Universiteit Utrecht 

Psychosocial Profiles of Adolescents with Chronic Fatigue Syndrome: Correlations with Fatigue Severity and FITNET Treatment Outcome

Master Thesis - Clinical and Health Psychology
Faculty of Social and Behavioural Sciences, Utrecht University

Emma Berkelbach van der Sprenkel (3979865)
August 2017

Supervisors:
Prof.dr. R. Geenen, Department of Clinical & Health Psychology, Utrecht University
Dr. S.L. Nijhof, Wilhelmina Children's Hospital, Utrecht
Dr. E.M. van de Putte, Wilhelmina Children's Hospital, Utrecht

Table of Contents

Abstract

Objectives: To further improve the treatment and prognosis of adolescent chronic fatigue syndrome (CFS), it is essential to consider the heterogeneity of the patient population and identify factors that contribute to treatment effectiveness or are associated with non-recovery. Although Fatigue In Teenagers on the interNET (FITNET) is considered an effective treatment for adolescent CFS, still one-third of the patient population does not recover. Profiles of co-occurring psychosocial factors may suggest potential targets for the treatment of CFS. The aim of this study was 1) to identify these psychosocial profiles in patients with CFS, 2) to assess the associated levels of fatigue before treatment initiation and 3) to examine whether the outcome of FITNET can be predicted using the psychosocial profiles.

Methods: Participants were 120 adolescent patients with CFS who underwent FITNET treatment in the Wilhelmina Children's Hospital (mean age 15.8 years old, 81.7% female). Baseline measurements included a broad set of adolescent and parental psychosocial variables, quantified by (subscales of) validated questionnaires, and adolescent activity levels measured using an actometer. Fatigue score and psychiatric comorbidities were assessed before inclusion. Treatment efficacy was determined by examination of fatigue severity, physical functioning, school presence and self-rated improvement. Exploratory factor analysis and cluster analysis were conducted to identify the psychosocial profiles.

Results: Principal factor analysis (oblimin rotation) yielded four factors: *Maternal Psychopathology*, *Paternal Psychopathology*, *Rearing Behaviour* and *Child Psychopathology*. Cluster analysis based on these four factors identified four profiles: *no psychopathology within system* (*n*=57), *deviant rearing behaviour* (*n*=24), *maternal psychopathology* (*n*=21) and *paternal psychopathology* (*n*=18). High *Child Psychopathology* factor scores were related with elevated baseline fatigue scores [*p*=.048]. High factor scores on *Maternal Psychopathology* were related with recovery from CFS [*p*=.040] in subjects that completed all FITNET modules (*n*=78). Identified profiles were neither found to be predicting for fatigue severity before treatment nor for effectiveness of the FITNET intervention.

Conclusions: Heterogeneity of CFS among adolescents was indicated by four clinically distinguishable profiles comprised of four factors. However, most included variables were not found to be distinctly predictive for fatigue severity or treatment outcome. Our study did not find an indication to develop personalized treatment forms for the adolescent with CFS, thus application of evidence-based therapy, such as FITNET, remain the preferred decision.

Preface

This thesis on psychosocial profiles in adolescents with chronic fatigue syndrome was written as part of the completion of my Master's degree in Clinical and Health Psychology at Utrecht University. Hereby I would like to thank a few truly inspiring people who supported me throughout the educational journey of writing this thesis.

Firstly, I would like to thank Prof. dr. Rinie Geenen, my supervisor from the Faculty of Social and Behavioural Sciences. Dear Rinie, your passion for research is contagious and has served as a true stimulus for me to perform at my utmost. Thank you for your helpful and positive attitude, for all your effort in guiding me through the statistical analyses and for your analytical feedback on my work.

Secondly, I want to thank dr. Sanne Nijhof and dr. Elise van de Putte, my supervisors from the Wilhelmina Children's Hospital. Dear Sanne, if the data you collected for your PhD would not have been as comprehensive and structured, my tasks would have gotten much more complex… Thank you for the great cooperation, for your involved attitude and for providing me with so many wonderful opportunities. Dear Elise, thank you for your critical feedback and your endless enthusiasm. I have learnt a great deal throughout the past half year and I am thankful and proud to be part of your research group.

Finally, I want to thank Linde Nijhof, who works as a FITNET-therapist in the Wilhelmina Children's Hospital and provided me with clinical examples and information that has been of great benefit for me to gain a more thorough understanding of the FITNET-therapy.

I hope you will enjoy reading my thesis.

Emma Berkelbach van der Sprenkel
Utrecht, June 30th, 2017

Introduction

Chronic fatigue syndrome (CFS) or myalgic encephalopathy (ME) is characterized by severe, medically unexplained, long-lasting fatigue that is known to have a devastating impact on daily functioning and the quality of life (Fukuda et al., 1994; Nijhof, Bleijenberg, Uiterwaal, Kimpen, & van de Putte, 2012; Wiborg, Knoop, Stulemeijer, Prins, & Bleijenberg, 2010). Complaints besides extreme fatigue regularly include headaches, myalgia, joint or muscle pain and cognitive problems, yet the adolescent CFS patient population is known to be heterogeneous (May, Emond, & Crawley, 2010; Nijhof et al., 2016). The disease has an impact on physical as well as psychological well-being (Nijhof et al., 2012). Whereas the exact cause of CFS remains unknown, the predisposing, triggering and perpetuating aspects have been widely investigated (Lievesley, Rimes, & Chalder, 2014). These aspects can be subdivided in biological, psychological and social factors, which are elucidated using the biopsychosocial model shown in Table 1 (Bakker & van de Putte, 2012; Knoop, Stulemeijer, de Jong, Fiselier, & Bleijenberg, 2010; Werker, Nijhof & van de Putte, 2013).

Table 1. *Biopsychosocial factors that are assumed to be involved in chronic fatigue syndrome among adolescents, adapted from Bakker & van de Putte (2012) and Werker et al. (2013).*

	Biological factors	**Psychological factors**	**Social factors**
Predisposing	1. Genetic vulnerability 2. Physical vulnerability 3. Physical diseases 4. Early physical and/or sexual trauma 5. Genetic vulnerability to stress	1. Parent's excessive attention to child's physical complaints 2. Disease/ somatic trauma 3. Neglect 4. Insecure attachment 5. Anxiety and depression	1. Family members with physical or mental diseases 2. Family's attitude in coping with illness 3. Little social support
Precipitating	1. Physical overload 2. Physical stress (trauma, infection, surgery, medication)	1. Stress 2. Psychotrauma	1. Life events
Perpetuating	1. Disturbed sleep-wake cycle 2. Disturbed food intake 3. Condition loss 4. Overactive or underactive life style 5. Increased muscle tension	1. Loss of concentration 2. Severe emotions 3. Anxiety and depression 4. Unhelpful beliefs 5. Fearful avoidance of activity	1. Social isolation 2. Excessive medical consumption 3. System interaction

Thus far, no golden standard for CFS treatment has been established, however cognitive behavioural therapy (CBT) is the most evident recommended treatment form for adolescents, of which effects are sustained at least two years after follow-up (Knoop et al., 2008; Nijhof et al., 2013). CBT is underpinned by the biopsychosocial model targeting disturbed cognitions of other perpetuating factors (Knoop et al., 2008; Werker, Nijhof, & van de Putte, 2013). These disturbed cognitions include negative attitudes towards the disease and its symptoms, extreme focus on fatigue and dysfunctional beliefs about physical movement and fatigue management (Knoop et al., 2008). Furthermore, research indicated that family-focused CBT may have additional advantageous effects with regards to school presence, indicating the importance of a system approach in treating children who suffer from CFS (Chalder, Deary, Husain, & Walwyn, 2010). However, unfortunately not all CFS patients benefit sufficiently from available treatment, therefore opportunities or improvements for effective therapy should be further examined. This study will focus specifically on adolescent and parental psychosocial factors that are assumed to be involved in CFS among adolescents, as profiles of co-occurring factors may suggest potential targets for the treatment of CFS in adolescents.

Fatigue In Teenagers on the interNET (FITNET) is an internet-based CBT that was designed for adolescent patients with CFS. Nijhof et al. (2012) studied the effectiveness of the FITNET intervention among a large cohort of adolescents with CFS (*n*=135). FITNET is readily available to all adolescents that have access to a computer, encompasses a system-approach by incorporating separate modules for adolescents as well as their parents and offers a broad-scale possibility to receive treatment from a specialized health-care professional (Nijhof et al., 2012). Furthermore, FITNET can be adjusted to the individual needs of the patient and treatment can be accessed at any time, possibly increasing therapy adherence and consumption. FITNET was compared to usual care in a randomized controlled trial which indicated that it was significantly more effective than usual care, with recovery rates of 63% and 8% respectively, after an intervention of approximately 6 months (Nijhof et al., 2012). Even though FITNET is considered effective and shows a higher recovery rate than many other treatments, roughly one-third of the adolescent CFS population still does not recover after FITNET (Nijhof et al., 2012). To improve

FITNET and the prognosis of CFS patients, factors associated with non-recovery in adolescents should be further explored.

The crucial factors that affect chance of recovery among paediatric CFS patients have not yet been identified (Nijhof et al., 2013). An overview of the literature search is shown in Appendix 1. Adolescents suffering from CFS often score relatively high on somatic complaints, perfectionism, have lower self-esteem and in severe cases present with various psychiatric complaints such as anxiety and depression (Fisher & Crawley, 2013; Garralda, Rangel, Levin, Roberts, & Ukoumunne, 1999; Pelcovitz et al., 1995; White & Schweitzer, 2000). Various elements have been associated with poor response to CBT in children with CFS, such as higher age at initial inclusion, presence of mental health problems, higher degree of pain, low self-esteem and disordered health perception (Nijhof et al., 2013; van Geelen, Bakker, Kuis, & van de Putte, 2010). Furthermore, the paediatric CFS population often presents with personality difficulties, which are associated with poor treatment outcome (Rangel, Garralda, Levin, & Roberts, 2000a; Rangel, Garralda, Hall, & Woodham, 2003). Factors that have been suggested to be related with non-recovery after FITNET specifically, are longer disease duration prior to treatment and higher degree of maternal focus on bodily symptoms (Nijhof et al., 2013).

System interactions, parental illness behaviour and parental expectations appear to be important in CFS manifestation and treatment effectiveness (Brace et al., 2000; Godfrey et al., 2009; Collin et al., 2016). More specifically, there may be a positive relationship between fatigue presence and severity of CFS patients and their mothers (van de Putte et al., 2006; Smith et al., 2010). Higher fatigue severity of the mother at baseline has been suggested to predict worse CBT treatment outcome (Knoop et al., 2008). Secondly, maternal psychopathology is suggested to be a risk factor for pediatric chronic disabling fatigue, whilst also possibly related to poor treatment outcome among adolescent CFS patients (Rangel, Garralda, Levin, & Roberts, 2000b; Collin et al., 2015). Moreover, research has indicated that families of children with CFS often portray more psychopathology, emotional over-involvement, family illness burden and parental overprotection compared to other families with chronically ill children (van de Putte, Engelbert, Kuis, Kimpen, & Uiterwaal, 2006; Rangel, Garralda, Jeffs, & Rose, 2005; Fisher & Chalder, 2003). On the other hand, a

supportive family or social environment can ameliorate adolescent CFS symptoms and seems to be of vital importance (Jelbert, Stedmon, & Stephens, 2010; Parslow et al., 2015). Even though the exact impact of these factors on the chance of recovery remains unknown, assessment of system-related factors and inclusion of family in the treatment process is highly advised (Chalder et al., 2010).

Diversity within the pediatric CFS patient population has primarily been described in terms of medical and physiological concepts (May et al., 2010; Crawley, 2014). As far as we know, no studies have yet been performed to assess the heterogeneity of adolescent CFS patients through identification of psychosocial profiles. However, research suggested that negative CBT outcome and low levels of well-being in CFS are possibly predominantly influenced by psychological factors and the subjective impact of chronic illness (Jackson & MacLeod, 2016). Moreover, studies have suggested that the CFS patient population is highly heterogeneous regarding perpetuating factors that should be targeted in CBT (van Houdenhove & Luyten, 2008). Therefore, it would be interesting to assess whether psychosocial profiles can be composed, to enhance understanding of treatment inefficacy and tailor treatment options to the patient's personal needs (Cella, Chalder, & White, 2011; Turk, 2005).

A few studies have provided evidence for the availability of subgroups within the adult CFS patient population (Ablin, Zohar, Zaraya-Blum, & Buskila, 2016; Cella et al., 2011). One study indicated that there are at least two personality profiles of adult CFS patients can be found based on psychological variables, one adaptive and maladaptive cluster, which were not found to differ in illness severity (Ablin et al., 2016). The observation of maladaptive and less adaptive clusters is in line with similar analyses in chronically diseased patient populations (Estévez-López et al., in press; van Leeuwen et al., 2014).

The objective of this research was to examine (1) whether it is possible to identify subgroups of patients based on a broad set of relevant psychological and social variables, (2) whether the subgroups differ in the fatigue severity before the start of therapy, and (3) whether the outcome of the FITNET treatment can be predicted from the subgroups. We hypothesize that an adaptive and a maladaptive personality profile can also be identified among adolescent patients with CFS. Furthermore, we expect that parental profiles with aberrant psychosocial features can

be identified and are related to fatigue severity and treatment outcome, as this correlation been regularly suggested in literature (Appendix 1). The identification of clinically distinctive subgroups among the adolescent CFS population could be used in further research on factors that influence fatigue severity and to offer or develop more personalized, efficacious interventions.

Methods

Study Design

A detailed description of the study protocol, the FITNET program and the sampling procedures is provided elsewhere (Nijhof, Bleijenberg, Uiterwaal, Kimpen, & van de Putte, 2011). This single-blinded randomized clinical trial was performed at the Wilhelmina Children's Hospital in Utrecht, in cooperation with the Expert Centre for Chronic Fatigue which was part of the Radboud University Nijmegen Medical Centre. The current analyses in the experimental group are cross-sectional and prospective. The study was reviewed and approved by the Medical Ethical Committee of the University Medical Centre Utrecht (reference 07/196-K) and the Medical Ethical Committee of the Radboud University Nijmegen Medical Centre (reference AMO nr. 07/105).

Study Population

All participants that took part in this study were recruited through referral by informed general practitioners and paediatricians from all over the Netherlands. Patients were diagnosed with CFS according to the CDC-criteria by a paediatrician (Fukuda et al., 1994; Nijhof et al., 2011). Afterwards, a researcher checked whether the inclusion criteria were met and whether no psychiatric comorbidities were present. Primary inclusion criteria included age between 12-18 years old, mastering the Dutch language and access to a computer. Further inclusion and exclusion criteria are described in Table 2. All interested participants were informed about the design and content of the study and asked to sign informed consent together with at least one parent according to the declaration of Helsinki. In total, 135 adolescents between the ages of 12-18 years old were included in the trial, 24 boys and 111 girls.

Measures/ Instruments

At baseline, validated self-reported questionnaires were used to evaluate various psychosocial factors in both CFS patients and their parents (Table 2).

The fatigue severity subscale of the *Checklist Individual Strength* (CIS-20) was used to assess subjective presence and severity of fatigue (range: 8-56, inclusion criterion CIS-fatigue ≥ 40). The CIS-20 has demonstrated discriminative validity for

CFS and the subscale has a good internal consistency (Cronbach's α = .88) (Vercoulen et al., 1994).

The physical functioning subscale of the *Child Health Questionnaire* (CHQ-CF87) consists of 9 questions (range: 0-100%) and was used to assess physical health. This subscale has been validated and the reliability is reported to be adequate (Cronbach's α =.69) (Raat, Mangunkusumo, Landgraf, Kloek, & Brug, 2007).

The *Child Depression Inventory* (CDI) was used to quantify depressive symptoms and if deemed essential refer patients for further psychological assessments before starting FITNET (range: 0-54, exclusion criterion CDI ≥ 20). The CDI has a good internal consistency (Cronbach's α = .86) (Ivarsson, Svalander, & Litlere, 2006).

The *State-Trait Anxiety Inventory for Children* (STAIC) was used to quantify trait anxiety and if deemed essential refer patients for further psychological assessments (range: 20-60, exclusion criterion adolescent STAIC ≥ 44). The trait anxiety scale was found to be highly reliable (Cronbach's α = .88) (Kirisci & Clark, 1996).

The *Children's Somatisation Inventory* (CSI) was used to monitor somatization and the perceived seriousness of physical complaints (range: 0-140). The CSI has been validated among a sample of Dutch children and has an excellent internal consistency (Cronbach's α = .90) (Meesters, Muris, Ghys, Reumerman, & Rooijmans, 2003).

The *Self-Efficacy Scale-28* (SE-28) was used to assess adolescent self-efficacy in terms of fatigue management (range: 7-28) and was found to have an excellent internal consistency (Cronbach's α = .91) (Serap Kurbanoglu, Akkoyunlu, & Umay, 2006).

The *Egna Minnen Beträffande Uppfostran* (EMBU-A) is the adolescent version of a self-reported questionnaire that evaluates perceived parental rearing style in terms of the following four subscales: overprotection, emotional warmth, rejection and anxious rearing behaviour (range: 40-160). Cronbach's α varied from .57 (anxious rearing behaviour) to .88 (emotional warmth) (Gerlsma, Arrindell, van der Veen, & Emmelkamp, 1991).

The *Achievement Motivation Test for Children* (PMT-K) was used to assess fear of failure in terms of the four subscales performance pressure, positive fear of failure, negative fear of failure and socially desirable behaviour. Reliability scores varied from

0.75 (socially desirable behaviour) to 0.82 (positive fear of failure) and validity of the subscales has been confirmed (Olivier & Steenkamp, 2004).

An *actometer* was worn for 12 subsequent days by the adolescent to measure physical movement and activity level (Nijhof et al., 2011).

The *Brief Symptom Inventory (BSI)* was used to assess psychological distress among the parent population, by nine subscales: somatization, obsessive-compulsive behaviour, interpersonal sensitivity, depression, anxiety, hostility, phobia, paranoia and psychoticism. Cronbach's α varied from .71 (psychoticism) to .88 (depression) (de Beurs, 2011). Outcomes of the BSI were assessed using the gender-specific standard table based on adult population samples and subjects were assigned to one of the seven scales, ranging from very low to very high norm scores (de Beurs, 2011).

The *Egna Minnen Beträffande Uppfostran* (EMBU-P) is the parent version of a self-reported questionnaire that evaluates one's own rearing behaviour in terms of the following four subscales: rejection, emotional warmth, control attempts and favouring subject. Cronbach's α varied from .66 (favouring subject) to .84 (emotional warmth) (Castro, de Pablo, Gómez, Arrindell, & Toro, 1997).

The *Body Consciousness Scale* (BCS) was used to assess parental focus on own bodily symptoms, using the private body scale that has good psychometric properties (Mehling, Gopisetty, Daubenmier, Price, & Hecht, 2009).

The *Causal Attribution List* (CAL) was used to assess parental attribution of the origin of their child's CFS: either physical or non-physical. The CAL has been validated and is reported to be reliable (Cronbach's α = .71) (Vercoulen et al., 1994).

Table 2. *Baseline measurements in adolescents and their parents before initiation FITNET therapy.*

Adolescents	Parents
- Checklist Individual Strength (CIS-20)	- Checklist Individual Strength (CIS-20)
Inclusion criterion ≥ 40	
- Self-Efficacy Scale-28 (SE-28)	- Brief Symptom Inventory (BSI)
- Egna Minnen Beträffande Uppfostran (EMBU-A)	- Egna Minnen Beträffande Uppfostran (EMBU-P)
- Child Depression Inventory (CDI)	- Body Consciousness Scale (BCS)
Exclusion criterion ≥ 20	
- State-Trait Anxiety Inventory for Children (STAIC)	- Causal Attribution List (CAL)
Exclusion criterion ≥ 44	
- Achievement Motivation Test for Children (PMT-K)	
- Children's Somatisation Inventory (CSI)	
- Child Health Questionnaire (CHQ-CF87)	
- Actometer	

After completing the FITNET intervention, measures were done to evaluate treatment outcome (Table 3). Recovery from CFS was defined post-hoc as a combination of four criteria: absence of severe fatigue (CISfat < 40), absence of physical constraints (CHQ > 84), acceptable degree of school presence (>90%) and positive outcome on the "self-rated improvement" (SRI) scale. SRI was measured using a 4-item tool in which patients indicating to be "completely recovered" or "feel much better" were considered recovered, whereas patients indicating to have "the same complaints" or "become much worse" were not considered recovered (Nijhof, 2012).

Table 3. *Follow-up measurements among adolescents after completion of FITNET therapy.*

Follow-Up Measurements Adolescents	Recovery Criteria
- Checklist Individual Strength (CIS-20)	Fatigue subscale < 40
- Child Health Questionnaire (CHQ-CF87)	Absence of physical constraints subscale > 84
- School presence	Attendance of > 90% of normal school schedule
- Self-Rated Improvement (SRI) scale	Indication of "complete recovery" or "feeling much better"

Procedures/ Data collection

By means of a randomized clinical trial, the effectiveness of the internet-based cognitive behavioural therapy FITNET was assessed. The patients in the control group received "usual care" that was obtainable in their area, such as rehabilitation programs or psychological support. Adolescents from the control group that did not recover after 6 months, the maximum total duration of the FITNET treatment, were offered to participate in FITNET treatment.

Initially, 68 participants were assigned to the FITNET treatment and 67 participants were assigned to "usual care". After 6 months, several patients (*n*=32) from the control group crossed-over to FITNET treatment. All participants and their parents were asked to fill out the above-mentioned questionnaires at baseline, before initiation with either FITNET or usual care. The outcome parameters were also assessed immediately after the intervention and at the 6-month follow-up.

Finally, 88 adolescents completed the entire FITNET treatment program and filled out the follow-up questionnaires. Reasons for study drop-out are described in the Figure 1 below.

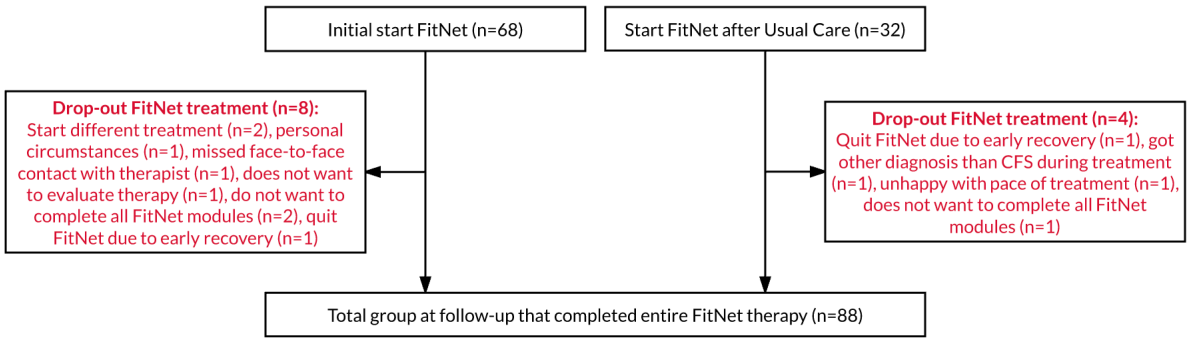

Figure 1. *Patient population that adhered to the entire FITNET treatment program.*

Statistical Analyses

To reduce the measures to an analysable set of variables, the 52 questionnaire scale scores were subjected to a higher-order principal axis factor analysis with oblimin rotation. For factor analysis, all variables should have a roughly normal distribution and should be measured at interval level (Field, 2009; Tabachnick & Fidell, 2007). Out of the 52 questionnaire scale scores, 34 scales had a skewness < 1, indicating a symmetric to moderately skewed distribution. The other 18 values with a skewness between 1.005 (BSI depression father) and 3.209 (BSI phobia father) were checked for multivariate outliers using Cook's distances. Three bivariate outliers were detected with a Cook's distance > 1, that were caused by four deviant variable scores. After questionnaire outcomes were checked, we concluded that the scores fell within the possible range and were plausible when taking in account patient file information. To normalize the scores, we corrected these four extremes to the maximum score + 1 or the minimum score -1, following Tabachnick & Fidell (2007). Subsequently, all analyses were repeated and multivariate outliers were no longer detected.

After assessing normal distribution and correcting for the extreme scores, all 52 scales were included in the factor analysis. Variables were not included in any factor when loadings were <0.40 or >0.32 on two or more factors (Osborne & Costello, 2009; Tabachnick & Fidell, 2007). The scree plot, internal consistency of the factors and factor interpretability were used to decide on the definite amount of retained factors (Field, 2009).

The mean and SD of the total sample were used to compute standardized z-scores for each participant on every scale. The variables in which a higher score signifies a lower health status (EMBU-K emotional warmth father/mother and

physical CAL father) were inverted. Afterwards, factor z-scores were calculated by averaging the z-scores of all subscales belonging to that factor. Factor scores were only computed for a subject if data was available for more than 50% of the variables within the factor. Internal consistency of factors was analysed by using Cronbach's α.

Identification of psychosocial profiles consisted of two distinctive phases, as within-group variability is in this way minimized and between-group differences are maximized (Estévez-López, in press; van Leeuwen et al., 2014). Firstly, a hierarchical cluster analysis with Ward's method was performed for identification of the number of profiles. The dendrogram was examined to appraise the number of clusters that could be considered. Secondly, *k*-means cluster analysis was carried out to allocate subjects to the clusters. The number of clusters was decided by practical concerns and interpretability of mean factor scores within clusters (van Leeuwen et al., 2014).

Differences between the psychosocial profiles were assessed by χ^2 tests for categorical data (gender, onset of disease and education level) or one-way analysis of variance (ANOVA) for continuous data (age, school presence, duration of symptoms and psychological questionnaires). In case the group effects in ANOVA was significant, post-hoc comparisons between the profiles were performed using a Bonferroni correction.

To examine whether the factors and psychosocial profiles differed in fatigue severity at baseline, linear regression analysis and univariate analysis of variance (ANOVA) were performed respectively. Age and gender were inserted as exploratory predictor variables in block 2 of the regression analysis (Field, 2009).

Predictive value of the established factors and psychosocial profiles on treatment outcome based on the outcome measure including the four criteria, were respectively assessed by binary logistic regression analysis and by χ^2 tests (Field, 2009). Patients were only included in these analyses when fulfilling the criterion of adhering to the FITNET treatment and finishing all modules (*n*=88).

All analyses were performed using SPSS for Macintosh version 23.0 (IBM, Armonk, NY). A *p*-value of <0.05 was considered significant.

Table 4. *Demographic, medical and psychological characteristics of the total patient group (n=120) and subgroups with different psychosocial profiles.*

Characteristics	Total (*n*=120)	No psychopathology within system (*n*=57)	Deviant rearing behaviour (*n*=24)	Maternal psychopathology (*n*=21)	Paternal psychopathology (*n*=18)	Comparison of psychosocial profiles
Age, mean (S.D.), years	15.8 (1.4)	15.7 (1.4)	15.4 (1.4)	16.3 (1.3)	15.9 (1.0)	$F = 1.786$, $p = .154$
Gender, *n* (%)						$\chi^2 = 2.762$, $p = .430$
- Female	98 (81.7%)	47 (82.5%)	17 (70.8%)	18 (85.7%)	16 (88.9%)	
- Male	22 (18.3%)	10 (17.5%)	7 (29.2%)	3 (14.3%)	2 (11.1%)	
Education level, *n* (%)						$\chi^2 = 1.922$, $p = .927$
- Low (VMBO)	34 (28.3%)	14 (24.6%)	6 (25.0%)	7 (33%)	7 (38.9%)	
- Medium (HAVO)	39 (32.5%)	19 (33.3%)	8 (33.3%)	7 (33%)	5 (27.8%)	
- High (VWO)	47 (39.2%)	24 (42.1%)	10 (41.7%)	7 (33%)	6 (33.3%)	
Duration of symptoms at entry, median (range), months	17 (6-96)	14 (6-54)	16 (6-72)	24 (10-84)	17 (8-96)	$F(3,116) = 3.710$, $p = .014$
Onset of disease, *n* (%)						$\chi^2 = 15.594$, $p = .016$
- Acute	17 (14.2%)	5 (8.8%)	9 (37.5%)	2 (9.5%)	1 (5.6%)	
- Gradual	68 (56.7%)	35 (61.4%)	12 (50%)	11 (52.4%)	10 (55.6%)	
- After infection	35 (29.2%)	17 (29.8%)	3 (12.5%)	8 (38.1%)	7 (38.9%)	
Fatigue severity, mean (S.D.) (CIS-20, range 8-56)	52 (4)	53 (4)	50 (5)	51 (5)	51 (5)	$F = 2.253$, $p = .086$
Physical functioning, mean (S.D.) (CHQ-CF87, range 0-100)	59 (18)	60 (16)	55 (18)	59 (20)	57 (20)	$F = .559$, $p = .643$
School presence over past half year, mean (S.D.), %	45 (31)	45 (32)	45 (31)	44 (31)	54 (32)	$F = .013$, $p = .998$
Depression score, mean (S.D.) (CDI, range 0-54)	11 (5)	10 (4)	14 (6)	9 (4)	12 (4)	$F = 4.883$, $p = .003$
Anxiety score, mean (S.D.) (STAIC, range 20-60)	33 (7)	32 (7)	37 (8)	29 (5)	35 (8)	$F = 5.074$, $p = .002$
Somatic complaints, mean (S.D.) (CSI, range 0-140)	34 (13)	32 (11)	35 (13)	31 (15)	40 (14)	$F = 1.805$, $p = .150$

Results

Psychosocial Profiles

Participants with missing values adding up to more than 50% of the variables within one of the factors, were listwise deleted from the factor and cluster analyses (*n*=15). The demographic, medical and psychological characteristics of the included patient population (*n*=120) can be found in Table 4.

Factor analysis of the 52 included scales yielded a Kaiser-Meyer-Olkin (KMO) statistic of 0.585, which reflects a relatively compact pattern of correlations, indicating that factor analysis should yield adequately distinct and reliable factors (Field, 2009). Bartlett's Test of Sphericity was significant (χ^2 = 2851,22, p < .001) indicating that the correlations between variables were significantly different from zero (Field, 2009). Furthermore, all included scales were roughly normally distributed and measured at an interval level. Hence, performance of factor analysis was appropriate.

Sixteen factors had an Eigenvalue >1.0. A parsimonious factor between four and seven factors was suggested by the scree plot (Field, 2009). Based on factor interpretability, sample size and high internal consistency of the factors (α > .71), we considered the four-factor solution most suitable: *Paternal Psychopathology*, *Maternal Psychopathology*, *Parental Rearing Behaviour* and *Child Psychopathology*. In the three-factor solution, the adolescent's perception of parental rearing behaviour and the adolescent's own psychopathological variables were combined in one factor, which are clearly different variables. For five or more factors, internal consistency on at least two factors was persistently questionable (α < .70).

Nineteen variables were excluded from the factor solution, as their loadings were <.40 on any factor or >.32 on two or more factors (Osborne & Costello, 2009; Tabachnick & Fidell, 2007). In Table 5, an overview of the factors, the internal consistency (Cronbach's α) and the 33 associated subscales is presented. The pattern matrix of factor loadings can be found in the appendix.

After performing hierarchical cluster analyses, the dendrogram suggested a cluster solution between three and six clusters. The project group decided to select the four-cluster solution, as it offers a face-valid distribution in *no psychopathology* (*n*=57, 47.5%), *deviant rearing behaviour* (*n*=24, 20%), *maternal psychopathology* (*n*=21,

17.5%) and *paternal psychopathology* (*n*=18, 15%). The three-cluster solution was not chosen as the *deviant rearing behaviour* cluster, with low maternal psychopathology, would then be combined with the *maternal psychopathology* cluster. The five-cluster solution was not preferred as *maternal psychopathology* (*n*=21) would be subdivided in *maternal psychopathology* (*n*=14) and *parental psychopathology* (*n*=11). As a result, subgroups were becoming extremely small, whereas no additional distinctive value was added. Furthermore, parental psychopathology is currently not directly addressed in the FITNET therapy, as only one parent takes part in the treatment. Thus, it did not seem valuable to take this distinction into account for the predictive analyses or possible treatment adjustments.

Table 5. *Psychosocial factors resulting from higher-order principal axis factor analysis with 52 scales, n =120*

Factor [a]	Cronbach's α	Scales [b]
Psychopathology father	.905	Paranoia score father (BSI), anxiety score father (BSI), interpersonal sensitivity score father (BSI), obsessive-compulsive behaviour score father (BSI), depression score father (BSI), somatization score father (BSI), fatigue score father (CIS-20, subscale fatigue), hostility score father (BSI), psychoticism score father (BSI) and phobia score father (BSI).
Psychopathology mother	.858	Anxiety score mother (BSI), obsessive-compulsive behaviour score mother (BSI), interpersonal sensitivity score mother (BSI), paranoia score mother (BSI), psychoticism score mother (BSI), somatization score mother (BSI), depression score mother (BSI), fatigue score mother (CIS-20, subscale fatigue), phobia score mother (BSI), body consciousness score mother (BCS) and hostility score mother (BSI).
Rearing behaviour parents	.774	Perceived anxious rearing style father (EMBU-A), perceived overprotection mother (EMBU-A), perceived overprotection father (EMBU-A), perceived anxious rearing style mother (EMBU-A), self-reported rejection mother (EMBU-P) and physical causal attribution of CFS father [c] (CAL).
Psychopathology child	.719	Perceived emotional warmth mother [c] (EMBU-A), depression score adolescent (CDI), perceived emotional warmth father [c] (EMBU-K), anxiety score adolescent (STAIC), negative fear of failure adolescent(PMT-K) and somatization score adolescent (CSI).

[a] Factors are shown in order of percentage of explained variance, as deducted from the factor analysis. [b] Scales are shown in order of their factor loadings. 19 variables were excluded from the factor solution, as their loadings were <0.40 on any factor or >0.32 on two or more factors. [c] Inverted scales: factor loadings are now all directed the same way and higher scores indicate better health status. BCS: Body Consciousness Scale. BSI: Brief Symptom Inventory. CAL: Causal Attribution List. CDI: Child Depression Inventory. CIS-20: Checklist Individual Strength. CSI: Children's Somatization Inventory. EMBU-A: Egna Minnen Beträffande Uppfostran Adolescent. EMBU-P: Egna Minnen Beträffande Uppfostran Parent. PMT-K: Achievement Motivation Test for Children. STAIC: State-Trait Anxiety Inventory for Children.

Figure 2 provides a visual overview of the mean factor scores at the four clusters. Subjects within the *no psychopathology* cluster reported low scores on all four factors, indicated by small negative deviations from the normal, representing a better health status. Patients within the *deviant rearing behaviour* cluster were characterized by somewhat positive psychopathological symptoms and highly deviant rearing behaviour. In both the *maternal* and *paternal psychopathology* cluster, large deviations from the normal were seen for the corresponding factors.

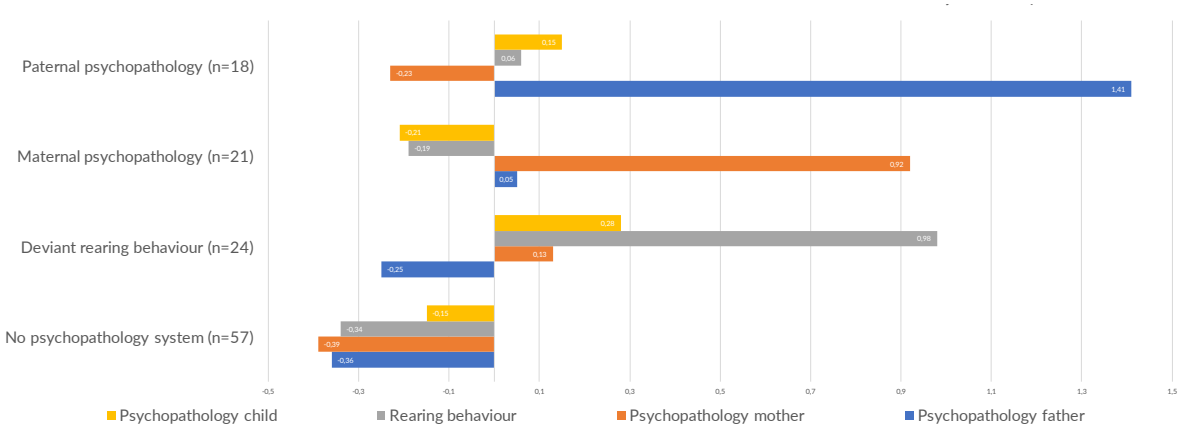

Figure 2. *Visual overview of the mean factor scores of the four clusters (n=120).*

The demographic, medical and psychological characteristics of the subgroups with different psychosocial profiles are shown in Table 4. Subjects within the *deviant rearing behaviour* cluster more commonly experienced an acute onset of the disease [χ^2 (6) = 15.594, *p* =.016]. Furthermore, subjects within the *deviant rearing behaviour* cluster were discernible from the *no psychopathology* and *maternal psychopathology* clusters as they exhibited higher adolescent depression scores [*F* (3,116) = 4.883, *p*=.003] and anxiety scores [*F* (3,114) =5.074, *p* =.002]. Lastly, significant differences were found in duration of symptoms before treatment initiation [*F* (3,116) = 3.710, *p* =.014], in which post-hoc tests indicated that the *maternal psychopathology* patient population suffered from significantly longer persisting disease symptoms than the *no psychopathology* [*p*=.011] and *deviant rearing behaviour* [*p*=.049] clusters. No significant results were found in differences between clusters for age and gender, hence corrections for these demographic variables were not applied in further analyses.

Fatigue Severity at Baseline

Linear regression analysis indicated that the established factors were not significantly associated with fatigue score at baseline [F (4, 115) = 2.123, p = .082]. The predicting value of independent factors is shown in Table 6, which shows that subjects who score higher on *Child Psychopathology* have significantly higher baseline fatigue scores [p=.048]. ANOVA showed no significant difference in fatigue score at baseline among the established clusters [F (3,116) = 2.253, p = .086].

Table 6. *Standardized Regression Coefficients (β), t and p statistics and R^2 and adjusted R^2 for all factors with fatigue at baseline as dependent variable (n=120).*

	β	*t*	*p*	R^2	*Adjusted* R^2
(Constant)		130.549		.069	.036
Paternal Psychopathology	-.094	-1.039	.301		
Maternal Psychopathology	-.094	-1.039	.202		
Parental Rearing Behaviour	-.117	-1.761	.081		
Child Psychopathology	.187	2.001	.048		

FITNET Treatment Outcome

A logistic regression was performed to ascertain the effects of the four established factors on the likelihood that the participant would recover from CFS after completing FITNET. The logistic regression model was not statistically significant, $\chi^2(4) = 6.451$, p = .168. However, significance of separate components included in the logistic regression model may still suggest coherence with the outcome variable. The model explained 10.9% (Nagelkerke R^2) of the variance in recovery and correctly classified 67.9% of the cases. Higher maternal psychopathology was associated with an increased likelihood to recover from CFS after finishing FITNET (p = .048, shown in Table 7).

Table 7. *Results of the binary logistic regression predicting for recovery after FITNET treatment (n=88).*

	B	S.E.	Wald	df	Sig.	Exp (B)
Paternal Psychopathology	.209	.391	.286	1	.593	1.233
Maternal Psychopathology	.910	.461	3.893	1	.048	2.485
Parental Rearing Behaviour	.033	.385	.007	1	.931	1.034
Child Psychopathology	.434	.430	1.019	1	.313	1.543

A Chi-Square Test of Independence was performed to examine the differences between the four established clusters and recovery from CFS after completing FITNET. The relationship between these variables was not significant, χ^2 (3) = 2.194, *p*=.533, showing that the clusters did not differ in chance of recovery.

Discussion

The aim of the present study was to provide insight into the heterogeneity of the adolescent CFS patient population by identifying various psychosocial scales through factor and cluster analyses. Four factors were revealed: *Paternal Psychopathology*, *Maternal Psychopathology*, *Rearing Behaviour* and *Child Psychopathology*. Moreover, four clinically distinctive psychosocial profiles were identified: *no psychopathology* (*n*=57), *deviant rearing behaviour* (*n*=24), *maternal psychopathology* (*n*=21) and *paternal psychopathology* (*n*=18). The four psychosocial profiles were not found to be predictive for fatigue score at baseline or FITNET treatment efficacy.

Heterogeneity of CFS among adolescents was indicated by four clinically relevant factors, which can be targeted in treatment and incorporate the system-perspective that is suggested to play an important role in the paediatric CFS population (Chalder et al., 2010). The distribution of the patient population over the clusters confirms the variety in system psychopathology and parental rearing styles. Several substantial differences were found among the clusters. Post-hoc tests indicated that subjects within the *maternal psychopathology* cluster had significantly longer persisting disease symptoms before treatment initiation, which might indicate that maternal psychopathology is associated with delayed report of paediatric CFS compared to other clusters. Additionally, subjects within the *deviant rearing behaviour* cluster presented with significantly higher self-reported depression scores and anxiety scores, in accordance with previous observations of an associated of self-reported anxiety and depression scores with self-reported parental overprotection and anxious rearing (Markus, Lindhout, Boer, Hoogendijk, & Arrindell, 2003; Muris, Meesters, Schouten, & Hoge, 2004). The cross-sectional correlation may indicate that an overprotective or anxious parental rearing style is the result of more severe adolescent psychopathology or vice versa, or that a third variable such as self-report is responsible for the association.

Self-reported fatigue at baseline, one of the measures for disease severity, was found to be significantly elevated among subjects with high factor-scores on *Child Psychopathology*. This is in line with findings that children with a higher score on mental health and somatization measures often present with more fatigue (van de

Putte et al. 2006; Viner et al., 2008). None of the other established factors or clusters was significantly associated with fatigue score at baseline.

With respect to the prediction of the effect of therapy from the profile scores, our data provide a tentative suggestion that high factor scores on *Maternal Psychopathology* at baseline are associated with higher chance of recovery from CFS after FITNET. These findings have not earlier been described in research, however system interaction is known to be one of the social perpetuating factors (Bakker & van de Putte, 2012; Lievesley et al., 2014; Werker et al., 2012). A clarification for our findings can be described from two perspectives.

First, maternal psychopathology can be a response to the health state of the child, as the impact of chronic illness is known to extend to the entire family of a patient (Christin, Akre, Berchtold, & Suris, 2016; Missen, Hollingworth, Eaton, & Crawley, 2012; van de Putte et al., 2006). Perhaps maternal psychopathology is especially high in children that show an unpredictable and variable pattern of fatigue that waxes and wanes. If these children respond most to therapy, it might explain why therapy was more beneficial in adolescents with a mother with more psychopathology. This suggestion is tentative and needs more research. Another suggestion that could not be examined with our data is that psychopathological symptoms of the mother diminish once the triggering factor, in this case the CFS, is reduced by therapy. Besides that, one could argue that mothers are taught novel illness attitudes and coping strategies through the FITNET therapy which may increase acceptance and enhance the mother-child interaction concerning the chronic fatigue (Brace, Smith, McCauley, & Sherry, 2000; Garralda & Chalder, 2005). This may ultimately lead to less disease burden within the family-system and lower maternal psychopathology (Garralda & Chalder, 2005; Missen et al., 2012). However, parental follow-up measurements were not performed and therefore this suggestion cannot be ascertained.

Conversely and perhaps more likely as an explanation of our findings is that the family's functioning in terms of psychological well-being also impact the child and may perpetuate the CFS symptoms (Brace et al., 2000; Christin et al., 2016). Possibly specific attitudes and dysfunctional cognitions that are targeted in treatment were shaped by maternal psychopathology. Through therapy, these disturbed cognitions

might be challenged or affected in a different way than in children who grew up in a family-system without psychopathological influences. Furthermore, emotional involvement is known to be high among parents of CFS patients, possibly involving enhanced focus on bodily symptoms of the child causing reinforcement of illness-behaviour (Brace et al., 2000; Rangel et al., 2005). These behaviours are perhaps amended through treatment, especially in children that are commonly living in a pathological system.

Even though clear explanation cannot be given based on these results, the importance of maintaining a system-approach in treating CFS in a paediatric sample is neither emphasized nor rejected. However, as the only significant predictor for a beneficial outcome was more psychopathology of the mother, a standard implementation of comprehensive psychological assessments for family members or system-adjusted treatment forms do not seem to be of extra value to increase therapy effectiveness.

Several strengths of the present study can be identified. Firstly, the large sample was representative of the Dutch paediatric CFS patient population, was strictly diagnosed with CFS according to the CDC criteria and recovery after treatment was assessed based on stringent criteria (Nijhof et al., 2013). Secondly, the four factors that were established in this study are replicable in studies that used alternative psychosocial constructs, as the factors signify the presence or absence of psychological well-being and rearing behaviour in a broad sense. Thirdly, we presented a profound characterisation of the patient sample incorporating a system-approach that is suggested to play a critical role within the paediatric CFS population.

A few limitations of the current study must also be acknowledged. Primarily, various psychometric cross-sectional measurements were only performed at baseline which impedes the opportunity to define causal relationships or attribute findings to the FITNET treatment. Secondly, several scales were lost through factor analysis and the remainder of the incorporated scales were mainly related to adolescent or parental psychopathology. Furthermore, it is important to realize that factor analysis proposes a subdivision based on correlations among input variables, which are in this case predominantly self-reported psychosocial measurements. This has implications for the establishment of the clusters and drawing conclusions, as the psychosocial

profiles are constituted of subjective measurements. Lastly, we decided to evaluate the FITNET intervention only among the population that adhered to the entire treatment programme, to obtain valid results on the efficacy of the treatment (Figure 1). This decision may produce more biased results compared to including all participants according to the intention-to-treat principle.

In conclusion, the present study provides insight into the heterogeneity of the adolescent CFS patient population, classified by multiple psychosocial (system-related) features that could potentially be targeted in therapy. Four clinically relevant psychosocial profiles were established; however, they were not found to be distinctive in fatigue severity at baseline or FITNET treatment outcome. Future research should aim to replicate our profiles in other samples and examine whether related disparities in fatigue severity and treatment response occur. Furthermore, the impact of family system-related predisposing or perpetuating factors in CFS should be further explored. Our results provide a tentative suggestion that self-reported maternal psychopathology at the time of treatment initiation is related with enhanced adolescent recovery from CFS after FITNET therapy. However, the causal underlying mechanisms and family-system interaction effects causing this finding are not elucidated by our study. The current study results do not imply that personalized, profile-tailored interventions should be developed. Evidence-based treatment such as FITNET could be applied to adolescents with CFS independent of the studied factors.

References

Ablin, J. N., Zohar, A. H., Zaraya-Blum, R., & Buskila, D. (2016). Distinctive personality profiles of fibromyalgia and chronic fatigue syndrome patients. *PeerJ*, *4*, 2421. doi: 10.7717/peerj2421

Bakker, R.J., van de Putte, E.M. (2012). De vermoeide puber. *Praktische Pediatrie*, *4*, 195–200. Retrieved from: http://www.kindergeneeskunde-mca.nl/images/stories/bart/moeheid_pubers.pdf

Brace, M. J., Smith, M. S., McCauley, E., & Sherry, D. D. (2000). Family reinforcement of illness behavior: a comparison of adolescents with chronic fatigue syndrome, juvenile arthritis, and healthy controls. *Journal of Developmental & Behavioral Pediatrics*, *21*, 332-339. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/11064960

Castro, J., de Pablo, J., Gómez, J., Arrindell, W. A., & Toro, J. (1997). Assessing rearing behaviour from the perspective of the parents: a new form of the EMBU. *Social Psychiatry and Psychiatric Epidemiology*, *32*, 230-235. doi: 10.1007/BF00788243

Cella, M., Chalder, T., & White, P. D. (2011). Does the heterogeneity of chronic fatigue syndrome moderate the response to cognitive behaviour therapy? An exploratory study. *Psychotherapy and Psychosomatics*, *80*, 353-358. doi: 10.1111/j.1468-2850.2011.01262.x

Chalder, T., Deary, V., Husain, K., & Walwyn, R. (2010). Family-focused cognitive behaviour therapy versus psycho-education for chronic fatigue syndrome in 11- to 18-year-olds: a randomized controlled treatment trial. *Psychological Medicine*, *40*, 1269-1279. doi: 10.1017/S003329170999153X

Christin, A., Akre, C., Berchtold, A., & Suris, J. C. (2016). Parent–adolescent relationship in youths with a chronic condition. *Child: Care, Health and Development*, *42*, 36-41. doi: 10.1111/cch.12266

Collin, S. M., Norris, T., Nuevo, R., Tilling, K., Joinson, C., Sterne, J. A., & Crawley, E. (2016). Chronic fatigue syndrome at age 16 years. *Pediatrics*, *137*, 1-10. doi: 10.1542/peds.2015-3434

Collin, S. M., Tilling, K., Joinson, C., Rimes, K. A., Pearson, R. M., Hughes, R. A., & Crawley, E. (2015). Maternal and childhood psychological factors predict

chronic disabling fatigue at age 13 years. *Journal of Adolescent Health*, *56*, 181-187. doi: 10.1016/j.jadohealth.2014.09.002

Crawley, E. (2014). The epidemiology of chronic fatigue syndrome. *Archives of Disease in Childhood*, *99*, 171-174. doi: 10.1136/archdischild-2012-302156

De Beurs, E. (2011). *Brief Symptom Inventory/ Brief Symptom Inventory 18 Handleiding, Herziene Editie*. Leiden, The Netherlands: PITS.

Estévez-López, F., Segura-Jiménez, V., Álvarez-1 Gallardo, I.C., Borges-Cosic, M., Pulido- Martos, M., Carbonell-Baeza, A., Aparicio, V.A., Geenen, R., & Delgado-Fernández, M. (in press). Adaptation profiles comprising objective and subjective measures in fibromyalgia: the al-Ándalus project. *Rheumatology*.

Field, A. (2009). *Discovering statistics using SPSS*. Los Angeles, California: SAGE Publications.

Fisher, L., & Chalder, T. (2003). Childhood experiences of illness and parenting in adults with chronic fatigue syndrome. *Journal of Psychosomatic Research*, *54*, 439-443. doi: 10.1016/S0022-3999(02)00458-0

Fisher, H., & Crawley, E. (2013). Why do young people with CFS/ME feel anxious? A qualitative study. *Clinical child psychology and psychiatry*, *18*, 556-573. doi: 10.1177/1359104512460862

Fukuda, K., Straus, S. E., Hickie, I., Sharpe, M. C., Dobbins, J. G., & Komaroff, A. (1994). The chronic fatigue syndrome: a comprehensive approach to its definition and study. *Annals of Internal Medicine*, *121*, 953-959. doi: 10.7326/0003-4819-121-12-199412150-00009

Garralda, E.M., & Chalder, T. (2005). Practitioner review: chronic fatigue syndrome in childhood. *Journal of Child Psychology and Psychiatry*, *46*(11), 1143- 1151. doi: 10.1111/j.1469-7610.2005.01424.x

Garralda, E., Rangel, L., Levin, M., Roberts, H., & Ukoumunne, O. (1999). Psychiatric adjustment in adolescents with a history of chronic fatigue syndrome. *Journal of the American Academy of Child & Adolescent Psychiatry*, *38*, 1515-1521. doi: 10.1097/00004583-199912000-00012

Gerlsma, C., Arrindell, W. A., Van der Veen, N., & Emmelkamp, P. M. (1991). A parental rearing style questionnaire for use with adolescents: Psychometric

evaluation of the EMBU-A. *Personality and Individual differences*, *12*, 1245-1253. doi: 10.1016/0191-8869(91)90196-I

Godfrey, E., Cleare, A., Coddington, A., Roberts, A., Weinman, J., & Chalder, T. (2009). Chronic fatigue syndrome in adolescents: Do parental expectations of their child's intellectual ability match the child's ability? *Journal of Psychosomatic Research*, *67*, 165-168. doi: 10.1016/j.jpsychores.2009.02.004

Ivarsson, T., Svalander, P., & Litlere, O. (2006). The Children's Depression Inventory (CDI) as measure of depression in Swedish adolescents. A normative study. *Nordic Journal of Psychiatry*, *60*, 220-226. doi: 10.1080/08039480600636395

Jackson, H., & MacLeod, A. K. (2016). Well-being in Chronic Fatigue Syndrome: Relationship to Symptoms and Psychological Distress. *Clinical Psychology & Psychotherapy*. doi: 10.1002/cpp.2051

Jelbert, R., Stedmon, J., & Stephens, A. (2010). A qualitative exploration of adolescents' experiences of chronic fatigue syndrome. *Clinical Child Psychology and Psychiatry*, *15*, 267-283. doi: 10.1177/1359104509340940

Kirisci, L. & Clark, D.B. (1996). Reliability and Validity of the State-Trait Anxiety Inventory for Children in an Adolescent Sample: Confirmatory Factor Analysis and Item Response Theory. *Journal of Child & Adolescent Substance Abuse*, *5*, 57-70. doi: 10.1300/J029v05n03_04

Knoop, H., Stulemeijer, M., de Jong, L.W., Fiselier, T.J., & Bleijenberg, G. (2008). Efficacy of cognitive behavioral therapy for adolescents with chronic fatigue syndrome: long-term follow-up of a randomized, controlled trial. *Pediatrics*, *121*, 619–625. doi: 10.1542/peds.2007-1488

Lievesley, K., Rimes, K. A., & Chalder, T. (2014). A review of the predisposing, precipitating and perpetuating factors in Chronic Fatigue Syndrome in children and adolescents. *Clinical psychology review*, *34*, 233-248. doi: 10.1016/j.cpr.2014.02.002

Markus, M. T., Lindhout, I. E., Boer, F., Hoogendijk, T. H., & Arrindell, W. A. (2003). Factors of perceived parental rearing styles: the EMBU-C examined in a sample of Dutch primary school children. *Personality and Individual Differences*, *34*, 503-519. doi: 10.1016/S0191-8869(02)00090-9

May, M., Emond, A., & Crawley, E. (2010). Phenotypes of chronic fatigue syndrome in children and young people. *Archives of Disease in Childhood*, *95*, 245-249. doi: 10.1136/adc.2009.158162

Meesters, C., Muris, P., Ghys, A., Reumerman, T., & Rooijmans, M. (2003). The Children's Somatization Inventory: further evidence for its reliability and validity in a pediatric and a community sample of Dutch children and adolescents. *Journal of Pediatric Psychology*, *28*(6), 413-422. doi: 10.1093/jpepsy/jsg031

Mehling, W. E., Gopisetty, V., Daubenmier, J., Price, C. J., & Hecht, F. M. (2009). Body Awareness: Construct and Self-Report Measures. *PLoS ONE*, *4*, 5614. doi: 10.1371/journal.pone.0005614

Missen, A., Hollingworth, W., Eaton, N., & Crawley, E. (2012), The financial and psychological impacts on mothers of children with chronic fatigue syndrome (CFS/ME). *Child: Care, Health and Development*, *38*, 505–512. doi:10.1111/j.1365-2214.2011.01298.x

Muris, P., Meesters, C., Schouten, E., & Hoge, E. (2004). Effects of perceived control on the relationship between perceived parental rearing behaviors and symptoms of anxiety and depression in nonclinical preadolescents. *Journal of Youth and Adolescence*, *33*, 51-58. doi: 10.1023/A:1027334314021

Nijhof, L. N., Nijhof, S. L., Bleijenberg, G., Stellato, R. K., Kimpen, J. L., Pol, H. E. H., & van de Putte, E. M. (2016). The impact of chronic fatigue syndrome on cognitive functioning in adolescents. *European Journal of Pediatrics*, *175*, 245-252. doi: 10.1007/s00431-015-2626-1

Nijhof, S. L., Bleijenberg, G., Uiterwaal, C. S., Kimpen, J. L., & van de Putte, E. M. (2011). Fatigue In Teenagers on the interNET-The FITNET Trial. A randomized clinical trial of web-based cognitive behavioural therapy for adolescents with chronic fatigue syndrome: study protocol. *BMC Neurology*, *11*, 23. doi: 10.1186/1471-2377-11-23

Nijhof, S. L., Bleijenberg, G., Uiterwaal, C. S., Kimpen, J. L., & van de Putte, E. M. (2012). Effectiveness of internet-based cognitive behavioural treatment for adolescents with chronic fatigue syndrome (FITNET): a randomised controlled trial. *The Lancet*, *379*, 1412-1418. doi: 10.1016/S0140-6736(12)60025-7

Nijhof, S. L., Priesterbach, L. P., Uiterwaal, C. S., Bleijenberg, G., Kimpen, J. L., & van de Putte, E. M. (2013). Internet-based therapy for adolescents with chronic fatigue syndrome: long-term follow-up. *Pediatrics*, *131*, 1788-1795. doi: 10.1542/peds.2012-2007

Olivier, M. A. J., & Steenkamp, D. S. (2004). Attention-deficit/hyperactivity disorder: Underlying deficits in achievement motivation. *International Journal for the Advancement of Counselling*, *26*, 47-63. doi: 10.1023/B:ADCO.0000021549.40409.c4

Osborne, J. W., & Costello, A. B. (2009). Best practices in exploratory factor analysis: Four recommendations for getting the most from your analysis. *Pan-Pacific Management Review*, *12*, 131-146. Retrieved from: http://pareonline.net/pdf/v10n7.pdf

Parslow, R., Patel, A., Beasant, L., Haywood, K., Johnson, D., & Crawley, E. (2015). What matters to children with CFS/ME? A conceptual model as the first stage in developing a PROM. *Archives of Disease in Childhood*, *100*, 1141-1147. doi: 10.1136/archdischild-2015-308831

Pelcovitz, D., Septimus, A., Friedman, S. B., Krilov, L. R., Mandel, F., & Kaplan, S. (1995). Psychosocial correlates of chronic fatigue syndrome in adolescent girls. *Journal of Developmental & Behavioral Pediatrics*, *16*, 333-338. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/8557833

Raat, H., Mangunkusumo, R. T., Landgraf, J. M., Kloek, G., & Brug, J. (2007). Feasibility, reliability, and validity of adolescent health status measurement by the Child Health Questionnaire Child Form (CHQ-CF): internet administration compared with the standard paper version. *Quality of Life Research*, *16*, 675-685. doi: 10.1007/s11136-006-9157-1

Rangel, L., Garralda, M. E., Hall, A., & Woodham, S. (2003). Psychiatric adjustment in chronic fatigue syndrome of childhood and in juvenile idiopathic arthritis. *Psychological Medicine*, *33*, 289-297. doi: 10.1017/S0033291702006529

Rangel, L., Garralda, M. E., Jeffs, J., & Rose, G. (2005). Family health and characteristics in chronic fatigue syndrome, juvenile rheumatoid arthritis, and emotional disorders of childhood. *Journal of the American Academy of Child &*

Adolescent Psychiatry, *44*, 150-158. doi: 10.1097/00004583-200502000-00007

Rangel, L., Garralda, E., Levin, M., & Roberts, H. (2000a). Personality in adolescents with chronic fatigue syndrome. *European Child & Adolescent Psychiatry*, *9*, 39-45. doi: 10.1007/s007870050114

Rangel, L., Garralda, M. E., Levin, M., & Roberts, H. (2000b). The course of severe chronic fatigue syndrome in childhood. *Journal of the Royal Society of Medicine*, *93*, 129-134. doi: 10.1177/014107680009300306

Serap Kurbanoglu, S., Akkoyunlu, B., & Umay, A. (2006). Developing the information literacy self-efficacy scale. *Journal of Documentation*, *62*, 730-743. doi: 10.1108/00220410610714949

Smith, M. S., Buchwald, D. S., Bogart, A., Goldberg, J., Smith, W. R., & Afari, N. (2010). Adolescent offspring of mothers with chronic fatigue syndrome. *Journal of Adolescent Health*, *46*, 284-291. doi: 10.1016/j.jadohealth.2009.08.001

Tabachnick, B. G., & Fidell, L. S. (2007). Using multivariate statistics. Boston, Massachusetts: Pearson/Allyn & Bacon.

Turk, D. C. (2005). The potential of treatment matching for subgroups of patients with chronic pain: lumping versus splitting. *The Clinical journal of pain*, *21*, 44-55. doi: 10.1097/00002508-200501000-00006

van de Putte, E. M., Engelbert, R. H. H., Kuis, W., Kimpen, J. L. L., & Uiterwaal, C. S. (2006). How fatigue is related to other somatic symptoms. *Archives of disease in childhood*, *91*, 824-827. doi: 10.1136/adc.2006.094623

Van de Putte, E. M., Engelbert, R. H., Kuis, W., Kimpen, J. L., & Uiterwaal, C. S. (2007). Alexithymia in adolescents with chronic fatigue syndrome. *Journal of Psychosomatic Research*, *63*, 377-380. doi: 10.1016/j.jpsychores.2007.07.009

van de Putte, E. M., van Doornen, L. J., Engelbert, R. H., Kuis, W., Kimpen, J. L., & Uiterwaal, C. S. (2006). Mirrored symptoms in mother and child with chronic fatigue syndrome. *Pediatrics*, *117*, 2074-2079. doi: 10.1542/peds.2005-2307

Van Geelen, S. M., Bakker, R. J., Kuis, W., & van de Putte, E. M. (2010). Adolescent chronic fatigue syndrome: a follow-up study. *Archives of Pediatrics and Adolescent Medicine*, *164*, 810-814. doi: 10.1001/archpediatrics.2010.145

Van Houdenhove, B., & Luyten, P. (2008). Customizing treatment of chronic fatigue syndrome and fibromyalgia: the role of perpetuating factors. *Psychosomatics*, *49*, 470-477. doi: 10.1176/appi.psy.49.6.470

van Leeuwen, N., Bossema, E. R., Knoop, H., Kruize, A. A., Bootsma, H., Bijlsma, J. W., & Geenen, R. (2014). Psychological profiles in patients with Sjögren's syndrome related to fatigue: a cluster analysis. *Rheumatology*, *54*, 776-783. doi: 10.1093/rheumatology/keu387

Vercoulen, J. H., Swanink, C. M., Fennis, J. F., Galama, J. M., van der Meer, J. W., & Bleijenberg, G. (1994). Dimensional assessment of chronic fatigue syndrome. *Journal of psychosomatic research*, *38*, 383-392. doi: 10.1016/0022-3999(94)90099-X

Viner, R. M., Clark, C., Taylor, S. J., Bhui, K., Klineberg, E., Head, J., & Stansfeld, S. A. (2008). Longitudinal risk factors for persistent fatigue in adolescents. *Archives of Pediatrics & Adolescent Medicine*, *162*, 469-475.

Werker, C. L., Nijhof, S. L., & van de Putte, E. M. (2013). Clinical practice: chronic fatigue syndrome. *European journal of pediatrics*, *172*, 1293-1298. doi: 10.1007/s00431-013-2058-8

White, C., & Schweitzer, R. (2000). The role of personality in the development and perpetuation of chronic fatigue syndrome. *Journal of Psychosomatic Research*, *48*, 515-524. doi: 10.1016/S0022-3999(00)00087-8

Wiborg, J. F., Knoop, H., Stulemeijer, M., Prins, J. B., & Bleijenberg, G. (2010). How does cognitive behaviour therapy reduce fatigue in patients with chronic fatigue syndrome? The role of physical activity. *Psychological Medicine*, *40*, 1281-1287. doi: 10.1017/S0033291709992212

Appendix

Appendix 1 - Literature Search

Results of the literature search on psychosocial factors that have been associated chronic fatigue syndrome in adolescents or have been suggested to be related with treatment efficacy are shown in the flow diagram and the table below. The literature search has been performed in Web of Science and PubMed, using the search terms "*Chronic Fatigue Syndrome* OR *myalgic encephalomyelitis*", "*adolescent-* OR *child-* OR *young*", "*psycho-* OR *psychosocial*" and "*predictor*".

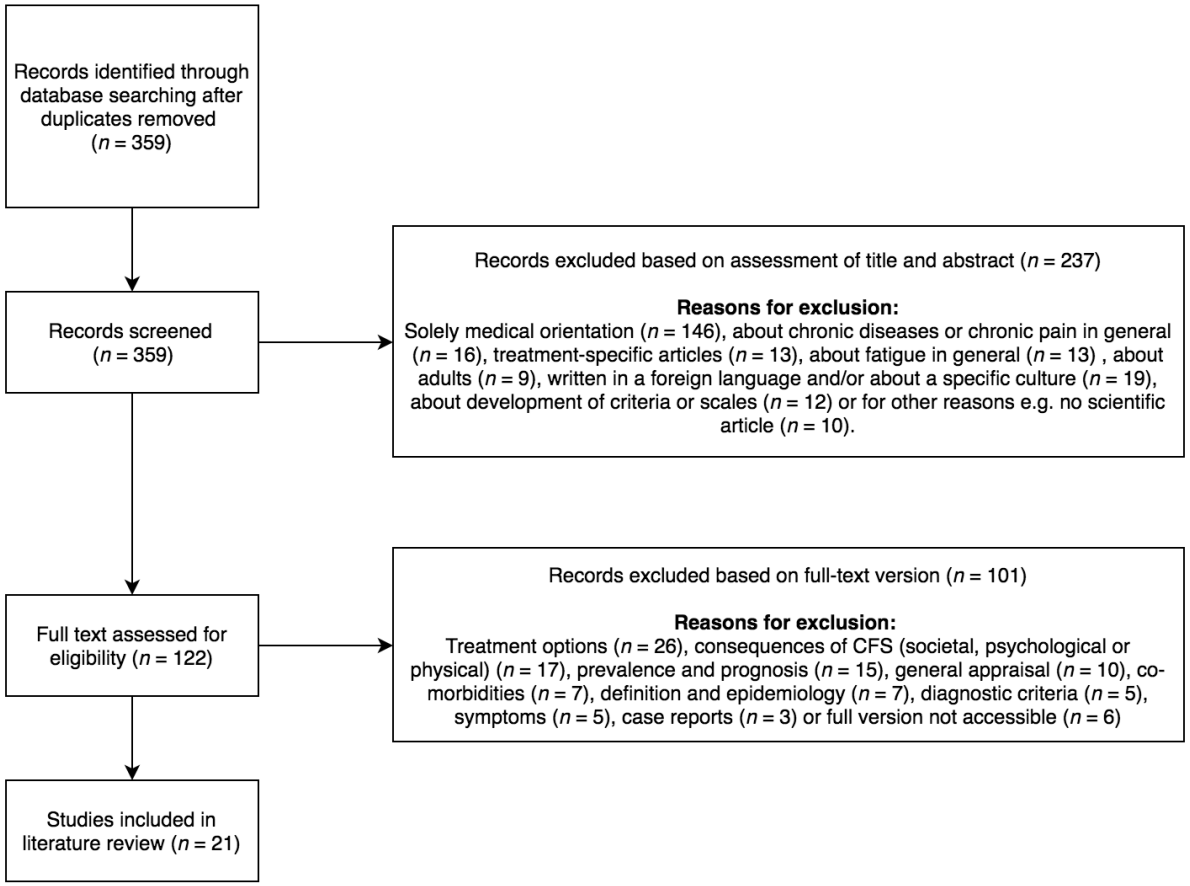

Figure 1. *Flow diagram of systematic research.*

Table 1. *Results of literature search on studied psychosocial factors in adolescent chronic fatigue syndrome.*

Author(s)	Year of Publication	Psychosocial factor
Pelcovitz, Septimus, Friedman, Krilov, Mandel & Kaplan	1995	Adolescents with CFS as well as their parents have higher scores on somatic complaints and internalizing symptoms.
Garralda, Rangel, Levin, Roberts, Ukoumunne	1999	Psychiatric disorders (such as anxiety disorder) were found to be increased in adolescents with more severe CFS.
Brace, Scott Smith, McCauley, Sherry	2000	Parental reinforcement of illness behaviors may be more prevalent among the CFS population, causing exacerbation and maintenance of the disease.
Rangel, Garralda, Levin & Roberts	2000	Maternal distress may lead to a poor treatment outcome among adolescent CFS patients.
Rangel, Garralda, Levin & Roberts	2000	CFS patients are more likely to have personality difficulties (features such as conscientiousness, vulnerability, worthlessness and emotional lability) which may be linked to poor treatment outcome.
White & Schweitzer	2000	Adolescents with CFS score high on perfectionism and have lower self-esteem scores compared to a control group.
Rangel, Gerralda, Hall, Woodham	2003	Children and adolescents with CFS commonly portray personality problems and psychopathology that cannot solely be explained through experience of chronic physical illness.
Rangel, Garralda, Jeffs & Rose	2005	CFS in childhood and adolescence is associated with more parental psychopathology, parental CFS-like illness, parental emotional over-involvement and family illness burden, compared to other families with chronically ill children.
van de Putte, van Doornen, Engelbert, Kuis, Kimpen, Uiterwaal	2006	Maternal distress and fatigue complaints are related with same complaints in children with CFS (causal direction unknown).
van de Putte, Engelbert, Kuis, Kimpen & Uiterwaal	2007	Some adolescents with CFS have alexithymia, however it is not a prognostic factor for recovery.
Godfrey, Cleare, Coddington, Roberts, Weinman & Chalder	2009	Parental expectations often do not match the child's intellectual ability among adolescent CFS patients.

Jelbert, Stedmon & Stephens	2010	Parental support is of vital importance according to adolescents suffering from CFS.
Smith, Buchwald, Bogart, Goldberg, Smith & Afari	2010	Higher prevalence of fatiguing states in offspring of CFS mothers, suggesting familial factors.
van Geelen, Bakker, Kuis & van de Putte	2010	Pain, poor mental health, low self-esteem and general health perception at outcome were associate with unfavourable treatment outcome in adolescent CFS patients.
Fisher & Crawley	2013	Young people with CFS regularly suffer from higher levels of psychological distress than healthy controls and children with other chronic diseases.
Nijhof, Priesterbach, Uiterwaal, Bleijenberg, Kimpen & van de Putte	2013	Maternal focus on bodily symptoms is related with worse treatment outcome.
Werker, Nijhof & van de Putte	2013	System interaction (parental distress or overprotection) are known to be one of the social perpetuating factors of adolescent CFS.
Lievesley, Rimes & Chalder	2014	Adolescents with CFS showed more psychiatric co-morbidity, mainly anxiety and depressive disorders, compared to healthy or illness control groups. Preliminary evidence implied a relationship between adolescent CFS and family history of CFS, high (parental) expectations and personality factors such as conscientiousness and physical illness attributions. Negative coping mechanisms seem to be fundamental perpetuating factors in pediatric CFS. The study implies that treatment of adolescent CFS should be tailored to specific personality types.
Collin, Tilling, Joinson, Rimes, Pearson, Hughes, Sterne & Crawley	2015	Maternal depression and anxiety are risk factors for pediatric chronic disabling fatigue, possibly leading to adolescent CFS.
Parslow, Patel, Beasant, Haywood, Johnson & Crawley	2015	A supportive family or social network can ameliorate symptoms of CFS.
Collin, Norris, Nuevo, Tilling, Joinson, Sterne & Crawley	2016	Family adversity is associated with an increased risk of CFS.

Appendix 2 – Pattern Matrix of Factor Loadings

Table 2. *Factor loadings after higher order Principal Component Analysis summarizing 52 psychosocial variables and Eigenvalue, Cronbach's alpha and percentage of explained variance for each of the four factors.*

Possible predictor variables	Factors [a]			
	Psychopathology father	Psychopathology mother	Rearing behavior parents	Psychopathology child
Paranoia score father (BSI)	**,823**			
Anxiety score father (BSI)	**,793**			
Interpersonal sensitivity score father (BSI)	**,793**			
Obsessive-compulsive behavior score father (BSI)	**,786**			
Depression score father (BSI)	**,772**			
Somatization score father (BSI)	**,736**			
Fatigue score father (CIS)	**,667**			
Hostility score father (BSI)	**,663**			
Psychoticism score father (BSI)	**,629**			
Phobia score father (BSI)	**,627**			
Self-reported overprotection father (EMBU-P)	,388		-,375	
Body consciousness score father (BCS)	,314		,313	
Self-reported emotional warmth father (EMBU-P)				
Self-reported favouring child father (EMBU-P)				
Anxiety score mother (BSI)		**,722**		
Obsessive-compulsive behavior score mother (BSI)		**,711**		
Interpersonal sensitivity score mother (BSI)		**,693**		
Paranoia score mother (BSI)		**,672**		
Psychoticism score mother (BSI)		**,665**		
Somatization score mother (BSI)		**,661**		
Depression score mother (BSI)		**,650**		
Fatigue score mother (CIS)		**,650**		
Phobia score mother (BSI)		**,547**		
Body consciousness score mother (BCS)		**,503**		
Hostility score mother (BSI)		**,500**		
Self-reported favouring child mother (EMBU-P)		,358		
Fatigue score child (CIS)				
Perceived anxious rearing style father (EMBU-A)			**-,742**	
Perceived overprotection mother (EMBU-A)			**-,716**	
Perceived overprotection father (EMBU-A)			**-,685**	
Perceived anxious rearing style mother (EMBU-A)			**-,671**	
Perceived rejection father (EMBU-A)			-,557	-,400
Perceived rejection mother (EMBU-A)			-,547	-,392
Self-reported rejection mother (EMBU-P)			**-,460**	
Causal attribution CFS father: physical (CAL)			**,424**	
Socially desirable behavior child (PMT-K)			,358	
Self-reported rejection father (EMBU-P)			-,346	
Causal attribution CFS mother: physical (CAL)			,328	
Self-reported overprotection mother (EMBU-P)			-,309	
Physical activity child (actometer)				
Perceived emotional warmth mother (EMBU-A)				**,637**
Depression score child (CDI)				**-,627**
Perceived emotional warmth father (EMBU-A)				**,621**
Anxiety score child (STAIC)				**-,616**
Negative fear of failure child (PMT-K)				**-,533**
Somatization score child (CSI)				**-,423**
Causal attribution CFS mother: non-physical (CAL)				-,388
Self-reported emotional warmth mother (EMBU-P)				,355
Performance pressure child (PMT-K)				,353
Positive fear of failure child (PMT-K)				,303
Causal attribution CFS father: non-physical (CAL)				
Self-efficacy score child (SE-28)				
Eigenvalue factors	6,74	5,43	4,08	2,77
Cronbach's alpha	,905	,858	,774	,719
Percentage explained variance	12,95 %	10,44 %	7,84 %	5,34 %

[a] Factor loadings <|0.30| are not shown to ensure clarity. Actometer: physical movement measurement. BCS: Body Consciousness Scale. BSI: Brief Symptom Inventory. CAL: Causal Attribution List. CDI: Child Depression Inventory. CIS-20: Checklist Individual Strength. CSI: Children's Somatization Inventory. EMBU-A: Egna Minnen Beträffande Uppfostran Adolescent. EMBU-P: Egna Minnen Beträffande Uppfostran Parent. PMT-K: Achievement Motivation Test for Children (Dutch: Prestatie-Motivatie Test voor Kinderen). SE-28: Self-Efficacy Scale-28.STAIC: State-Trait Anxiety Inventory for Children.