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ARTICLE

Individual outcomes after tailored versus generic self-management strategies for persistent fatigue in youth with a fatigue syndrome or rheumatic condition: A multiple single-case study

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Abstract

Objective: To examine individual outcomes after tailored lifestyle (PROfeel) or generic dietary advice as self-management intervention for persistent fatigue in adolescents and young adults with a chronic condition, to compare participants who did and did not benefit and to explore changes to factors in the biopsychosocial model of fatigue after PROfeel.

Method: A multiple single-case AB-phase design was embedded in a randomized crossover trial ($N = 45$). Intensive longitudinal data (ILD) on outcomes 'fatigue severity', 'self-efficacy' and 'quality of life' (QoL) were collected through weekly smartphone measurement for 20 weeks. ILD on biopsychosocial factors were collected through experience sampling methodology for 28 days pre-post first intervention. Baseline characteristics were compared with *t*-tests and chi-square tests. Permutation distancing tests were used to assess change over time in all ILD.

Results: Regarding weekly measurements, nineteen participants (42.22%) showed small to large positive outcomes ($d_{range} = .05$ to 2.59), mostly after PROfeel. Eleven participants (24.44%) showed small to moderate negative outcomes ($d_{range} = -.02$ to -2.46), mostly after dietary advice. Fatigue severity improved most, followed by self-efficacy. Participants who benefitted showed higher QoL levels and

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lower fatigue and pain levels compared with others at baseline (all $p < .02$). When positive outcomes were observed after PROfeel, typically ≥1 biopsychosocial factor had been targeted successfully.

Conclusion: Self-management advice has more potential when tailored to individual characteristics, including the biopsychosocial model of fatigue. PROfeel appears particularly useful as fatigue intervention for individuals with relatively less severe symptoms.

KEYWORDS

adolescents, diet, experience sampling methodology, lifestyle, persistent fatigue, personalized medicine

INTRODUCTION

Persistent fatigue can be defined as excessive tiredness that typically lasts for at least six months (Thomas, 2018; Viner et al., 2008). Unlike the normal tiredness that most people experience from time to time, persistent fatigue is not relieved by rest (Higson-Sweeney et al., 2022). It is often a complex and poorly understood symptom in various chronic health conditions (Higson-Sweeney et al., 2022) which can persist despite low or absent disease activity (der Vlist et al., 2019). Persistent fatigue can be detrimental to the individual's functioning in daily life and can reduce their quality of life (Armbrust, Lelieveld, et al., 2016; der Vlist et al., 2019; Higson-Sweeney et al., 2022; Lamers et al., 2013; Scheeres et al., 2009; Thomas, 2018; Viner et al., 2008). In adolescents, persistent fatigue has also been associated with impaired social development and lower school performances and attendance (der Vlist et al., 2019; Higson-Sweeney et al., 2022). These adverse outcomes in adolescence can hinder further development in young adulthood, a life stage spanning the age of 18 to early 30's, characterized by identity development, establishing relationships and pursuing educational and career goals (Konstam, 2007). To minimize long-term consequences, it is important to treat persistent fatigue as early and effectively as possible.

There is a growing literature on treatment of persistent fatigue, especially in adolescents and adults with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) (Higson-Sweeney et al., 2022; Malouff et al., 2008; Noor et al., 2021), but also in people suffering from persistent fatigue after infection with for example Coxiella burnetii (Q fever) or COVID-19 (Islam et al., 2020; Koc et al., 2022; Raijmakers et al., 2019), in people with a rheumatic condition (Kant-Smits et al., 2021; Nijhof et al., 2023), in those who survived cancer (Higson-Sweeney et al., 2022; Schellekens et al., 2021), or who have a diagnosis such as fibromyalgia or irritable bowel syndrome (Aman et al., 2018; Higson-Sweeney et al., 2022). Thus far, no curative treatment has been developed. Therefore, treatment focuses on alleviating persistent fatigue and its' impact on daily life (Noor et al., 2021). Nonpharmacological interventions for adolescents often focus on psychoeducation, cognitive behavioural therapy (CBT) and/or physical activity (Higson-Sweeney et al., 2022). Several of these interventions show promising results, but none of these treatments work for every individual (Higson-Sweeney et al., 2022; Noor et al., 2021). Regarding CBT, for example, one out of three adolescents with ME/CFS shows no clinical improvement directly after treatment (Nijhof et al., 2012). To understand this better, studies have focused on identifying predictors of treatment success. Several predictors have been found, such as lower fatigue severity and/or higher levels of physical activity at the start of treatment, shorter symptom or disease duration, higher sense of control over symptoms (i.e., self-efficacy) and lower levels of frustration in response to fatigue (Janse et al., 2019; Prins et al., 2002; Schreurs et al., 2011). Pain severity has been associated with fatigue severity in some studies and identified as a treatment success predictor in others (Nijs et al., 2012). Which

cognitive behavioural factors perpetuate fatigue can be an important predictor of treatment success as well (Schreurs et al., 2011). Considering the heterogeneity of the population suffering from persistent fatigue and the variety in treatment success predictors, studies have advocated personalized or tailored treatment of persistent fatigue (Geenen & Dures, 2019; Schellekens et al., 2021; Vroegindeweij, Levelt, et al., 2023; Worm-Smeitink et al., 2021).

In tailored treatment, persistent fatigue can be addressed as a complex phenomenon resulting from a variety of multifaceted processes that differ across individuals and time (Armbrust, Siers, et al., 2016; Higson-Sweeney et al., 2022; Hulme et al., 2017; Vroegindeweij, Levelt, et al., 2023). The biopsychosocial model of fatigue is one way to conceptualize the complexity, and it states that persistent fatigue is the outcome of an interaction between risk factors, perpetuating factors, and protective factors that can be categorized in biological, psychological or social domains (Bolton & Gillett, 2019; Geenen & Dures, 2019; Vroegindeweij, Levelt, et al., 2023; Wade & Halligan, 2017). A systematic review on risk factors for persistent fatigue has documented a large heterogeneity in involved biopsychosocial factors across adolescents and (young) adults with post-infection fatigue (Hulme et al., 2017). The level of distress and fatigue during acute infection were common risk factors (Hulme et al., 2017). Other potential risk factors were identified in several domains, including the biological, behavioural, cognitive, emotional and social domain (Hulme et al., 2017). In a preceding article, we also identified a large heterogeneity in perpetuating and protective biopsychosocial factors across adolescents and young adults (AYA) with a (post-infection) chronic fatigue syndrome or rheumatic condition – suggesting there are many ways to tailor treatment to the needs of an individual patient (Vroegindeweij, Levelt, et al., 2023). An illustration of the biopsychosocial model of fatigue, including examples of factors, is presented in Figure 1.

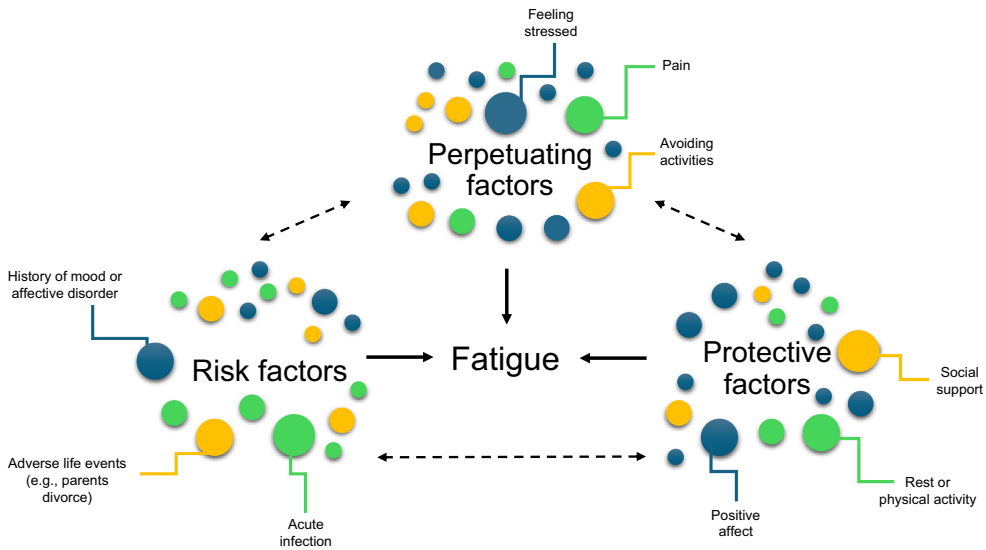

FIGURE 1 Illustration of the biopsychosocial model of fatigue. This figure illustrates the biopsychosocial model of fatigue as used in the current study, in which biological (green), psychological (blue) and social (yellow) factors can be risk factors, perpetuating factors or protective factors of fatigue. The figure provides a few examples of the factors identified or described in the literature (Armbrust, Siers, et al., 2016; Bolton & Gillett, 2019; Geenen & Dures, 2019; Hulme et al., 2017; Vroegindeweij, Levelt, et al., 2023; Wade & Halligan, 2017). Not all individuals have the same factors included in their biopsychosocial model of fatigue, and if they do share a similar factor, they may differ in terms of which role they play (e.g., risk, perpetuating, protective) (Armbrust, Siers, et al., 2016; Bolton & Gillett, 2019; Geenen & Dures, 2019; Hulme et al., 2017; Vroegindeweij, Levelt, et al., 2023; Wade & Halligan, 2017). The factors, or their relationship with fatigue, may also change within persons over time (Armbrust, Siers, et al., 2016; Geenen & Dures, 2019; Hulme et al., 2017; Vroegindeweij, Levelt, et al., 2023; Wade & Halligan, 2017). Therefore, the biopsychosocial model can be used to study the dynamics of fatigue.

The AYA from our preceding article were diagnosed with ME/CFS, Q fever Fatigue Syndrome (QFS), post-COVID-19 condition (PCC) or Juvenile Idiopathic Arthritis (JIA) and participated in a randomized crossover trial (RCT) in which they were assigned to self-management intervention strategies targeting persistent fatigue. This was a lifestyle advice tailored to the participant's biopsychosocial model of fatigue through a method called PROfeel (Nap-van der Vlist, Houtveen, et al., 2021; Vroegindeweij et al., 2022) followed by a generic dietary advice or vice versa (Brink et al., 2019; Vroegindeweij et al., 2022). We expected the tailored PROfeel lifestyle advice to outperform the generic dietary advice due to its tailoring to individual-specific factors. Yet, on cross-sectional group-level, we observed similar improvements in fatigue severity, self-efficacy and aspects of quality of life across the two intervention groups (Vroegindeweij, Wulffraat, et al., 2023). The improvements were small, ranged in level of clinical relevancy and suggested that both self-management strategies could be used effectively and interchangeably in any patient, particularly to bridge waiting list time of more intensive treatments (Vroegindeweij, Wulffraat, et al., 2023).

However, the discussion of the findings raised, among others, two questions. First, whether the intervention strategies can truly be used in *any* AYA suffering from persistent fatigue. Second, to what extent the intervention strategies make direct and indirect impact. With direct impact, patients benefit from the active treatment ingredients of the intervention. Yet, patients may also benefit from indirect processes through contextual or non-specific effects (Cuijpers, 2022; Cuijpers et al., 2019; Wampold, 2015). These are factors contributing to the overall effectiveness of the intervention, despite not being the specific active ingredients – for example when the expectation of the patient plays a role in treatment outcome (Cuijpers, 2022; Cuijpers et al., 2019; Wampold, 2015). In the tailored PROfeel lifestyle advice, we assume that direct impact would be reflected through intended (targeted) changes to biopsychosocial factors related to fatigue, whereas indirect impact would be reflected through non-intended changes.

The current study builds on the RCT and investigates the questions mentioned above. Using single-case analyses, we will examine whether the self-management intervention strategies can be used in all individuals suffering from persistent fatigue. This will be done in two steps. First, we will derive individual intervention effect sizes on fatigue severity, self-efficacy and quality of life, using intensive longitudinal data (ILD). These data have been collected during the first half of the RCT and have not been analysed before. Second, we will compare the baseline characteristics of participants who improved after their intervention to those who did not. Doing so will identify potential predictors of self-management treatment success and non-success. To explore whether the assumed impact of the tailored PROfeel lifestyle advice is visible, we will assess pre–post intervention changes in the biopsychosocial factors related to fatigue (e.g., did the amount of daytime resting change as intended by the lifestyle advice). For this purpose, we collected ILD on biopsychosocial factors multiple times per day during four weeks before and after the intervention.

METHOD

Study background and ethics

The current study is part of a larger research effort at the Wilhelmina Children's Hospital, the paediatric hospital of University Medical Center Utrecht (UMC Utrecht) (Vroegindeweij et al., 2022). The research effort focuses on identifying fatigue interventions and disrupted biological factors in AYA with QFS, ME/CFS, PCC and JIA, using a RCT with a multiple single-case design and biological assessments embedded. More information can be found in the protocol paper (Vroegindeweij et al., 2022). The current study focuses on the ILD from the multiple single-case design. Institutional Review Board (IRB) approval was given by UMC Utrecht, reference number 20-166. All participants provided written informed consent before inclusion, as did legal guardians of participants younger than 16.

Participants

Patient associations and paediatricians informed eligible participants (aged 12–29) with a diagnosis of QFS, ME/CFS, PCC or JIA about the research effort. They were screened by a paediatrician at the Wilhelmina Children's Hospital if interested in participation. To be included, participants had to exhibit severe fatigue, defined as a Checklist Individual Strength (CIS)-8 total score of >39 in QFS, PCC and ME/CFS (Vroegindeweij et al., 2022; Worm-Smeitink et al., 2017) and of >34 in JIA (Hewlett et al., 2011; Vroegindeweij et al., 2022) during screening. These inclusion cut-offs are consistent with previous research and indicate similar fatigue levels among these groups (Hewlett et al., 2011). Inclusion would be finalized if candidate-participants completed at least 70% of the Experience Sampling Methodology (ESM) diaries during the first four weeks of the study (i.e., part of ILD collection). Exclusion criteria were an acute or chronic infection, inflammatory flare-ups or any concomitant diagnosis that could explain severe fatigue (Vroegindeweij et al., 2022). Ultimately, 60 AYA were included in the RCT in which our multiple single-case design was embedded. For the analyses of the current study, we did not include the data of participants with more than 8 out of 20 weekly measurements missing (i.e., another part of ILD collection). Therefore, we used the data of 45 out of 60 participants.

Study design

This study made use of a multiple single-case design, which is used to evaluate the effect of a (personalized) treatment or intervention in individuals based on repeated measurement data (Barlow et al., 2009; Lobo et al., 2017; Morley, 2017). More specifically, we made use of a multiple single-case AB-phase design, which consists of a baseline phase (Phase A) and intervention phase (Phase B). The starting point of Phase B can be experimentally assigned or fixed across participants, making it, respectively, a single-case experimental design (SCED) or single-case observational design (SCOD) (Barlow et al., 2009; Lobo et al., 2017; Morley, 2017; Vroegindeweij, Nijhof, et al., 2023). The internal validity of SCEDs is typically higher due to the randomization element (Barlow et al., 2009; Lobo et al., 2017). Although we originally intended to use a SCED (Vroegindeweij et al., 2022), we realized that if we embedded a SCOD within the first half of a RCT, we would still incorporate randomization into our design (i.e., random assignment to one of the two interventions). We would also need less observations to reach sufficient statistical power using the Permutation Distancing Test for SCOD-data (Vroegindeweij, Nijhof, et al., 2023). For these reasons, we used a fixed starting point after four baseline weeks in all participants. ILD were collected per participant through repeated measurement in Phases A and B. More details on the study design and data collection will be provided in Figure 2 and the following subsections.

Data collection

In this study, two sets of ILD were collected using the smartphone application *Ethica* (Vroegindeweij et al., 2022; Vroegindeweij, Levelt, et al., 2023). The first set was collected with ESM diaries during four weeks before and after the intervention (i.e., two times 28 days). Generally, participants completed at least 3 and maximally 5 ESM diaries per day, which took about 1 minute per diary (Nap-van der Vlist, Houtveen, et al., 2021; Vroegindeweij et al., 2022; Vroegindeweij, Levelt, et al., 2023). The diaries were sent with a 3-h time interval and could be completed within 30 min upon receiving. The ESM diaries before the intervention were used to identify the biopsychosocial model factors of fatigue per participant, through items inquiring after the level of fatigue, other symptoms, activities, emotions and other (personalized) topics in the last three hours (e.g., 'In the last three hours, I felt fatigued', 'In the last three hours, I worried about my symptoms' or 'In the last three hours, I performed my hobby') (Nap-van der Vlist, Houtveen, et al., 2021; Vroegindeweij et al., 2022; Vroegindeweij, Levelt, et al., 2023). Items were answered on a Visual Analogue Scale (VAS) of 0 ('not at all') to 100 ('very much') (Nap-van der Vlist,

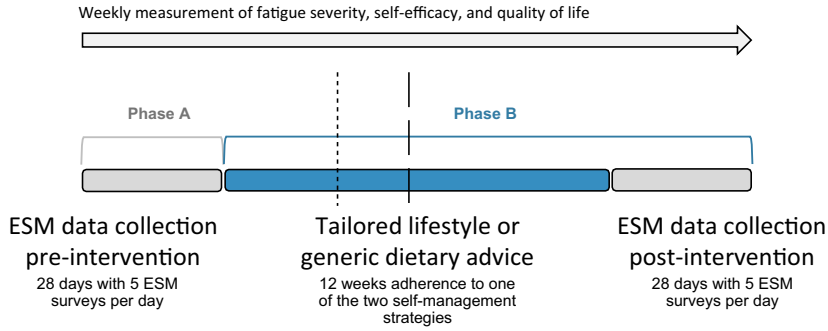

FIGURE 2 Study design and data collection. ESM, Experience Sampling Methodology; semi-personalized surveys in the format of a diary to identify the biopsychosocial model of fatigue. The black lines are important for the statistical analyses of the data. They represent the analytical starting point of Phase B (i.e., the lag). In other words, they represent the moment we expect the start of a self-management treatment effect. The dotted line indicates lag = 4 for the tailored PROfeel lifestyle advice. The dashed line indicates lag = 6 for the generic dietary advice. For more information, see subsection 'Statistical analyses'.

Houtveen, et al., 2021; Vroegindeweij et al., 2022; Vroegindeweij, Levelt, et al., 2023). The same ESM diaries were used after the intervention to explore changes in the biopsychosocial model factors of fatigue.

The second ILD set was collected through a weekly repeated questionnaire that had to be completed during the SCOD study period (i.e., 20 weeks, see Figure 2). The weekly questionnaire was sent to the smartphone on a fixed time and day. It monitored primary outcome 'fatigue severity' and secondary outcomes 'self-efficacy' (i.e., feeling a sense of control over fatigue) and 'quality of life'. To measure fatigue severity, the CIS-8 was included in the weekly measurement (Vroegindeweij et al., 2022; Worm-Smeitink et al., 2017). To limit participant burden, the secondary outcomes were measured with one VAS-item each, namely 'Last week, I thought I could influence my own fatigue' on a scale of 0–100 ('not at all' to 'very much') and 'Last week, I saw my life as…' on a similar scale (with text range 'the worst life possible' to 'the best life possible') (Vroegindeweij et al., 2022). Both items were derived from the Wilhelmina Children's Hospital PROactive cohort study (Nap-van der Vlist, Hoefnagels, et al., 2021). During the intervention, the weekly questionnaire also included one item measuring adherence: 'On a scale of 1 (no adherence) to 10 (perfect adherence), I adhered to my advice…'. The baseline characteristics were derived from the RCT's baseline visit questionnaires (Vroegindeweij et al., 2022; Vroegindeweij, Wulffraat, et al., 2023).

Self-management intervention strategies

The interventions were intended as self-management strategies. Therefore, each participant adhered for 12 weeks to their advice without the help of a healthcare professional. Adherence reminders were prompted through the weekly repeated measurements (Vroegindeweij et al., 2022).

The input for the tailored PROfeel lifestyle advice was obtained through descriptive analyses and dynamic modelling (i.e., Residual Dynamic Structural Equation Modelling) of the ESM data collected in the first four weeks of the study, see previous work for more information (Vroegindeweij et al., 2022; Vroegindeweij, Levelt, et al., 2023; Vroegindeweij, Wulffraat, et al., 2023). The researcher discussed the outcomes with the participant. The participant's lifestyle advice was formulated during the discussion by using shared decision-making (Vroegindeweij et al., 2022; Vroegindeweij, Wulffraat, et al., 2023). The advice could concern topics such as improving sleep hygiene, replacing daytime resting with physical, social or mental activities, or releasing stimuli overload through mindfulness exercises. Each advice was formulated in detail to facilitate behavioural change (Vroegindeweij et al., 2022; Vroegindeweij, Wulffraat, et al., 2023) and shared in a report of which participants received a physical and digital copy.

The generic dietary advice was based on the age and sex-specific healthy, sustainable food-based dietary guidelines from the Netherlands Nutrition Center (NNC) (Brink et al., 2019). Participants who were assigned to the dietary advice first completed the Eetscore™ tool. This is a diet quality screener using the Dutch Healthy Diet-index 2015 (DHD15) to assess dietary guideline adherence (Looman et al., 2017). Based on the assessment, the tool returns personalized dietary advice on 16 different dietary components (e.g., intake of vegetables, fruits, meat and dairy) (de Rijk et al., 2022). The researcher discussed the personalized advice with the participant and used it to explain how adherence to the NNC guidelines could be improved (Vroegindeweij et al., 2022; Vroegindeweij, Wulffraat, et al., 2023). Participants received a physical copy of the personalized advice and could also freely access the tool online.

Statistical analyses

To examine individual outcomes after the self-management strategies, we used the Permutation Distancing Test (PDT) (Vroegindeweij, Nijhof, et al., 2023) on the weekly measurements from Phase A and Phase B to derive individual effect sizes. The PDT is a nonparametric test used to analyse SCOD AB-phase data (Vroegindeweij, Nijhof, et al., 2023). Traditional permutation methods examine the null hypothesis of two independent groups having identical distributions of observations, using cross-sectional data (Berry et al., 2021). The PDT, in turn, is an adapted version that examines whether a single participant has identical distributions over Phases A and B, whilst dealing with autocorrelation (Vroegindeweij, Nijhof, et al., 2023). In this study, it was tested whether the mean levels of fatigue severity, self-efficacy and quality of life differed significantly between the two phases. We hypothesized that all three outcomes improved, meaning that fatigue severity would decrease, whereas self-efficacy and quality of life would increase. Because it takes time to fully incorporate lifestyle or diet changes in your daily life and their effects will not immediately show, we consulted expert opinions on the lag of improvement. Subsequently, we added to our hypothesis that we expected improvement to start after four weeks of tailored PROfeel lifestyle adherence (lag = 4) or after six weeks of generic dietary adherence (lag = 6). Phase B data skipped by the lag were included in Phase A (see Figure 2). The PDT returns individual AB-phase effect sizes (*d*) expressing the amount of change over time, with values of .00–.99 considered small, 1.00–2.49 medium and ≥2.50 large (Vroegindeweij, Nijhof, et al., 2023). The simulation protocol used in the PDT validation article (Vroegindeweij, Nijhof, et al., 2023) was adapted to compute the power with 20 weekly measurements and zero to medium levels of autocorrelation, which yielded between 83% and 92% power to detect medium effects.

To identify potential predictors of self-management treatment success, we compared the baseline characteristics of participants with and without significant PDT effect sizes using *t*-test and chi-square when appropriate. Alpha level was set at .05. Cohen's *d* effect sizes were reported alongside significant findings, with values around .20 considered small, around .50 medium and around .80 large (Goulet-Pelletier & Cousineau, 2018).

To explore the impact of the tailored PROfeel lifestyle advice on the biopsychosocial factors of fatigue, we used the PDT to test mean level differences in the ESM data pre–post intervention (see Figure 2). We did this for all participants with significant effect sizes after PROfeel. Participants completed on average 185 ESM diaries and with medium to large levels of autocorrelation (Vroegindeweij, Nijhof, et al., 2023), computation of the PDT power yielded 85%–99% power to detect small effects. Significant changes were inventoried per participant and stratified by targeted and non-targeted factors (i.e., biopsychosocial factors that the lifestyle advice did and did not focus on). Given that this part of the exploratory analyses involved extensive multiple testing per participant, we set the significance level at .01 and *p*-values between .01 and .05 were considered as indicating trends. To the best of our ability, the direction of the changes was labelled as 'beneficial', 'neutral' or 'adverse' based on the formulated lifestyle advice. Beneficial changes in targeted factors were intended, whereas other changes in (non-targeted) factors were typically non-intended.

This study used packages 'pdt', 'tidyverse' and 'ggplot2' in Rstudio version 4.2.2.

RESULTS

Baseline characteristics

Fifteen out of 60 participants did not have enough ILD to be included in our analyses because they needed referral to specialist healthcare and could not continue study participation ($n = 3$), decided to drop-out ($n = 4$) or had too many missing ILD due to technical or motivational issues ($n = 8$). Participants who needed referral or dropped out were significantly more fatigued than included participants, as indicated by a mean difference (M_{dif}) of 4.11 units on the CIS-8 total score ($SD_{dif} = 2.39$, $p = .049$, Cohen's $d = .22$). Participants with too many missing ILD due to technical or motivational issues showed no significant differences as compared to included participants at baseline.

Of the 45 participants included for analyses, 26 were randomly assigned to the tailored PROfeel lifestyle advice (57.78%) and 19 to the generic dietary advice (42.22%). There were no significant differences between the tailored PROfeel lifestyle advice group and the generic dietary advice group at baseline (see Table 1).

On a scale of 1 to 10, with higher scores indicating more adherence, participants in the tailored PROfeel lifestyle advice group reported an average adherence of 7.74 ($SD = 1.82$). Participants in the generic dietary group reported an average of 7.87 ($SD = 1.49$). This difference was not significant ($p > .05$).

TABLE 1 Baseline characteristics of all included participants ($N = 45$).

	Mean (SD) or frequency (%)			
	Lifestyle advice group ($n = 26$)	Diet advice group ($n = 19$)	Possible range	Observed range
Diagnosis				
QFS	7 (26.92%)	6 (31.58%)		
JIA	9 (34.61%)	4 (21.05%)		
ME/CFS	5 (19.23%)	7 (36.84%)		
PCC	5 (19.23%)	2 (10.53%)		
Sex (female)	20 (76.92%)	16 (84.21%)		
Age in years	19.88 (5.83)	17.17 (4.03)	12–29	12–29
Fatigue duration in years	4.18 (3.90)	4.39 (4.01)	.5–12	.5–12
Fatigue severity[a]	45.36 (6.50)	45.72 (6.74)	8–56	35–56
Self-efficacy[b]	17.39 (2.37)	16.56 (2.97)	7–28	11–23
Quality of life[b]	59.22 (14.49)	56.35 (13.65)	0–100	29–98
Sleep/wake problems[a]	41.49 (12.01)	50.00 (16.98)	0–100	12–79
Pain severity[a]	5.13 (2.90)	5.59 (3.28)	0–10	0–9
Depression/anxiety symptoms[a]	79.12 (17.62)	84.76 (22.50)	47–188	52–130
Overall diet quality[b]	96.88 (21.70)	99.78 (22.55)	10–160	61–148

Note: Baseline characteristics were retrieved from the randomized crossover trial and measured with the following questionnaires: Checklist Individual Strength-8 (fatigue severity), Self-Efficacy Scale-28 (self-efficacy), PedsQL-Generic Core Scales (quality of life), PedsQL-Multidimensional Fatigue Scale sleep/wake subscale (sleep/wake problems), Pain VAS-item (pain severity), Revised Child Anxiety and Depression Scale (total level of depression and anxiety symptoms), Eetscore™ (overall diet quality).

[a]Higher score indicates worse outcome.

[b]Higher score indicates better outcome.

Individual outcomes: fatigue severity, self-efficacy and quality of life effect sizes

Figure 3 displays the PDT effect sizes for participants who followed the tailored PROfeel lifestyle advice or the generic dietary advice. Significant positive effect sizes (improvements) were observed among 19 participants in total (42.22%). Effects ranged from small to large (d_{range} = .05–2.59). Significant positive effect sizes were most frequently observed in the tailored PROfeel lifestyle advice group ($X^2 = 3.411$, $p = .033$), although most of the larger positive effect sizes were observed in the generic dietary advice group. Fatigue severity improved most frequently, followed by self-efficacy. Quality of life improved in only two participants who both followed the generic dietary advice. The positive effect sizes were observed among 2 participants with PCC, 4 with QFS, 6 with ME/CFS and 7 with JIA.

Significant negative effect sizes (deteriorations) were observed among 11 participants (24.44%) and ranged from small to moderate (d_{range} −.02 to −2.46). Significant negative effect sizes were most frequently observed in the generic dietary advice group ($X^2 = 2.737$, $p = .049$). Most negative effect sizes concerned self-efficacy, followed by quality of life and last fatigue severity. The deteriorations were observed among 2 participants with PCC, 2 with QFS, 3 with JIA and 4 with ME/CFS.

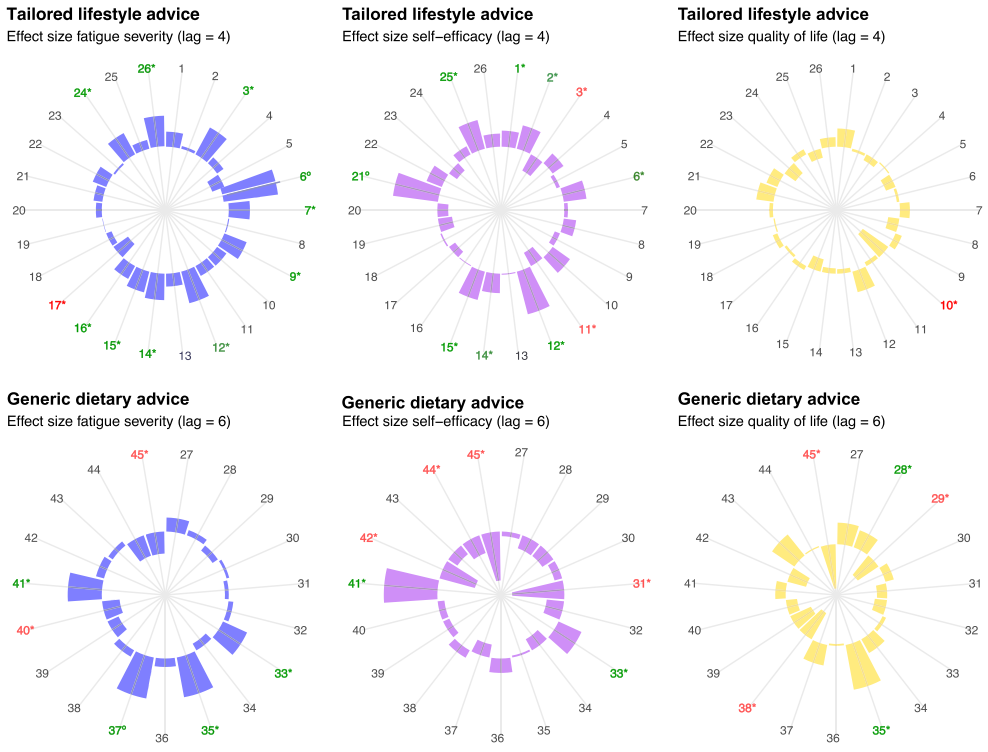

FIGURE 3 Individual outcomes after tailored PROfeel lifestyle advice or generic dietary advice expressed in PDT effect sizes. There are 26 participants in the tailored PROfeel lifestyle advice group, and 19 participants in the generic dietary advice group. Each bar represents the effect size of one participant, ranging from –3 to +3. Outwards extended bars represent positive outcomes (improvements). Inwards extended bars represent negative outcomes (deteriorations). The longer the bar, the larger the effect. Effect sizes significant at the 5% alpha level are printed in bold and marked with an asterisk. Three positive effect sizes are printed in bold and labelled with a ° instead of * to indicate that these analyses were slightly underpowered due to missing observations.

Predictors of self-management treatment success at baseline

The 19 participants with positive PDT effect sizes displayed significantly lower baseline levels of fatigue severity (M_{dif} = 3.21, SD_{dif} = 1.89, p = .004, Cohen's d = .51) and pain severity (M_{dif} = 2.40, SD_{dif} = .87, p = .004, Cohen's d = .87), as well as higher baseline levels of quality of life (M_{dif} = 8.56, SD_{dif} = 4.03, p = .020, Cohen's d = .65) compared to all other participants. The 11 participants with negative effect sizes displayed a trend for lower self-efficacy levels (M_{dif} = 1.28, SD_{dif} = .90, p = .081, Cohen's d = .50) compared to all other participants.

Exploration of biopsychosocial factor changes pre-post PROfeel intervention

Table 2 presents the significant changes in the biopsychosocial factors after the tailored PROfeel lifestyle intervention. The table is limited to the PROfeel participants for which significant effect sizes were observed: 14 participants with positive effect size(s), one participant with a positive and negative effect size and three participants with a negative effect size. Table 2 also shows which lifestyle advice participants adhered to. It stands out that their advice can be divided into three general topics, namely improving sleep hygiene at night, balancing daytime resting and increasing physical activity.

The upper part of Table 2 shows the participants who improved in terms of fatigue severity and/or self-efficacy. It differed largely between participants how many biopsychosocial factors were successfully targeted by the lifestyle advice. Yet, there was a tendency for at least one targeted factor to be changed beneficially (except in participants 2, 7, 9 and 15). Beneficial changes or trends in non-targeted factors were also observed in all participants (except participants 2 and 14). Participant 3 showed an improvement for fatigue severity, but a lowered level of self-efficacy (see Figure 3). The latter may be due to decreased levels of physical activity and feeling happy.

The lower part of Table 2 shows the remaining participants who deteriorated in terms of fatigue severity (participant 17), self-efficacy (participant 11) or quality of life (participant 10). In these participants, only one biopsychosocial factor was targeted successfully in total. All other observed changes were not intended, nor beneficial.

DISCUSSION

This multiple single-case study embedded in a randomized crossover trial (RCT) investigated individual outcomes after tailored PROfeel lifestyle advice or generic dietary advice as self-management intervention strategies for persistent fatigue. In contrast to the RCT, the current study design focused on individual outcomes, which revealed individual differences that were gone unnoticed in the RCT. Our findings indicated that more individuals benefitted from the tailored PROfeel lifestyle advice. Participants who benefitted, showed lower baseline levels of fatigue and pain and higher baseline levels of quality of life. When improvements were observed after the PROfeel lifestyle advice, typically at least 1 factor in the biopsychosocial model of fatigue had been targeted successfully.

The first aim of this study was to derive individual effect sizes on fatigue severity, self-efficacy and quality of life after adhering to self-management advice. By analysing intensive longitudinal data (ILD), we found a range of small to large positive effect sizes in 19 out of 45 participants (42.22%), of which 14 (73.68%) adhered to the tailored PROfeel lifestyle advice. Fatigue severity improved most often (n = 14), followed by self-efficacy (n = 10). Quality of life only improved in two participants who both adhered to the generic dietary advice, which suggests that quality of life is either a particularly stable trait and/or most difficult to improve through self-management. Although more improvements were observed in the PROfeel group, it does not necessarily indicate that the tailored PROfeel lifestyle advice is more effective than the generic dietary advice. After all, some of the largest positive effect sizes were observed in the generic dietary advice group. However, it does indicate that the tailored PROfeel lifestyle advice

TABLE 2 Significant or trending biopsychosocial factor changes pre-post PROfeel intervention.

	Targeted factors		Non-targeted factors	
Participant and lifestyle advice	**Significant change ($p < .01$)**	**Trend change ($p < .05$)**	**Significant change ($p < .01$)**	**Trend change ($p < .05$)**
Participant 6: 'Balancing daytime resting and activities'	Ignoring symptoms decreased ($d = 1.02$) Daytime resting decreased ($d = .80$)	Mental activity increased ($d = .88$)	Severity of symptoms (overall) decreased ($d = 2.74$) Feeling hindered by symptoms decreased ($d = 1.64$)	Pain in neck and shoulders decreased ($d = 2.81$)
Participant 3: 'Improving sleep hygiene at night'	Wake up feeling rested increased ($d = .99$)		Daytime resting decreased ($d = 2.53$) Feeling hindered by symptoms decreased ($d = 1.48$) Severity of symptoms (overall) decreased ($d = 1.3$)	Physical activity decreased ($d = 1.32$) Feeling happy decreased ($d = .75$)
Participant 21: 'Decrease daytime resting and choose consciously what to spend energy on'	Stress by wanting or doing too much decreased ($d = 1.10$) Physical activity increased ($d = .88$) Ignoring symptoms increased ($d = .69$)			Feeling hindered by symptoms decreased ($d = .80$)
Participant 1: 'Improving sleep hygiene at night and start exercising with friends'		Physical activity increased ($d = 1.29$) Wake up feeling rested increased ($d = .75$) Daytime resting decreased ($d = .50$)	Feeling hindered by symptoms increased ($d = 1.27$)	Severity of symptoms (overall) increased ($d = .88$)
Participant 16: 'Increasing physical activity'	Physical activity increased ($d = 1.00$)			Having a short fuse decreased ($d = .79$)

TABLE 2 (Continued)

	Targeted factors		Non-targeted factors	
Participant and lifestyle advice	**Significant change ($p<.01$)**	**Trend change ($p<.05$)**	**Significant change ($p<.01$)**	**Trend change ($p<.05$)**
Participant 12: 'Replacing daytime resting with activities'		Mental activity increased ($d=1.07$) Physical activity increased ($d=.61$)	Feeling hindered by symptoms increased ($d=2.33$) Feeling bored decreased ($d=1.26$) Headache increased ($d=1.16$) Severity of symptoms (overall) increased ($d=1.08$) Being busy with what others think of me increased ($d=.96$)	
Participant 24: 'Improving sleep hygiene at night'		Wake up feeling rested increased ($d=1.44$)		Pain in joints decreased ($d=1.98$) Level of stress increased ($d=1.20$) Severity of symptoms (overall) increased ($d=1.09$)
Participant 14: 'Handling stimulus sensitivity through meditation and walks'		Mental activity increased ($d=.84$) Concentration issues decreased ($d=.74$) Daytime resting decreased ($d=.64$)		
Participant 26: 'Incorporate time to rest and relax'		Mental activity decreased ($d=.52$)	Enthusiasm increased ($d=.61$)	Stomach-ache decreased ($d=1.13$)
Participant 9: 'Improving sleep hygiene at night and handling school stress'			Ignoring symptoms decreased ($d=.97$)	Severity of symptoms (overall) decreased ($d=.64$) Daytime resting increased ($d=.58$)
Participant 2: 'Decrease daytime resting'			Avoiding activities increased ($d=1.32$)	Severity of symptoms (overall) increased ($d=1.40$) Feeling nervous increased ($d=1.04$)
Participant 15: 'Increasing physical activity'		Daytime resting increased ($d=.87$)		Having a short fuse decreased ($d=.47$)

(Continues)

TABLE 2 (Continued)

	Targeted factors		Non-targeted factors	
Participant and lifestyle advice	**Significant change ($p < .01$)**	**Trend change ($p < .05$)**	**Significant change ($p < .01$)**	**Trend change ($p < .05$)**
Participant 7: 'Improving sleep hygiene at night and decreasing daytime resting'				Ignoring symptoms increased ($d = .67$)
Participant 10: 'plan a social activity weekly'	Feeling happy decreased ($d = 1.42$)		Severity of symptoms (overall) increased ($d = 1.29$)	
Participant 11: 'improve sleep hygiene at night and increase physical activity'		Daytime resting decreased ($d = .58$)	Feeling uncomfortable in own skin increased ($d = 1.04$)	Feeling stressed increased ($d = .56$)
Participant 17: 'Increase physical activity'		Daytime resting increased ($d = 1.47$)		Headaches increased ($d = .74$) Wake up feeling rested decreased ($d = .45$)

Note: Changes were tested with the Permutation Distancing Test and considered significant if $p < .01$ or trending if $p = .01–.05$. The Permutation Distancing Test effect size was denoted as 'd'. Based on the formulated lifestyle advice, we tried to label each change as beneficial (green), adverse (red) or neutral (black). Participant 25 could not be included in the table due to missing post-intervention ESM data.

might be the better fit for more patients. The most promising lifestyle advice categories in this study were: improving sleep hygiene, balancing daytime resting and increasing physical activity. Considering that 7 out of 11 participants with negative effect sizes (24.44%) adhered to the dietary advice, self-management strategies using a generic dietary approach should be facilitated with caution. Yet, to explain why a smaller number of patients might benefit from a dietary approach, we refer to studies that have linked the gut microbiome to ME/CFS symptoms (Varesi et al., 2021). Some of these studies have suggested that patients can suffer from a disrupted gut barrier. Dietary interventions could restore the barrier and thereby alleviate symptoms (Varesi et al., 2021). This hypothesis is known as the 'leaky gut hypothesis' (Varesi et al., 2021). The fact that the 5 participants who benefitted from the generic dietary advice had a ME/CFS or QFS diagnosis, could be in harmony with that hypothesis.

The second aim of this study was to compare the baseline characteristics of participants who did and did not benefit from their self-management strategy to identify potential predictors of self-management treatment success. The RCT group-level results hinted that the self-management strategies were more effective in relatively younger participants who were less impacted by fatigue (Vroegindeweij, Wulffraat, et al., 2023). Except for age, we found a similar pattern in the current individual-level results, as participants with positive effect sizes showed significantly lower baseline levels of fatigue and pain severity, and higher baseline quality of life levels. In addition, participants with negative effect sizes showed an almost significant trend for lower levels of self-efficacy. Our observations align with previous research indicating lower fatigue severity, pain severity and higher self-efficacy as treatment success predictors (Janse et al., 2019; Prins et al., 2002; Schreurs et al., 2011). Associations between fatigue severity and quality of life have also been reported before (Armbrust, Lelieveld, et al., 2016; der Vlist et al., 2019; Higson-Sweeney et al., 2022; Lamers et al., 2013; Scheeres et al., 2009; Thomas, 2018; Viner et al., 2008). Altogether, the synthesis of our group-level and individual-level findings indicates that self-management strategies may be most useful in patients with relatively less severe symptoms. If patients display lower levels of self-efficacy, healthcare providers may opt not to select a self-management strategy and instead choose a fully guided treatment or an intervention specifically addressing self-efficacy.

The third aim was to explore the impact of the tailored PROfeel lifestyle advice through changes to the factors in the biopsychosocial model of fatigue. In 10 out of 14 participants who showed improvement after PROfeel, we noticed that at least one biopsychosocial factor was targeted successfully. We assume that these changes are the working mechanisms of the intervention, demonstrating the direct impact the lifestyle advice can make on the study outcomes. The data of the three participants with negative effect sizes, in which only one biopsychosocial factor in total (instead of minimally one per individual) had been targeted successfully, support this assumption. Note that in 12 out of 14 participants, we also observed untargeted improvements that may be considered the positive by-products of the intervention. These by-product changes often had higher effect sizes than the intended changes. The network approach, a framework used in the field of psychiatry (Borsboom, 2017), may be used to explain this. In the network approach, symptoms are seen as interconnected nodes from which mental disorders emerge (Borsboom, 2017). The emphasis is placed on understanding the dynamic interactions between symptoms (Borsboom, 2017). Network interventions can be used to alter the connections, so that one change within the network can lead to a new change, which triggers another change and so on (Borsboom, 2017). Although the current research is not a study on a mental disorder, we did use a similar approach by computing dynamic networks per participant (to tailor advice to their biopsychosocial model of fatigue). Based on the observed by-product changes, it may be speculated that the tailored PROfeel lifestyle advice, when applied successfully, functions as a network intervention. This can be tested in future research, for example as done by Houtveen et al. (2022) for self-compassion training.

An important strength of the current study was the embedment of the multiple single-case design in the first half of the RCT. This design choice facilitated the synthesis of results at both the individual-level (current study) and group-level (RCT). Most of our findings aligned. In the current study, 14 participants improved on fatigue severity, most with medium and large effect sizes. In the RCT, there was a significant average improvement of fatigue severity which was clinically relevant in 14 participants after the first intervention (Vroegindeweij, Wulffraat, et al., 2023). Regarding

quality of life, only two participants showed significant improvement in the current study. Similarly, the average improvement of quality of life was not significant in the RCT after the first intervention (Vroegindeweij, Wulffraat, et al., 2023). The findings differed on self-efficacy. After the first intervention, the RCT reported no average improvement of self-efficacy (Vroegindeweij, Wulffraat, et al., 2023). Yet, in the current study, 10 participants showed significant improvement. The fact that multiple individual improvements were masked by the average group outcome demonstrates that researchers should not neglect to study the individual-level. Two other strengths of this study were statistical power, which was typically well above 80%,[1] and the fact that we could explore factor changes in the biopsychosocial model of fatigue using ILD collected pre–post intervention. This improved our insight in the potential (in)direct impact of the tailored PROfeel lifestyle intervention and encourages the use of stricter alpha levels (e.g., by using a Bonferroni correction) in future research, enabling an increasingly rigorous evaluation of PROfeel.

The current study also dealt with limitations, such as the reliability and validity of the weekly questionnaire on the smartphone. We measured primary outcome 'fatigue severity' extensively by using the CIS-8 questionnaire which is a reliable and validated instrument (Worm-Smeitink et al., 2017). However, to prevent participant burden, we limited the measurement of the secondary outcomes 'self-efficacy' and 'quality of life' to one VAS-item each. It is possible that we missed individual improvements, especially regarding quality of life, due to our narrow measurement. In addition, we may have missed improvements due to testing only one lag (i.e., the expected start of improvement) for each intervention. Although the lags were based on expert opinion, it is probable that the timing of improvement varied among individuals. It is also likely that fatigue severity, self-efficacy and quality of life did not improve at the same time, warranting different lags per study outcome. We did not incorporate these options in the current study as it would require substantially more explorative testing, thereby increasing the likelihood of Type I errors. Our study was also limited by a relatively high exclusion rate. Four participants decided to drop-out and eight participants could not complete data collection sufficiently due to technical or motivational reasons. This may have introduced bias in our sample, with included participants being more motivated to complete the study with good adherence. Finally, for the measurement of adherence we relied on weekly retrospective self-report which may have a recall bias. It is possible that the true adherence differs from the reported adherence. We have reflected more elaborately on this matter in the RCT study (Vroegindeweij, Wulffraat, et al., 2023).

From this study followed directions for future research. First, we decided to use labels to gain more insight in how the tailored PROfeel lifestyle advice might have impacted factors in participants' biopsychosocial model of fatigue. Each observed change was labelled as 'beneficial', 'neutral' or 'adverse' based on the formulated lifestyle advice. It is possible that not all readers agree with each label. Moreover, it is possible that participants experienced some changes differently than labelled. In future research, it would be insightful to discuss the observed changes with the participants. By means of structured interviews, we could learn how the changes were perceived, which were considered most important, and which were the direct or more indirect result of the formulated lifestyle advice. Second, through structured interviews, individuals could reflect on adverse changes observed after the tailored PROfeel lifestyle advice. We observed several adverse changes in this study, which is intriguing given that their fatigue severity and/or self-efficacy still improved over time. From interviews could follow whether those adverse changes were relevant to the individual biopsychosocial model and to what extent their impact was diminished by the beneficial changes. Perhaps the adversities were false positives caused by multiple testing (although we tried to prevent those by lowering the alpha level) or the result of biases in self-reported data. It is possible, for example, that participants found it difficult to recognize improvement in some factors (e.g., the factor 'overall symptom severity'). Individual differences in bodily or interoceptive and emotional awareness are known in literature (Grabauskaitė et al., 2017;

[1]Except in three participants who had a few weekly measurements missing, which lead to a power slightly below 80%. These participants are identified in Figure 3.

Murphy et al., 2019). Yet, self-reported measurements rely heavily on all respondents having the same level of awareness. In future research, alternative ways to collect intensive longitudinal diary data could be explored, for example by involving body and emotion maps in Experience Sampling Methodology (Reitsema et al., 2023).

Altogether, the individual outcomes from this study implicate that tailored PROfeel lifestyle advice can be used as self-management strategy for persistent fatigue in adolescents and young adults with a chronic condition. PROfeel might be most useful to patients with relatively less severe symptoms.

AUTHOR CONTRIBUTIONS

Anouk Vroegindeweij: Investigation; Visualization; Formal analysis; Writing – original draft; Methodology; Data curation; Project administration. **Jan Houtveen:** Conceptualization; Data curation; Methodology; Writing – review & editing; Resources; Validation. **Desiree A. Lucassen:** Methodology; Writing – review & editing; Resources. **Elise M. Van De Putte:** Conceptualization; Methodology; Funding acquisition; Writing – review & editing; Supervision. **Nico M. Wulffraat:** Conceptualization; Supervision; Methodology; Writing – review & editing; Funding acquisition. **Sanne L. Nijhof:** Conceptualization; Methodology; Supervision; Writing – review & editing; Funding acquisition; Validation; Project administration. **Joost F. Swart:** Conceptualization; Methodology; Supervision; Writing – review & editing; Funding acquisition; Validation; Project administration.

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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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