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ARTICLE

Targeting persistent fatigue with tailored versus generic self-management strategies in adolescents and young adults with a fatigue syndrome or rheumatic condition: A randomized crossover trial

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Abstract

Objectives: To evaluate the use of two self-management intervention strategies for persistent fatigue in adolescents and young adults with a fatigue syndrome or rheumatic condition.

Design: A randomized crossover trial administering tailored lifestyle advice and generic dietary advice, each 12 weeks, with a four-week washout period between.

Methods: Sixty participants (aged 12–29) were included. Tailoring was achieved through the PROfeel method. Dietary guidelines were conceptualized by the Netherlands Nutrition Centre. Questionnaires were used pre–post-interventions to measure primary outcome 'fatigue severity' (Checklist Individual Strength-8) and secondary outcomes 'self-efficacy' (Self-Efficacy Scale-28) and 'quality of life' (QoL) (Paediatric Quality of Life Inventory 4.0). Feasibility and adherence were self-rated on a scale of 1 to 10 (low to high). Linear mixed modelling was used to assess change over time, compare strategy effectiveness and study the impact of intervention order.

Results: Fatigue severity, self-efficacy and QoL regarding 'physical' and 'emotional' functioning improved significantly over time (all $p < .015$). The average improvement of the two QoL subscales was clinically relevant, as was the fatigue improvement in 20 out of 46 participants who completed the trial and 5 dropouts. The interventions

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were equally effective, and intervention order did not impact the improvement level (p_{range} = .242–.984). The self-management strategies received similar feasibility (M = 6.45, SD = 1.91) and adherence (M = 7.67, SD = 1.67) ratings.
Conclusions: As small to clinically relevant improvements were observed, self-management strategies might be particularly useful to bridge waiting time for guided treatments such as Cognitive Behavioural Therapy.

KEYWORDS
chronic fatigue syndrome, diet, fatigue, juvenile idiopathic arthritis, lifestyle, q fever, self-management

INTRODUCTION

Fatigue is defined as 'extreme tiredness resulting from physical or mental exertion or illness' (Thomas, 2018). When fatigue is unresolved by rest and becomes persistent over time, the consequences for daily functioning and quality of life can be debilitating (Thomas, 2018). This has been observed in children and adolescents with a chronic condition, in which fatigue has been associated with impaired physical, social and academic functioning as well as lower mental well-being (Nap-van der Vlist, Dalmeijer, et al., 2021). Fatigue is four times more prevalent among children and adolescents with a chronic condition as compared to healthy peers (der Vlist et al., 2019). Fatigue, however, is not entirely explained by disease-related factors (e.g., pathophysiology, symptoms, disease severity, treatment, complications) as it is often observed in patients with diseases in remission (der Vlist et al., 2019; Nap-van der Vlist, Dalmeijer, et al., 2021). Fatigue is present across all age, sex and disease groups (der Vlist et al., 2019; Nap-van der Vlist, Dalmeijer, et al., 2021). Overall, fatigue is considered a generic symptom in chronic conditions, rather than a disease-specific one (der Vlist et al., 2019; Nap-van der Vlist, Dalmeijer, et al., 2021; Vroegindeweij et al., 2023).

The initial onset of fatigue can often be traced to a biological origin, such as an infection. Subsequently, post-infection fatigue syndromes have been identified. Examples are Q fever Fatigue Syndrome (QFS) after infection with *Coxiella burnetii* (Keijmel et al., 2013; Parker et al., 2006; Raijmakers et al., 2019) and post-COVID-19 condition (PCC; also known as long COVID) after infection with SARS-CoV-2 (Brodin et al., 2022; Islam et al., 2020; Kuut et al., 2023). Both are long-term and debilitating manifestations that became apparent after major outbreaks (Islam et al., 2020; Keijmel et al., 2013; Kuut et al., 2023; Raijmakers et al., 2019). For Q fever, the largest outbreak ever reported was in the Netherlands between 2007 and 2010 (Keijmel et al., 2013; Raijmakers et al., 2019). For COVID-19, the outbreak started near the end of 2019 and is still ongoing globally (Kuut et al., 2023). As symptoms of a Q fever infection are generally non-specific, a QFS diagnosis is often missed and rarely reported – especially during childhood and up to adolescence (Maltezou & Raoult, 2002; Parker et al., 2006). Despite the global impact of COVID-19, the disease burden for adolescents was considered limited initially but reports of persistent symptoms are now emerging (Brodin et al., 2022; Lopez-Leon et al., 2022). Patients with post-infection fatigue syndromes regularly meet the *Centers for Disease Control and Prevention* (CDC) criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) (Hickie et al., 2006), characterized by debilitating fatigue for over six months, unrefreshing sleep, post-exertional malaise, cognitive impairment or orthostatic intolerance and other symptoms (Afari & Buchwald, 2003; Hickie et al., 2006; Nijhof et al., 2012; Noor et al., 2021). Hence, they often receive the ME/CFS diagnosis and its recommended treatment.

Aside from infectious triggers, various other biological causes for persistent fatigue have been hypothesised in ME/CFS research. Studies have investigated, among others, endocrine abnormalities, microbiome disruptions and intracellular dysfunctions (Afari & Buchwald, 2003; Noor et al., 2021). Some

assume that ME/CFS is an autoimmune-like disease with various subtypes in which the immune response plays a part in the pathogenesis (Kerr, 2019). In accordance, persistent fatigue occurs frequently among adolescent patients with an autoimmune disease. In Juvenile Idiopathic Arthritis (JIA), for instance, 25% of the patients report severe fatigue (Nijhof et al., 2016). Therefore, fatigue has become a major topic of the national JIA Research Agenda established collectively by JIA patients, their parents and healthcare professionals (Verwoerd et al., 2021).

Different treatment strategies for persistent fatigue have been investigated, such as pharmaceutical therapies, alternative medicine, graded exercise therapy, acceptance and commitment therapy, psychoeducation therapy and self-management strategies (Castro-Marrero et al., 2017; Friedberg et al., 2013; Noor et al., 2021; Rowe, 2023). Thus far with mixed results (Castro-Marrero et al., 2017; Noor et al., 2021; Rowe, 2023). No curative treatment has been identified that works for all patients. Yet, treatments focusing on health behaviour can be important to improve overall health and quality of life (Middleton et al., 2013). Increasing moderate exercise, for example, has been shown to improve fatigue severity, quality of sleep, physical functioning and health perception in some patients (Noor et al., 2021). There is also some evidence for a dietary approach, based on an established relationship between the gut microbiome and fatigue (Newberry et al., 2018). The relationship implies that adopting a healthier diet leads to positive changes in the gut microbiome and hence reduce fatigue. In one study of children with various chronic conditions, a nutrient-rich diet has indeed been found effective in reducing persistent fatigue symptoms (Steenbruggen et al., 2015). A systematic review concluded that healthier diets (e.g., with higher intake of fruits and vegetables, whole grain products and other foods) were associated with better health-related quality of life in adolescents with chronic conditions (Wu et al., 2019). However, due to varying study designs and inconsistent findings it is difficult to determine the overall impact of dietary approaches (Noor et al., 2021).

Some of the most effective treatments to alleviate symptoms are based on Cognitive Behavioural Therapy (CBT) (Nijhof et al., 2012; Thomas, 2018). The basis of CBT revolves around cognitive restructuring of unhelpful thoughts about fatigue-related factors (e.g., physical activity, sleep patterns, affect and social support), behavioural activation to regain daily functioning, stressor exposure to reduce stress responses and learning strategies to cope with fatigue-related problems (Malouff et al., 2008; Nijhof et al., 2012; Wenzel, 2017). Despite the extent of the treatment, CBT is not effective in all patients. Of patients with ME/CFS, between 33% and 73% are no longer clinically fatigued after CBT at the latest follow-up (Malouff et al., 2008). In adolescent patients specifically, a recovery percentage of 64% has been reported with internet-based CBT (Nijhof et al., 2012, 2013). The first RCT in adults with PCC indicated a recovery percentage of 63% after CBT (Kuut et al., 2023). In adults with QFS, CBT tends to be less effective (Keijmel et al., 2013; Raijmakers et al., 2019). In younger patients with QFS, research on treatment effectivity is yet to be conducted.

The patient population suffering from persistent fatigue is heterogeneous (der Vlist et al., 2019; Nap-van der Vlist, Dalmeijer, et al., 2021; Noor et al., 2021). To explain who benefits from treatment, studies have focused on identifying predictors of treatment success and found a variety of important factors such as disease duration, symptom severity, self-efficacy levels, frustration levels in response to fatigue, physical activity levels and cognitive behavioural factors perpetuating fatigue (Janse et al., 2019; Prins et al., 2002; Schreurs et al., 2011). Therefore, studies have advocated that treatments should be tailored to the patient's needs (Noor et al., 2021; Vroegindeweij et al., 2023; Worm-Smeitink et al., 2021). To do so, researchers have referred to the biopsychosocial model of fatigue which states that persistent fatigue is the result of an interaction between biological, psychological and social factors (Armbrust et al., 2016; der Vlist et al., 2019; Geenen & Dures, 2019; Kusnanto et al., 2018; Nap-van der Vlist, Dalmeijer, et al., 2021; Noor et al., 2021; Vroegindeweij et al., 2023). Each factor triggers, maintains or protects against the fatigue and these reciprocal relationships vary from individual to individual (Kusnanto et al., 2018; Nap-van der Vlist, Dalmeijer, et al., 2021; Nap-van der Vlist, Houtveen, et al., 2021; Noor et al., 2021; Vroegindeweij et al., 2023; Worm-Smeitink et al., 2021). By designing treatment with respect to the biopsychosocial model, all factors perpetuating fatigue may be addressed, thereby improving treatment effectivity (Noor et al., 2021; Vroegindeweij et al., 2023).

In this randomized crossover trial, we used the biopsychosocial model to design tailored lifestyle advice named PROfeel. Realizing that treatments by specialized healthcare providers such as CBT have long wait lists, we decided to implement the advice as a self-management strategy that could potentially be used during waiting time. The aim is to study whether persistently fatigued adolescents and young adults (AYA) with QFS, ME/CFS, PCC and JIA can benefit from tailored lifestyle advice as self-management strategy, and if it is more effective than using a generic dietary advice as conceptualized by the Netherlands Nutrition Centre (Brink et al., 2019). We expected that improvement could be achieved in all four subgroups and that the tailored PROfeel lifestyle advice would be more effective due to its tailoring to individual-specific factors. We expected that the order of the interventions would not be significantly relevant to the level of observed improvement.

METHOD

Study design

This open-label randomized crossover trial is part of a larger research effort on QFS in AYA, conducted at the Wilhelmina's Children Hospital, an academic hospital unit of University Medical Centre Utrecht, the Netherlands. The call for this study was initiated by patient association Q-Support (https://www.q-support.nu). The study received Institutional Review Board (IRB) approval by UMC Utrecht (reference number 20-166). A protocol paper of the entire research project is available in which readers will find that biological assessments and a multiple single-case design were embedded in the randomized crossover trial (Vroegindeweij et al., 2022). The current study focuses on the group-level data from the randomized crossover trial only.

Participants

Participants were recruited through screening by a paediatrician, which consisted of a medical check-up and psychoeducation on the biopsychosocial model of fatigue, from October 2020 to April 2022. Participants in the study were adolescents and young adults. Note that a variety of age ranges are used in literature to define these developmental stages (Branje et al., 2021; Konstam, 2007). In this study, eligible participants were 12–29 years old and able to speak and write in Dutch. Participants had to be diagnosed with QFS according to the Dutch guidelines, JIA according to the International League of Associations for Rheumatology (ILAR) classification or ME/CFS according to the CDC criteria (Vroegindeweij et al., 2022). A biological trigger could not always be identified for ME/CFS. Participants with PCC had to meet the ME/CFS CDC criteria combined with seropositivity for the SARS-CoV-2 virus (Vroegindeweij et al., 2022). Fatigue had to be severe at the time of screening, as expressed by a total score of >39 on the Checklist Individual Strength (CIS)-8 questionnaire (range 8–56) in participants with QFS, ME/CFS or PCC (Worm-Smeitink et al., 2017). In JIA, total scores of >34 indicate severe fatigue similar to the levels observed in chronic fatigue syndromes (Hewlett et al., 2011). Participants were excluded if they had an acute or chronic infection, an inflammatory disease flare-up or any concomitant diagnosis that could explain fatigue during screening and required treatment accordingly. Participants were required to complete Experience Sampling Methodology (ESM) surveys on their smartphone throughout 4 weeks to complete inclusion, preferably with ≥70% compliance. The ESM data were later used as input for the tailored PROfeel lifestyle advice (see section Interventions). For an overview of all inclusion and exclusion criteria, we refer to the protocol paper (Vroegindeweij et al., 2022).

Participants provided written informed consent before inclusion. When participants were younger than 16, their legal guardian(s) also provided written informed consent.

Procedures

The study consisted of five visits. At baseline (T0), baseline questionnaires would be completed, and ESM surveys would start. If participant-candidates completed the four weeks of ESM surveys with sufficient compliance, inclusion would become official. After the four ESM weeks, the randomisation visit (T1) would take place in which participants were randomly assigned to the 'lifestyle advice first' or the 'dietary advice first' group using computer-generated concealed block randomisation (1:1). Up till this moment, both the participants and the researcher (AV) were blinded to allocation. Researcher (AV) unblinded the participants and provided them with the information needed to adhere to their first self-management strategy. Participants adhered for 12 weeks. They were expected to adhere independently, without additional interventions or supervision from healthcare professionals. Afterwards, post-intervention I visit (T2) took place. This visit marked the start of a washout period of four weeks. At the pre-intervention II visit (T3), researcher (AV) provided the information needed to adhere to the second self-management strategy. Again, participants adhered for 12 weeks independently. Participation was wrapped-up during the post-intervention II visit (T4). Participants could start with CBT almost immediately afterwards if required. From T0 to T4, the trial lasted 32 weeks.

Interventions

To derive the tailored lifestyle advice for each participant, we used a process called 'PROfeel' (Nap-van der Vlist, Houtveen, et al., 2021; Vroegindeweij et al., 2022). Its feasibility has been demonstrated before in persistently fatigued adolescents with a chronic condition (Nap-van der Vlist, Houtveen, et al., 2021). Per day, participants received 5 ESM survey prompts on their smartphone for 4 weeks. The ESM surveys were structured within the framework of the biopsychosocial model and consisted of fixed items on potentially fatigue-perpetuating biological, psychological or social factors (e.g., somatic symptoms, symptom-related behaviours, cognitions and feelings), to which participants could add a few personalized items of their choice (Vroegindeweij et al., 2022, 2023). Examples of items are: 'In the last 3 hours, I felt fatigued', 'In the last 3 hours, I felt happy' and 'In the last 3 hours, I was physically active'. Items were answered on a visual analogue scale ranging from 0 ('not at all') to 100 ('very much'). After completing the ESM period with sufficient compliance, descriptive and Residual Dynamic Structural Equation Modelling (RDSEM) analyses were performed by an independent statistician to derive an output report (Vroegindeweij et al., 2022, 2023). The researcher (AV) discussed the output report with the participant and used shared decision-making to formulate the tailored lifestyle advice. The advice could concern, for example, improving sleep hygiene, increasing or decreasing physical or social activity or working on mental health through exercises. Dietary advice was not part of the tailored lifestyle advice. Adherence reminders were prompted weekly through smartphone notifications (Vroegindeweij et al., 2022). More details of the PROfeel process, from ESM measurement and analyses to lifestyle advice examples, are available in the protocol paper and previously published work (Vroegindeweij et al., 2022, 2023).

The generic dietary advice was based on the healthy and sustainable food-based dietary guidelines from the Netherlands Nutrition Centre, which contains age and gender-specific guidelines (Brink et al., 2019). These guidelines are well-known in the Netherlands as the 'Wheel of Five', a national counselling model that helps consumers make more healthy dietary choices (Brink et al., 2019). At the start of their dietary intervention, participants completed the Eetscore™ tool. The Eetscore™ is a diet quality screener which assesses adherence to the dietary guidelines using the Dutch Healthy Diet-index 2015 (DHD15) (Looman et al., 2017), followed by a personalized dietary advise based on the screening results (de Rijk et al., 2022). For instance, participants were informed about their adherence regarding vegetable consumption. In cases where compliance was lacking, a subsequent explanation was provided which highlighted the health benefits of consuming vegetables, listed various vegetables and included practical advice for incorporating more vegetables into one's daily routine. During the intervention, participants could access the Eetscore™ tool to consult their advice. After finishing

the intervention, participants completed the Eetscore™ for a second time, enabling a progress report (de Rijk et al., 2022). Adherence reminders were prompted weekly through smartphone notifications (Vroegindeweij et al., 2022).

Outcomes

The primary outcome 'fatigue severity' and secondary outcomes 'self-efficacy' and 'quality of life' (QoL) were measured at T0-T4 on a computer.

Fatigue severity was measured with the CIS-8 questionnaire (Worm-Smeitink et al., 2017). The CIS-8 has good reliability and discriminative validity (Worm-Smeitink et al., 2017). CIS-8 total scores range from 8 to 56, with higher scores indicating more fatigue. Increases of ≥6 points indicate deterioration whereas decreases of ≥6 points indicate clinically relevant improvement (Worm-Smeitink et al., 2017).

Self-efficacy was defined as a sense of control over fatigue symptoms and was measured with the Self-Efficacy Scale-28 (SES-28) (Bleijenberg et al., 2001). The SES-28 has good internal consistency (Bleijenberg et al., 2001). Total scores range from 7 to 28, with higher scores reflecting higher sense of control (Bleijenberg et al., 2001). Increases of 2.4 points (i.e., ≥1 *SD*) were considered clinically relevant (Vroegindeweij et al., 2022).

QoL was measured with the Paediatric Quality of Life Inventory 4.0 Generic Score (PedsQL-GCS), which consists of the subscales physical, emotional, social and school or work functioning (Engelen et al., 2009; Varni et al., 2003). The PedsQL-GCS has good validity and reliability (Engelen et al., 2009; Varni et al., 2003). The total scores range from 0 to 100, with higher scores indicating higher QoL (Engelen et al., 2009; Varni et al., 2003). Clinically relevant changes on the four subscale scores were, respectively, ≥6.66, 8.94, 8.36 and 9.12 (Varni et al., 2003).

Adherence to the self-management strategies was measured weekly with the smartphone survey item 'On a scale of 1 (no adherence) to 10 (perfect adherence), I adhered to my advice…' between T1–T2 and T3–T4. Feasibility of the self-management strategies was measured with the item 'On a scale of 1 (low) to 10 (high), I rate the feasibility of the advice…' at T2 and T4.

To measure diet quality, the Eetscore™ was used pre-post dietary intervention. The Eetscore™ consists of 16 components (e.g., vegetables, fruits and nuts), each scored between 0 and 10, with higher scores indicating better diet quality (de Rijk et al., 2022). The sum of the component scores represents the overall diet quality score with a range of 0–160 (de Rijk et al., 2022). A difference of 14.5 points was considered the minimal detectable change, indicating true change (de Rijk et al., 2022). The original Eetscore™ was developed and validated for adults (>18 years old) (de Rijk et al., 2022). For the younger participants in this study, Wageningen University & Research simplified the language of the Eetscore™ and adapted the DHD15 according to the age-specific dietary guidelines provided by the Netherlands Nutrition Centre (de Rijk et al., 2022).

Other participant characteristics were collected at T0, such as age, sex, diagnosis, disease duration, the number and severity of other symptoms (e.g., pain VAS-scale), the level of sleep/rest problems (PedsQL Multidimensional Fatigue Scale; PedsQL-MFS) and the level of depression and anxiety symptoms (Revised Child Anxiety and Depression Scale; RCADS). All measurements can be found in the protocol paper (Vroegindeweij et al., 2022).

Statistical analyses

The target sample size to achieve 80% power was calculated a priori using G*Power version 3.1. The calculation was based on a repeated measures (M)ANCOVA (Vroegindeweij et al., 2022). With an alpha level of .05, repeated measures correlation of .23, and effect size of Cohen's $f = .50$, the sample size calculation yielded $n = 48$. Given an expected 20% dropout percentage our target sample was $N = 60$. All

input values were based on previous studies (Rowe, 2023). As we observed a higher dropout percentage (23.3%) and some data missing at random, we decided to change our analysis plan to linear mixed modelling to make optimal use of all available data.

Baseline characteristics of the total sample were derived with descriptive analyses ($N = 60$). Correlations between baseline characteristics and fatigue severity, self-efficacy and quality of life subscales were inspected and considered as covariates in the main analyses if $r > .70$. Next, *t*-test and chi-square tests were performed to compare baseline characteristics of participants randomized to the tailored PROfeel lifestyle advice first versus generic dietary advice first. *p*-values were adjusted for multiple testing using Bonferroni correction. Significant or trending differences would be considered as covariates again.

Linear mixed modelling with maximum likelihood estimation was used to assess change over time (T0, T2, T4) in fatigue severity, self-efficacy and the quality of life subscales. Inspection of the AICs and BICs showed that linear mixed modelling was warranted. The models included a random intercept across participants with a fixed slope. To compare the effectiveness of the tailored PROfeel lifestyle advice versus the generic dietary advice, we added a fixed contrast to each respective model (0 = baseline, 1 = lifestyle advice, −1 = diet advice). To evaluate the importance of intervention order, we added a fixed interaction between time and randomisation group (lifestyle advice first vs. diet advice first group). Based on previously described inspections, we added age and baseline levels of anxiety and depression symptoms, self-efficacy,[1] and sleep/rest problems as fixed covariates in all linear mixed models.

To evaluate the adherence to and feasibility of the self-management strategies, we computed the mean adherence and feasibility, as well as the pre–post-intervention mean differences on the overall diet quality score. Linear regression was used to examine associations between the levels of adherence, feasibility and overall diet quality change and the change in fatigue severity, self-efficacy and quality of life subscales at T2 and T4, whilst controlling for the covariates from previous analyses.

Analyses were performed in IBM SPSS Statistics 28.0.1. Data were plotted in Rstudio 4.2.2 using the package 'ggplot2'.

RESULTS

Trial completion

The total sample consisted of 60 participants. The first intervention was completed by 53 participants (88.33%). The second intervention was completed by 46 participants (76.67%). The study flow is presented in Figure 1.

Baseline characteristics

The total sample included 20 participants with QFS, 12 with ME/CFS, 8 with PCC and 20 with JIA. *Coxiella burnetii* seropositivity was observed among all participants with QFS, one participant with ME/CFS and three participants with PCC. The sample had relatively high levels of social phobia and major depression symptoms, and the total level of depression and anxiety levels was highly correlated to outcome measures of this study ($r > .70$). The patient groups differed significantly at baseline regarding age, disease/fatigue duration in years and fatigue severity (due to lower JIA inclusion cut-off). More details can be found in Table S1. After randomisation, only trend differences remained at baseline. The

[1]Except when self-efficacy was the dependent variable. By allowing random intercepts across participants, baseline self-efficacy levels were accounted for.

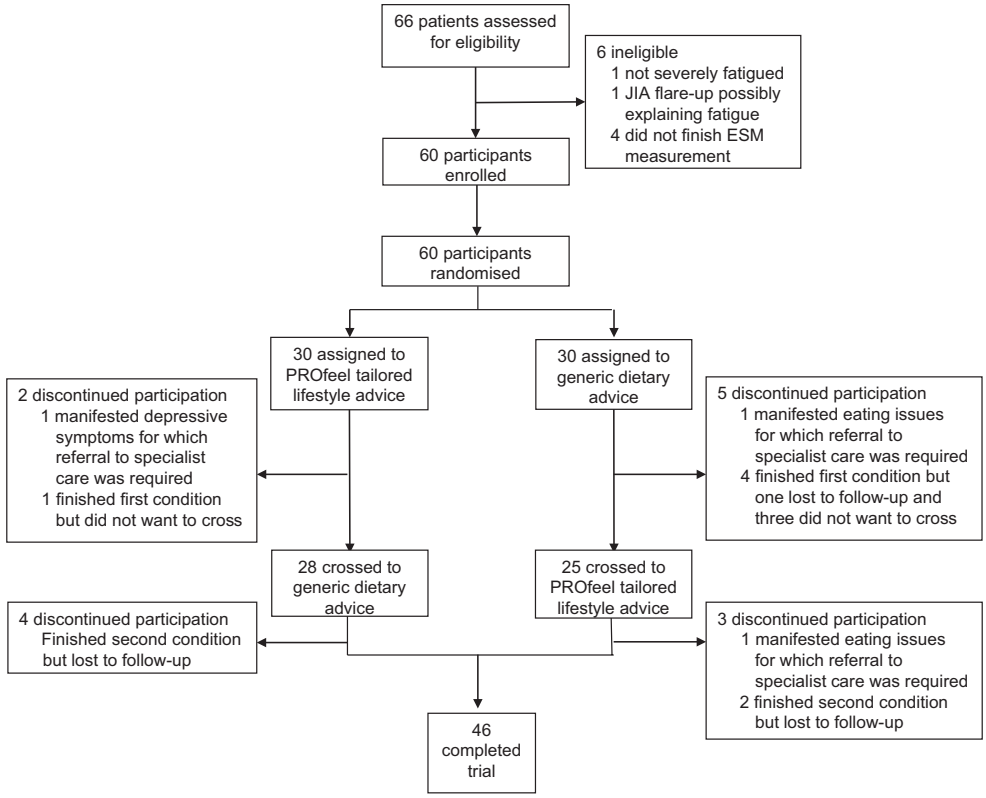

FIGURE 1 Study flow. ESM, experience sampling methodology.

participants in the 'tailored PROfeel lifestyle advice first' group tended to be older, with higher self-efficacy levels and less sleep/wake problems at baseline (see Table 1).

Study outcomes over time

Linear mixed modelling showed that fatigue severity improved significantly over time, $F(2, 89) = 8.36$, $p < .001$, as did self-efficacy, $F(2, 87) = 4.38$, $p = .015$. QoL subscales 'physical functioning', $F(2, 124) = 4.60$, $p = .012$ and 'emotional functioning', $F(2, 131) = 6.21$, $p = .003$ improved with clinical relevance. QoL subscales 'social functioning' and 'work/school functioning' did not improve significantly (respectively $p = .575$ and .106). The marginal R^2 was highest for 'emotional functioning' ($R^2 = .540$), followed by fatigue severity ($R^2 = .314$). The increased conditional R^2s support the modelling of random intercepts. For more details on the intercepts and the changes over time adjusted for covariates, see Table 2.

For a summary of the data's central tendency without adjustment for covariates, see Figure 2. Text is printed in bold if the average changed significantly compared to T0.

Tailored PROfeel lifestyle advice versus generic dietary advice

Linear mixed modelling showed no significant differences between the interventions regarding level of improvement (all $p > .999$) and no statistical relevance of intervention order ($p_{range} = .277$ to .831).

TABLE 1 Baseline characteristics of the total sample ($N = 60$).

Baseline	Mean (*SD*) or *n* (%)			Questionnaire	Observed
Characteristic	Lifestyle first ($n = 30$)	Diet first ($n = 30$)	*p*-Value	Min – Max	Min – Max
Age in years	19.93 (5.73)	17.09 (3.72)	.026[t]		12.00–29.00
Sex (female)	23 (76.67%)	29 (96.67%)	.105		
Disease duration in years	4.41 (3.85)	5.73 (4.68)	.242		.50–17.00
Fatigue duration in years	3.95 (3.71)	4.44 (3.88)	.622		.50–12.00
Cox. Bur.[a] seropositive	12 (40.00%)	12 (40.00%)	.825		
SARS-CoV-2[b] seropositive	9 (30.00%)	7 (23.33%)	.453		
Fatigue severity[c]	45.55 (6.42)	46.03 (5.79)	.762	8.00–56.00	35.00–56.00
Quality of life[d]					
Physical	51.19 (19.96)	50.86 (16.13)	.946	.00–100.00	6.25 – 93.75
Emotional	62.41 (21.37)	58.97 (18.43)	.513	.00–100.00	20.00–100.00
Social	71.38 (12.46)	69.10 (14.76)	.528	.00–100.00	5.00 – 100.00
School/work	47.59 (19.02)	51.21 (18.21)	.462	.00–100.00	15.00–100.00
Self-efficacy[e]	17.74 (2.40)	16.31 (2.29)	.026[t]	7.00–28.00	12.00–21.00
Fatigue symptoms[f]					
General	22.29 (3.87)	21.66 (3.80)	.537	.00–100.00	.00 – 70.83
Sleep/rest	40.33 (13.13)	49.28 (15.59)	.023[t]	.00–100.00	12.50–79.17
Cognitive	18.54 (5.41)	19.10 (5.01)	.682	.00–100.00	.00 – 95.83
Level of pain[g]	5.31 (2.77)	5.50 (3.28)	.818	.00–10.00	.00 – 10.00
Pain catastrophising[h]	24.52 (8.17)	29.41 (12.55)	.088	13.00–65.00	13.00–58.00
Anxiety/depression[i]	80.07 (17.88)	83.64 (19.22)	.479		
Generalized anxiety	9.67 (2.74)	9.18 (2.28)	.476	6.00–24.00	6.00 – 15.00
Separation anxiety	9.52 (2.29)	10.11 (3.21)	.405	7.00–28.00	7.00 – 18.00
Social phobia	17.93 (5.08)	19.71 (5.66)	.223	9.00–36.00	10.00–32.00
Panic disorder	13.74 (4.06)	14.71 (4.51)	.439	9.00–36.00	9.00 – 23.00
Obsessive-compulsive	8.52 (3.03)	9.00 (2.98)	.555	6.00–24.00	6.00 – 17.00
Major depression	20.70 (4.79)	20.93 (3.93)	.850	10.00–40.00	12.00–33.00
Overall diet quality[j]	98.04 (24.11)	94.74 (21.20)	.582	.00–160.00	53.00–154.00

Note: Bonferroni corrected *p*-value is significant if < .002 and [t]trending if between .002 and .05. *T*-tests and chi-square tests were used when appropriate.

[a]*Coxiella Burnetii*, an intracellular bacterium that causes acute Q fever infection which can develop into QFS (Keijmel et al., 2013; Parker et al., 2006; Raijmakers et al., 2019).

[b]Seropositive for acute SARS-CoV-2 infection (not for vaccination).

[c]Measured with the CIS-8, higher scores indicating higher fatigue severity.

[d]Measured with the PedsQL-GCS, higher scores indicating higher quality of life regarding physical functioning, emotional functioning, social functioning or school/work functioning.

[e]Measured with the SES-28, higher scores indicating higher control over fatigue symptoms.

[f]Measured with the PedsQL-MFS, higher scores indicating higher levels of general fatigue, sleep/rest issues or cognitive fatigue.

[g]Measured with a VAS, higher scores indicating higher level of pain.

[h]Measured with the PCS, higher scores indicating higher levels of pain catastrophising.

[i]Measured with the RCADS, higher scores indicating higher levels of generalized anxiety, separation anxiety, social phobia, panic disorder, obsessive-compulsive disorder or major depression disorder symptoms.

[j]Measured with the Eetscore, higher scores indicating a better overall diet quality.

TABLE 2 Linear mixed modelling results.

	Intercept		Change over time[a]	R^2	
Study outcome	Fixed estimate (*SE*)	Random variance (*SE*)	T0 to T4 (95% CI)	Marg.	Cond.
Fatigue severity	51.31 (8.63)	17.49 (5.44)	−4.14 (−6.87 to −1.41)*	.314	.799
Self-efficacy	20.57 (2.10)	2.69 (.75)	1.11 (.19 to 2.04)*	.149	.781
Physical QoL	43.45 (21.07)	56.12 (19.41)	7.43 (1.27 to 13.60)*	.205	.803
Emotional QoL	70.75 (13.96)	38.96 (17.79)	9.04 (3.21 to 14.87)*	.540	.830
Social QoL	73.97 (35.86)	55.22 (22.70)	−2.26 (−8.60 to 4.08)	.283	.750
Work/school QoL	84.12 (21.22)	21.76 (15.05)	1.14 (−5.07 to 7.35)	.173	.796

Abbreviations: 95% CI, 95% confidence interval; Cond., Conditional *R*-squared, measure reflecting the amount of explained variance in the study outcome by the fixed effects and random intercept together (Nakagawa & Schielzeth, 2013); Marg., Marginal *R*-squared, measure reflecting the amount of explained variance in the study outcome by the fixed effects (i.e., time slope and covariates) (Nakagawa & Schielzeth, 2013); QoL, Quality of Life; *SE*, standard error.

[a]Based on estimated marginal means (adjusted for covariates).

*Significant with $p < .05$.

Clinically relevant improvement of primary outcome

Fatigue improved with clinical relevance in 20 out of 46 participants (43.48%) who completed the trial and in 5 out of 11 dropouts (45.46%), thus in 43.86% in total. Fatigue deteriorated in 3 participants (6.52%). Figure 3 shows the frequency of clinical improvement in participants who completed the trial. Table S2 shows additional details on fatigue improvement per patient group.

Feasibility, adherence and observed diet quality change

On a scale of 1 (low) to 10 (high), participants rated the feasibility of the tailored PROfeel lifestyle advice with a 6.4 ($SD = 1.96$) and the generic dietary advice with a 6.5 ($SD = 1.86$). The average self-rated adherence to the self-management strategies was, respectively, 7.7 ($SD = 1.74$) and 7.63 ($SD = 1.59$). However, comparing the pre–post-intervention scores indicated that the overall diet quality level did not improve on average ($\Delta M = -10.30$, $SD = 20.84$) because participants tended to consume less whole-wheats products ($\Delta M = -1.49$, $SD = 3.41$) and nuts ($\Delta M = -1.90$, $SD = 4.00$), and more processed meats ($\Delta M = -1.36$, $SD = 3.86$) and unhealthy choices (e.g., high-sugar snacks) ($\Delta M = -1.04$, $SD = 3.91$). Overall diet quality levels decreased in 30 participants ($\Delta M = -19.36$, $SD = 18.48$), were stable in 2 participants and improved in 14 participants ($\Delta M = 9.79$, $SD = 7.50$).

The distributions of the self-ratings and overall diet quality change can be found in the Supporting Information. Levels of feasibility, adherence or overall diet quality change were not associated with change in fatigue severity, self-efficacy or quality of life subscales at T2 and T4 ($p_{range} = .052–.943$).

DISCUSSION

This randomized crossover trial of 32 weeks investigated the potential use of two self-management intervention strategies for persistent fatigue in AYA with a (post-infection) fatigue syndrome (QFS, ME/CFS and PCC) or rheumatic condition (JIA). Overall, we observed small to clinically relevant improvements in fatigue severity, self-efficacy and quality of life subscales. Clinically relevant improvement of fatigue was observed in almost half of the participants and present in all four patient groups. No significant differences between the effectiveness of the tailored PROfeel lifestyle advice and generic dietary

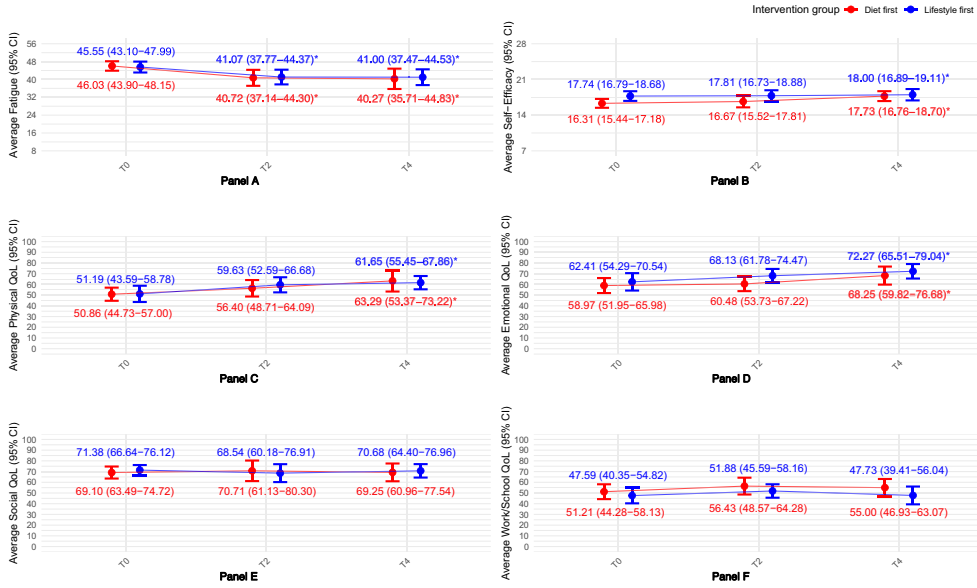

FIGURE 2 The study outcomes over time expressed in average with 95% CI. *Note*: Printed in text are the study outcome averages with 95% CI. Averages are not adjusted for covariates. The text is printed in bold if the average significantly changed compared to baseline (*$p < .05$). There were no significant differences between the intervention groups at T0, T2 or T4 (red = diet-first group; blue = lifestyle-first group). Panel A = fatigue severity, Panel B = self-efficacy, Panels C through F = Quality of Life (QoL) subscales physical functioning, emotional functioning, social functioning and work/school functioning.

advice were found. Intervention order was irrelevant to the observed level of improvement. Participants rated the feasibility and the adherence to each strategy similarly.

In line with previous research (Noor et al., 2021), the findings of the current study suggest that self-management interventions may be effective in reducing fatigue. Fatigue severity improved with clinical relevance in 43.5% of participants who finished the crossover trial, with 14 participants at T2 and 6 participants at T4 showing improvement. Twelve participants sustained their T2 improvement throughout the trial. Fatigue severity also improved in 5 out of 11 participants who dropped out, which was the main reason for not wanting to crossover. Ultimately, fatigue severity improved most frequently in the ME/CFS group (70%) and least in the QFS group (26.70%), which parallels results from CBT trial in adults with QFS (Keijmel et al., 2013; Kuut et al., 2023; Nijhof et al., 2012; Raijmakers et al., 2019). In the current study, the smaller improvement may be due to baseline differences between the groups. The QFS group was notably older, with longer fatigue duration. The QFS group also reported more general fatigue issues, suggesting greater fatigue-related impairment. Older age, longer disease duration, and more severe fatigue are typically associated with a less favourable treatment outcome (Afari & Buchwald, 2003; Thomas, 2018). We could not conduct analyses between patient groups in this study, given their small size and limited statistical power, but considering the baseline differences it is possible that relatively younger patients with shorter fatigue duration and less fatigue-related impairment benefit more from self-management strategies.

We expected the PROfeel lifestyle advice to outperform the generic dietary advice, by tailoring it to individual-specific factors, but found no significant differences between the two self-management strategies. The findings align with the 'Dodo Bird Verdict', which suggests that all therapies have comparable effects (Cuijpers, 2023; Cuijpers et al., 2019). To explain the Dodo Bird Verdict, theoretical models address factors that therapies have in common, such as time, and non-specific or contextual factors (e.g., a rationale that provides credibility to the delivered treatment or the patient's own expectations) (Cuijpers et al., 2019; Frank & Frank, 1993; Wampold, 2015). Those factors can also be

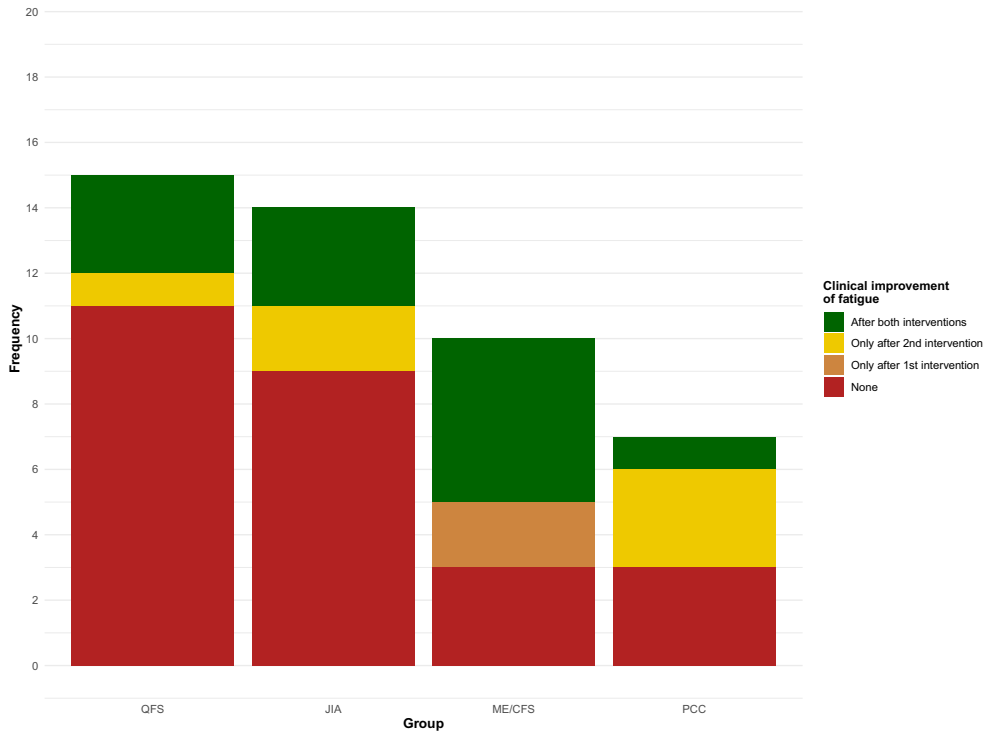

FIGURE 3 Clinically relevant improvement of fatigue throughout the study. *Note*: Clinically relevant improvement of fatigue was defined as decreases of ≥6 points on the CIS-8 total score compared to baseline. All 46 participants who completed the randomized crossover trial are presented. There were no significant frequency differences regarding clinically relevant improvement across subgroups (Kruskal-Wallis $H = 4.34$, $p = .227$). JIA, Juvenile Idiopathic Arthritis; ME/CFS, Myalgic Encephalomyelitis/Chronic Fatigue Syndrome; PCC, post-COVID-19 condition; QFS, Q fever Fatigue Syndrome.

relevant to the self-management strategies. Alternatively, the self-management strategies were equally effective because they both successfully focused on one area of life, which in time carried over to other areas (Cuijpers et al., 2019; DeRubeis et al., 2005). Then, the observed improvements in self-efficacy and quality of life subscales at T4 were rather the result of fatigue improvement at T2, rendering the second intervention redundant. However, it should be noted that there was a four-month period between T2 and T4 (i.e., four-week washout period followed by twelve weeks of self-management). The time gap makes it less likely that all observed improvements are the result of only the first self-management strategy. It is more likely that recontinued use of any self-management strategy (i.e., Dodo Bird Verdict) allowed improvements to build over time, which suggests that recontinued use of the first sel—management strategy could have led to the same level of improvement as observed in the current study. That would also explain why the intervention order was irrelevant to the level of observed improvement at T4.

Thus far, the findings suggest that both self-management strategies could be used in clinical practice to improve persistent fatigue, self-efficacy and quality of life domains in AYA. With on average small to clinically relevant improvements, the self-management strategies could be useful to bridge waiting time for more intensive treatments such as CBT. However, several limitations should be considered. First, inclusion was withdrawn in two participants because maladaptive preoccupations with healthy eating manifested after introduction to the dietary guidelines of the Netherlands Nutrition Centre. This may be an important indication that dietary advice is not suitable as self-management strategy for all patients. Second, the crossover trial lasted 32 weeks. Natural recovery is always possible in a longer time span. However, in our sample the average disease duration was 4.41 years (lifestyle-first

group) and 5.73 years (diet-first group), and natural recovery becomes less likely with longer disease duration. Moreover, the quality of life subscales 'physical functioning' and 'emotional functioning' improved with clinical relevance on average, as did fatigue severity in a larger number of patients than we would expect if the improvements were merely the effect of time. Third, it is possible that the observed improvements were partially the result of psychoeducation on the biopsychosocial model of fatigue during the paediatrician's screening, or through gained self-awareness during the ESM data collection, as such effects have been reported before (Noor et al., 2021; Schellekens et al., 2021). Fourth, the study had a higher dropout rate than anticipated (23.3% instead of 20%) and some data missing at random. Consequently, the study was slightly underpowered when using the original statistical analysis plan (Vroegindeweij et al., 2022). We switched to linear mixed modelling to make optimal use of the collected data, but it is still possible that some effects are overlooked or misinterpreted due to narrower statistical power.

The final limitation concerns the feasibility and adherence ratings of the self-management strategies. Both elements are a frequently reported limitation of interventions targeting health behaviour (Deslippe et al., 2023; Middleton et al., 2013). On a scale of 1 (low) to 10 (high), participants rated the feasibility of the tailored PROfeel lifestyle advice and generic dietary advice with scores of, respectively, 6.4 and 6.5 and explained that the self-management aspect could be challenging. The self-rated adherence was, respectively, 7.7 and 7.6, but despite relatively high adherence, the overall diet quality did not reach a true positive change on average. A true change would be expected given that healthier diets are associated to better quality of life regarding 'physical functioning' and 'emotional functioning' (Wu et al., 2019). Yet, in this study, levels of diet quality change were not significantly related to improvement on the study outcomes. Perhaps participants estimated their diet quality too positively before introduction to the dietary guidelines, leading to biased diet quality change scores after the intervention. Then, one might expect that the level of adherence could be related to the level of improvement on the outcome measures, but that was also not that case in this study.

Altogether, the limitations raise the question whether the self-management strategies impact fatigue severity, self-efficacy and quality of life directly, or rather indirectly through non-specific and contextual treatment effects (Cuijpers, 2023; Cuijpers et al., 2019; DeRubeis et al., 2005; Frank & Frank, 1993; Wampold, 2015) that we are not yet aware of. It is important to understand through which mechanisms a treatment works to apply it adequately in clinical practice. However, much like the biopsychosocial model of fatigue (Vroegindeweij et al., 2023), it is possible that the working mechanisms differ from individual to individual – especially with tailored treatment. The large amount of explained variance by allowing random intercepts in this study also hints at the importance of individual differences. With a randomized crossover design it is difficult to investigate those. Therefore, we embedded a multiple single-case design within the randomized crossover trial in which we collected intensive longitudinal data that might increase our understanding of the self-management working mechanisms per individual. Our future research will focus on this. More information can be found in the protocol paper (Vroegindeweij et al., 2022).

Finally, this study shows that continued research on the treatment of persistent fatigue in AYA is vital. It is the first randomized crossover trial including AYA with QFS. Yet, clinical improvement of fatigue was least observed in this group. Discussing treatment experiences with patients may help to gain a picture of which elements should be adjusted to improve treatment outcome. Not only in AYA with QFS, but with ME/CFS, PCC or JIA as well, viewing persistent fatigue as a generic symptom rather than a disease-specific one (der Vlist et al., 2019; Nap-van der Vlist, Dalmeijer, et al., 2021; Vroegindeweij et al., 2023). The findings of this study suggest that using self-management strategies during waiting list time for treatments such as CBT might be valuable. Yet, more research is needed to attribute all the observed improvements to the self-management strategies. Ways to improve the feasibility and adherence should be evaluated, and ultimately, it should be studied whether a stepped-care model (self-management followed by CBT) is more effective than only CBT.

To conclude, small to clinically relevant improvements in fatigue severity, self-efficacy and quality of life regarding physical and emotional functioning were observed in this randomized crossover trial.

The results are promising and suggest that adolescents and young adults with persistent fatigue may benefit from tailored PROfeel lifestyle advice or generic dietary advice as self-management strategy. More research on self-management strategies should lead to informed treatment recommendations for persistent fatigue.

AUTHOR CONTRIBUTIONS

Anouk Vroegindeweij: Investigation; writing – original draft; formal analysis; methodology; data curation; visualization. **Nico M. Wulffraat:** Conceptualization; funding acquisition; methodology; writing – review and editing; supervision. **Elise M. Van De Putte:** Conceptualization; funding acquisition; methodology; writing – review and editing; supervision. **Hanne B. T. De Jong:** Writing – review and editing; methodology; resources. **Desiree A. Lucassen:** Methodology; writing – review and editing; resources. **Joost F. Swart:** Conceptualization; funding acquisition; methodology; validation; writing – review and editing; supervision. **Sanne L. Nijhof:** Conceptualization; funding acquisition; methodology; validation; writing – review and editing; supervision.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to report.

DATA AVAILABILITY STATEMENT

With publication, all data collected in the present study will be made available to others upon reasonable request, including (deidentified) individual participant data and a data dictionary defining each field in the data set. Requests should be directed to both JFS (j.f.swart@umcutrecht.nl) and SLN (s.l.nijhof@umcutrecht.nl). The data will be shared after approval of a proposal, with a signed data access agreement.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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