1. SUPPLEMENTARY INFORMATION

6.1. Design

The research methodology used in the study is a two-phase single-case experimental design (SCED), with randomisation of the time interval prior to the start of the FITNET-plus intervention. The randomisation component in a SCED increases the internal validity of the findings (Smith et al, 2012). The baseline A-phase represents the no-treatment baseline period. This phase is followed by the B-phase representing the intervention and follow-up periods. During both phases, weekly self-reported outcome measurements were performed of fatigue, pain, physical functioning and school absence.

SCED is an approach that may be used to establish evidence-based practices. This approach is particularly appropriate when unaddressed areas are explored, and pilot data are generated or when studying small-n populations, such as an adolescent with an immune dysregulation disease (IDD) in the current study. In contrast to a randomized controlled trial, SCEDs do not require a substantial number of participants, thus providing a cost-effective approach to explore whether CBT is potentially efficacious in reducing chronic fatigue among adolescent with a chronic disease.

The feasibility of this FITNET-plus intervention, in terms of treatment adherence and the user-friendliness of the web-based tool, was explored with a clinical interview.

6.2. Measurements of severity of the symptoms and fatigue perpetuating factors

Table 1. Overview of all the T0 and T1 measures and the perpetuating factors targeted in the optional treatment modules in personalized internet-delivered cognitive behavioural therapy (I-CBT) of Sarah. A score in bold indicates that the score is above the cut-off score and a relevant perpetuating factor.

	Measurements	**Cut-off scores**	**T_0**	**T_1**
Main outcome measure				
Fatigue severity	Checklist Individual Strength (CIS, subscale fatigue, range 8-56) (S L Nijhof et al., 2012)	>40	**50**	19
Secondary outcome measures*				
Physical functioning⊥	Child Health questionnaire, subscale physical functioning (range 0-100%) (Raat et al., 2002)	≤ 85%	**37.0**	96.3
School absence ⊥	Attended lessons divided by compulsory lessons, last 2 weeks (range 0-100% (Nijhof et al., 2011)	>10%	**86**	0
Pain severity ⊥	Visual analogue scale (VAS) scores for pain (0-100mm) (Wulffraat et al., 2001)	>40	**75**	**65**
Indicators for modules				
Sleep pattern (only at T_0)	Diary of bedtimes for 14 days, visual analyses (see Figure 6.1) (Nijhof et al., 2011)	-	-	X
Dysfunctional cognitions with respect to fatigue	Self-Efficacy Scale (SES, range 7-28) (Vercoulen et al., 1998)	≤ 19	21	26
	Jacobson Fatigue Catastrophising Scale (J-FCS, 10-50) (Jacobsen et al., 2004)	≥ 16	**22**	15
Level of physical activity (only at T_0)	Actigraphy (van der Werf et al., 2000)**			
	Relatively active	≥2/12	**1/12**	X
	Low active	1/12		
Dysfunctional cognitions with respect to pain	Pain Catastrophising Scale (PCS, range 0-52) (Sullivan et al., 1995)	≥30	14	2
Other measures				

	Measurements	**Cut-off scores**	**T_0**	**T_1**
Depression (only at T_0)	Child Depression Inventory (CDI, range 0-54) (Kovacs, 1985)	≥ 15	6	X
Anxiety (only at T_0)	Spielberger State-Trait Anxiety Inventory for Children (STAIC, range 20-60) (Papay & Spielberger, 1986)	≥44	26	X
Cognitions regarding symptoms of chronic illness	Illness Cognition Questionnaire (ICQ) (Kraaimaat et al., 1998)			
	Helplessness (range 6-24)	-	16	8
	Disease benefits (range 6-24)	-	14	14
	Disease acceptance (range 6-24)	-	17	23

Note: T0, baseline assessment; T1, post-intervention assessment;
* The secondary outcomes are based on previous studies determining the effectiveness of cognitive behavioural therapy for chronic fatigue. It was repeatedly found that severe fatigue among adolescents with CFS or a medical condition is related to impediments in daily functioning (Nap-van der Vlist et al., 2021; Nap-van der Vlist et al., 2019; Nijhof et al., 2016, 2021; Nijhof et al., 2011) and that there is a reduction in disability after effective treatment of fatigue (Albers et al., 2021; Nijhof et al., 2012). For adolescents, this is expressed in increased school absenteeism and reduced physical functioning. In addition, pain is associated with the severity of fatigue in patients with IDD (Nijhof et al., 2016), which is described in the introduction to our article, and makes it relevant to measure the severity of pain before, during and after treatment.

**Actigraphy, the actigraphy is deliberately not assessed at T1. Various treatment studies of chronic fatigue have shown that an increase in physical activity does not mediate the response to CBT (Poort et al., 2021; Wiborg et al., 2010). Actigraphy helps to determine which treatment protocol a patient has to follow (for low active or relative active patients) and is therefore only used at baseline. Sarah followed the treatment protocol for low active patients

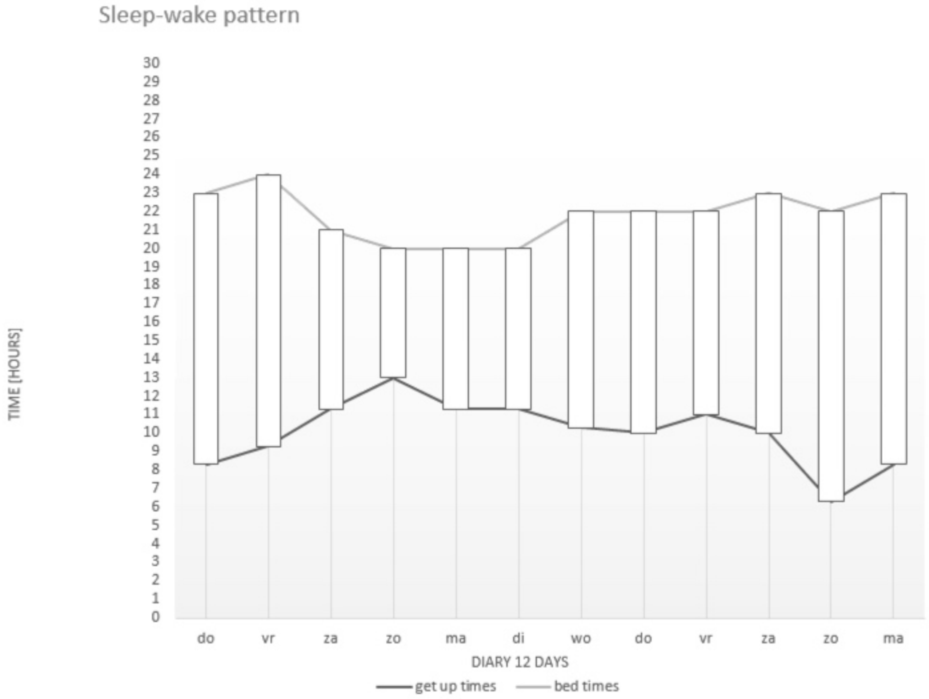

Figure 1. sleep-wake pattern of Sarah with her get up- and bed times during 12 days

6.3. Holistic theory and treatable factors

The holistic theory is divided into predisposing factors (temperament, family of origin, traumatic events, protective factors), triggering factors (cause for development of symptoms) and perpetuating factors based on biopsychosocial model (Engel, 1977).

Predisposing factors: Sarah has a greater chance of developing chronic fatigue because of her gender. In addition, there are negative life events (divorce of parents and no contact with her father), premorbid psychopathology (mood disorder) and personality traits, especially perfectionism, that may made her more prone to develop fatigue.

Triggering factors: in the period in which Sarah presumably developed her symptoms, disease activity had triggered severe fatigue and pain symptoms.

Perpetuating factors (summary of the questionnaires in table 1 and figure 1): low activity pattern, disturbed sleep-wake rhythm, tendency to catastrophise fatigue and JIA (e.g. JIA makes me feel useless). Self-efficacy is not low, but she is still mainly passive in response to the fatigue; at the start of treatment, she is not yet convinced that she can learn to influence her fatigue herself.

6.4. Sarah's treatment plan and treatment goals

Sarah's treatment plan
Internet-delivered cognitive behavioural therapy for chronic fatigue

The goal of my treatment is that I am no longer chronically fatigued. This means that at the end of the treatment I am able to: (as clearly as possible formulate the behaviour/activities I want to do again and how often per day/week and how long in a row) when fatigue no longer impedes me.

Goals			
Date: XX-XX-XXXX			
I want to do the following things again when fatigue no longer impedes me:			
Type of activity	I would like to do the following again:	How long and how often?	
School	- Full school attendance - Homework and schoolwork	- Follow full schedule, 5 days a week - 1 hour per day during the week, 1.5 hours per day at the weekend	

Going to School	- My mother brings me to school by car during my time in high school - At the start of my college, I want to be able to travel by public transport independently	How long does it take me? - By car to school 20 minutes - By public transport to college 45 minutes	
Sport	- Fitness - Running	- 2 times per week, 60 minutes - 1 time per week in the weekend, at least 2 km	
Meeting up with friends	- Meeting up with friends - A day of shopping or a trip to another city	- 1-2 times week, +/- 3 hours - 1 time per 3 months, whole day	
Hobbies/other leisure activities	- Reading a book and/or being creative (drawing, mandelas, writing in my journal)	- 3 times a week 45 minutes	
Family	- Having Dinner until later in the evening at a restaurant - Going to birthdays or family visits	- 1 time per two months - 1 time per month, +/- 4.5 hours	
Side job	After getting back into the swing of things at school, look for a job on the side for work experience, e.g. as a cashier in a supermarket	8 hours per week	

My mother or another important person is involved in the treatment as much as possible.

I am going to follow the proposed treatment modules in order to achieve the above-mentioned goals. These modules will start with an explanation of the content of the module, followed by exercises. At each step, the therapist will help me to solve the problems I encounter.

I am committed to make each module a success. The treatment modules that apply to me are:

a. Establishing a regular sleep-wake rhythm, without sleeping or lying down during the day
b. Maintaining helpful thoughts in response to extreme fatigue
c. Shifting attention from fatigue to activities or to my surroundings
d. Change the way I respond to pain
e. Gradual increase of physical activity
f. Increasing mental and social activities

g. Achieving my goals step by step
h. Practicing with disruption of my sleep-wake pattern
i. Mastering fatigue and prevention of relapse
j. Evaluation
k. After treatment: assessment (T1)
l. Evaluation of treatment in a face-to-face session

Sara: therapist:

Signature Signature

6.5. Content of the treatment modules

FITNET-plus is with permission derived from FITNET which is based on the face face to face CBT protocol for ME/CFS in adolescents. FITNET-plus is enriched with elements of evidence-based CBT protocols for fatigued adults with a chronic medical condition (Abrahams et al., 2015; Menting et al., 2017; Nijhof et al., 2012) and adapted for adolescents with an IDD. For this adaptation we conducted clinical interviews with adolescents with IDD to gain insight into beliefs and behaviours related to their fatigue and medical condition, to ensure that the content of the treatment portal was well suited to this target group. Based on the interviews it was decided to extend FITNET-plus with a module aimed at coping with pain.

The online FITNET-plus intervention consists of a combination of assignments, information and e-mail contact with a therapist delivered via an internet portal. The total duration of the intervention is six months. During these months patients get online information and assignments, and have weekly to biweekly e-mail contact with their therapist. At the therapist’s initiative or at the patient's request, the frequency of contacts may be temporarily increased to weekly. The patient would receive an immediate response to an emergency email. Additionally, for emergency situations, telephone contact details were available to the patients.

Parents have their own restricted online portal with general information on the treatment, suggestions on how to support their child in therapy in the different treatment modules. The suggestions for the parents become available when the treatment module is opened for the patient. There is an e-mail option available to the parents if they want to communicate with the therapist and ask questions. In children <= 15 years, parents often act as a coach. If children are > 15 years (like Sarah), parents are encouraged to step back and stimulate their child to take responsibility for their own treatment.

The FITNET-plus intervention is aimed at changing cognitions and behaviours thought to perpetuate fatigue; these are depicted in Figure 2.

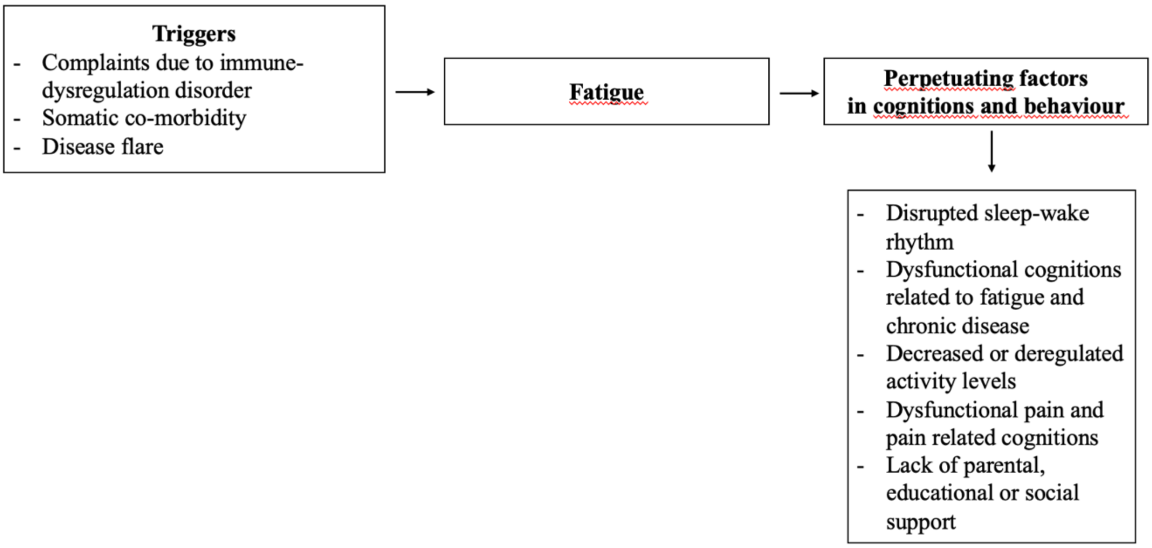

Figure 2. Cognitive behavioural model of perpetuating factors of fatigue in adolescent patients with an immune-dysregulation disease

Which cognitions and behaviours are relevant and applicable for the individual patient will be determined on the basis of cut-off scores on various questionnaires filled in at baseline assessment and the face to face clinical interview by the therapist. For each fatigue-perpetuating factor a treatment module is developed. In this way the intervention can be tailored based on the applicable factors. Patients can follow the following treatment modules:

1. *Module: Introduction of I-CBT and treatment rationale.* All patients receive this module which introduces CBT and explain the role of the therapist, and the context of the family. A rationale based on a multi-factorial model about fatigue in immune-dysregulation disease that distinguishes predisposing, precipitating and perpetuating factors is presented. Parents are actively involved in supporting their child, and parents' beliefs and behaviours regarding the condition of their child will be explored and addressed. The aims of therapy take into account the specific developmental tasks of adolescents.

2. *Module: Goal setting.* All patients receive this module. The patient will formulate treatment goals which, if attained, imply that a patient is no longer severely fatigued and no longer limited by fatigue in daily functioning. If possible, return to full time education is always a goal of treatment, and a plan for returning to school will be discussed early with everyone involved.

3. *Module: Regulation of the sleep-wake pattern.* At baseline, patients register bedtimes, times that they get up and the time slept during the day for two consecutive weeks. This module is indicated if the sleep-wake pattern is disrupted. In the module the importance of a regular sleep-wake cycle is discussed. Patients are asked to maintain fixed bedtimes and to stop sleeping or lying down during the day. Sarah followed this optional module.

4. *Module: Formulating helpful beliefs about fatigue and the chronic disease.* This module addresses low self-efficacy with respect to fatigue, fatigue catastrophising, the tendency of patients to focus on fatigue and dysfunctional beliefs regarding chronic disease. Dysfunctional beliefs related to fatigue and chronic disease will be

reformulated and patients will practice applying helpful beliefs in their daily life. If patients score 19 or lower on the Self Efficacy Scale (SES) for fatigue and/or 16 or higher on the Fatigue Catastrophising Scale (FCS) (Menting et al., 2017), they will follow this module. Patients will learn to formulate more helpful beliefs and shift their attention away from fatigue to an activity or the environment. Patients will also be asked to stop talking about fatigue and to ask significant others to stop talking about fatigue. Cognitions regarding symptoms of chronic illness are assessed with the illness cognition questionnaire (ICQ) (Kraaimaat et al., 1998). At item level of the ICQ, cognitions about the chronic disease are examined and in case of dysfunctional beliefs these will be reformulated to helpful beliefs in this module. Sarah followed this optional module.

5. *Module: Activity regulation and increasing the level of activity.* This module is applicable for all patients and focuses on gradually increasing activity. There are two treatment protocols, depending on the pattern of physical activity of the patient. The physical activity pattern of patients is assessed with an actometer, a small device which is worn at the ankle during two consecutive weeks and measures physical activity (van der Werf et al., 2000). On the basis of the actigraphy scores, each patient is categorised in one of the two activity patterns: relatively active or low active. The physical activity of relatively active patients varies from day to day and is often characterised by ‘all or nothing’ behaviour. Relatively active patients first learn to divide their activities more evenly and then increase their physical activity level with a graded activity program. Patients can choose to increase their physical activity level either by walking or biking. They start walking or biking at least two times a day and increase their walking or biking time step by step. Patients with a low active pattern immediately start with

graded activity (like Sarah). After patients have increased their physical activity level, and indicate that their ability to become active has increased they apply the same principles to social or mental activities.

6. *Module: Coping with pain.* This module focuses on dysfunctional cognitions regarding pain. It is assumed that catastrophising in response to pain makes it difficult for patients to increase their activity level. Therefore, patients practice with more helpful beliefs with respect to pain. Patients who score 30 or higher on the Pain Catastrophising Scale (PCS) (S et al., 2002) will receive this module. Sarah followed this optional module.

7. *Module: Step-by-step realisation of goals*. All patients continue to this module about the realisation of personal goals. Patients realise the pre-set goals and evaluate the treatment effects. Patients who have school absence because of their fatigue will step by step resume school in this module.

8. *Module: Relapse prevention.* All patients receive this module which focuses on maintaining gains and how to prevent relapse.

6.6. Sarah’s treatment experience and implications

At post-therapy assessment, Sarah reflected on the treatment period. In the first 1,5 month of treatment, she experienced temporary increases in symptoms, which made it challenging for her to continue treatment. Her confidence in the treatment and her concrete goals however encouraged her to continue. According to Sarah, the therapy was helpful in achieving her goals, including reducing the fatigue severity and impairments. The fact that the treatment was available online, thus eliminating the need to travel or skip activities because of therapy, was seen as a benefit. During treatment, she was more able to cope with the fatigue and to build up her activities. In the last weeks of treatment, her fatigue decreased more and more. She did not report a reduction in pain severity, but pain no longer hampered her activities.

At a telephone interview at one year follow-up, Sarah indicated that she was inspired by the intervention, had continued optimizing her daily structure and experienced an improved quality of life with less fatigue interference. She participated fulltime in school, resumed her hobbies and felt more confident about the future.

These qualitive findings, in relation to quantitative findings, offer support for the usability of I-CBT for an adolescent patient with JIA and provides preliminary evidence that the focus should be on tailoring the intervention to perpetuating cognitions and behaviour specific for the individual and not so much on disease-specific characteristics.

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