury and multiple sclerosis.

In 2015, Kuni also started working part-time as a lecturer in the Occupational Therapy program at AP Hogeschool Antwerpen. Since 2017, she has balanced her clinical work as an occupational therapist and academic work as a lecturer with doctoral research as an external doctoral researcher at the University of Antwerp and Maastricht University.

Since 2019, Kuni has been solely employed at AP Hogeschool Antwerpen as a lecturer-researcher. Currently, she combines teaching with practice-oriented scientific research and a coordinating role in an international research project.

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COURSES

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- Cognitive rehabilitation for occupational therapists (6-day course) (translated: Cognitieve revalidatie voor ergotherapeuten; ergoacademie, Ergotherapie Nederland)
- Basic Bobath course: The Assessment and Treatment of Adults with Neurological Conditions (15-day course) (Jessa Ziekenhuis Campus Sint-Ursula, Herk-de-Stad)
- Post conference workshop: Get to know Acceptance and Commitment Therapy (ACT) (Pain Science in Moton IV, Maastricht, Nederland)

2019-2020

- Basic parametric statistics (FLAMES summer school)
- Research design (FLAMES summer school)
- Basic regression analysis (FLAMES summer school)

2018-2019

- Workshop: Een overtuigend onderzoeksvoorstel schrijven

2017-2018

- PowerPoint
- Writing academic papers
- Giving presentations in English
- Time management
- Excel: Intermediate tips and tricks
- Excel: Database management and PivotTables

PUBLISHED PAPERS

1. **Vergauwen K**, Huijnen IPJ, Smeets RJEM, Kos D, van Eupen I, Nijs J, Meeus M. An exploratory study of discrepancies between objective and subjective measurement of the physical activity level in female patients with chronic fatigue syndrome. Journal of Psychosomatic Research 2021:144:110417. doi: 10.1016/j.jpsychores.2021.110417
2. **Vergauwen K**, Huijnen IPJ, Depuydt A, Van Regenmortel J, Meeus M. Measuring the physical activity level and pattern in daily life in persons with chronic fatigue syndrome/myalgic encephalomyelitis: a systematic review. Physical Therapy Reviews 2017, 22:1-2, 23-33. doi: 10.1080/10833196.2017.1300624
3. **Vergauwen K**, Huijnen IPJ, Kos D, Van de Velde D, van Eupen I, Meeus M. Assessment of activity limitations and participation restrictions with persons with chronic fatigue syndrome: a systematic review. Disability and Rehabilitation 2015: 37(19):1706-16. doi: 10.3109/09638288.2014.978507

PUBLISHED ABSTRACTS

1. **Vergauwen K**, Amajjar I, Meeus M, Huijnen IPJ, Nijs J, Smeets, RJEM. Health-related quality of life and physical activity level in a specific and non-specific pain and fatigue disorder. PSiM IV – Pain Practice. Pain Practice 2022; 22: 8-64. doi: 10.1111/papr.13128.
2. Amajjar I, **Vergauwen K**, Willigenburg N, Ham J, Smeets RJEM. The assessment of fatigue and pain in multiple osteochondromas: A Dutch Cohort Study. PSiM IV – Pain Practice. Pain Practice 2022; 22: 8-64. doi: 10.1111/papr.13128.

PRESENTATIONS AT INTERNATIONAL CONGRESSES, SYMPOSIA AND COLLOQUIA

ORAL PRESENTATION

2022 Looking beyond diagnosis: measurement and identification of physical functioning and physical activity level in a specific and non-specific pain and fatigue disorder. **Vergauwen K**, Amajjar I, Meeus M, Huijnen IPJ, Nijs J, Smeets RJEM. World Federation of Occupational Therapist Congress, Paris, France. 3 minute thesis oral presentation.

POSTER PRESENTATION

2022 Occupational therapy as a crucial partner in primary care: the need for a competency profile. **Vergauwen K**, Vanneste L, Kos D, Lécharny M. World Federation of Occupational Therapist Congress, Paris, France.

2022 Health-related quality of life and physical activity level in a specific and non-specific pain and fatigue disorder. **Vergauwen K**, Amajjar I, Meeus M, Huijnen IPJ, Nijs J, Smeets RJEM.Pain Science in Motion IV, Maastricht, The Netherlands.

2017 Measuring the physical activity level and pattern in daily life in persons with chronic fatigue syndrome/myalgic encephalomyelitis: a systematic review. **Vergauwen K**, Huijnen IPJ, Depuydt A, Van Regenmortel J, Meeus M. Pain Science in Motion International and Interdisciplinary Colloquium on Research Methods in Pain Sciences, Stockholm, Sweden.

PRESENTATIONS AT NATIONAL CONGRESSES, SYMPOSIA AND COLLOQUIA

ORAL PRESENTATION

2024 Competentieprofiel van de ergotherapeut in de eerste lijn. **Vergauwen K**, Lécharny M. Symposium Ergotherapie Vlaanderen: ERGO netWERKT in de 1ste lijn, Antwerp, Belgium. Invited plenary lecture.

2023 Ergotherapie in de eerste lijn. Opmaak van een Vlaams toekomstgericht competentieprofiel voor ergotherapeuten werkzaam in de Vlaamse eerste lijn. **Vergauwen K**, Lécharny, M. Webinar AP University College, Antwerp, Belgium.

2023 Vlaams competentieprofiel voor ergotherapeuten in de eerste lijn. **Vergauwen K**, Lécharny, M. Invited lecture during webinar for Ergotherapeutenkring Antwerpen, Antwerp, Belgium.

POSTER PRESENTATION

2023 AUHA Onderzoeksnamiddag, Antwerp, Belgium
Vergauwen K, Lécharny M. Power in partnership: Occupational therapy in primary care.

2018 Creating Connections - Building Bridges, Leuven, Belgium
Vergauwen K, Smeets RJEM, Huijnen IPJ, Meeus M. Physical activity and chronic fatigue syndrome: Are there differences between patients' perception and reality?

NATIONAL COURSES AND WORKSHOPS

2023 Chronische pijn: Onzichtbaar, maar continu en overweldigend. Introduction to course Ergotherapeutische benadering bij aspecifieke rugklachten: meer dan hef- en tiltechnieken? **Vergauwen K**. AP University College, Antwerp, Belgium.

2023 Ergotherapie in de eerste lijn. **Vergauwen K**, Lécharny M, Willekens K. Workshop Onderwijsdag Ergotherapie, HoGent, Ghent, Belgium.

WEBSITE PUBLICATIONS

2023 Lécharny M, **Vergauwen K,** Empsten K. Competentieprofiel Ergotherapie in de eerste lijn. https://www.ap.be/project/ergotherapie-in-de-eerste-lijn

2023 **Vergauwen K**. Duiding Minerva Evidence-Based Practice: "Nut van gedragsinterventies voor primaire preventie van cardiovasculaire aandoeningen bij volwassenen?" https://minerva-ebp.be/NL/Article/2333

2022 Vergauwen K. Duiding Minerva Evidence-Based Practice: "Effect van multicomponente thuisrevalidatie na heupfractuur bij ouderen?" https://minerva-ebp.be/NL/Article/2294

2022 Vergauwen K. Duiding Minerva Evidence-Based Practice: "Mortaliteit na een heupfractuur na implementatie van een orthogeriatrisch zorgprogramma onder begeleiding van een verpleegkundige" https://minerva-ebp.be/NL/Analysis/20624

2020 Vergauwen K. Blogpost Pain in Motion: Occupational performance and chronic pain. https://paininmotion.be/blog/detail/occupational-performance-and-chronic-pain

2018 Vergauwen K. Blogpost Pain in Motion: Chronic pain management – what is the role of the occupational therapist? https://paininmotion.be/blog/detail/chronic-pain-management-what-role-occupational-therapist

2016 Vergauwen K. Blogpost Pain in Motion: Measuring activity limitations and participation restrictions in patients with chronic fatigue syndrome. https://paininmotion.be/blog/detail/measuring-activity-limitations-and-participation-restrictions-patients-chronic-fatigue-syndrome

RESEARCH PROJECTS

2023-2026 Researcher practice-oriented research: MoederschAP met een chronische aandoening

2022-2025 Projectcoordinator SIMBA (Simulation-based learning in occupational therapy) (Erasmus+)
https://simba.turkuamk.fi/meettheteam/

2019-2023 Researcher practice-oriented research: Ergotherapie in de eerste lijn. Opmaak van een Vlaams toekomstgericht competentieprofiel voor ergotherapeuten werkzaam in de Vlaamse eerste lijn. https://www.ap.be/project/ergotherapie-in-de-eerste-lijn

TEACHING EXPERIENCE

2016 – current	2nd Bachelor:	Occupational therapy in geriatrics 2
		Professional reasoning 2
		Professional reasoning 3
		Supervisor internships
	3rd Bachelor:	Supervisor bachelor theses
		Professional development
		Supervisor internships
2015-2016	2nd Bachelor:	Occupational therapy in geriatrics 2
		Supervisor internships
	3rd Bachelor:	Supervisor bachelor theses
		Supervisor internships