



# Dynamic modeling of experience sampling methodology data reveals large heterogeneity in biopsychosocial factors associated with persistent fatigue in young people living with a chronic condition

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## ABSTRACT

**Objective:** To evaluate associations between self-reported biopsychosocial factors and persistent fatigue with dynamic single-case networks.

**Methods:** 31 persistently fatigued adolescents and young adults with various chronic conditions (aged 12 to 29 years) completed 28 days of Experience Sampling Methodology (ESM) with five prompts per day. ESM surveys consisted of eight generic and up to seven personalized biopsychosocial factors. Residual Dynamic Structural Equation Modeling (RDSEM) was used to analyze the data and derive dynamic single-case networks, controlling for circadian cycle effects, weekend effects, and low-frequency trends. Networks included contemporaneous and cross-lagged associations between biopsychosocial factors and fatigue. Network associations were selected for evaluation if both significant ( $\alpha < 0.025$ ) and relevant ( $\beta \geq 0.20$ ).

**Results:** Participants chose 42 different biopsychosocial factors as personalized ESM items. In total, 154 fatigue associations with biopsychosocial factors were found. Most associations were contemporaneous (67.5%). Between chronic condition groups, no significant differences were observed in the associations. There were large inter-individual differences in which biopsychosocial factors were associated with fatigue. Contemporaneous and cross-lagged associations with fatigue varied widely in direction and strength.

**Conclusions:** The heterogeneity found in biopsychosocial factors associated with fatigue underlines that persistent fatigue stems from a complex interplay between biopsychosocial factors. The present findings support the need for personalized treatment of persistent fatigue. Discussing the dynamic networks with the participant can be a promising step towards tailored treatment.

**Trial registration:** No. NL8789 (<http://www.trialregister.nl>)

## 1. Introduction

Most childhood diseases can be better controlled today thanks to continuous development in pediatric medicine. Nevertheless, many

children with a chronic condition face somatic or psychosocial challenges in daily life, such as persistent fatigue [1,2]. Persistent fatigue has no widely used definition [3], but can be described as excessive tiredness, lack of energy, and exhaustion for at least three months [4].

**Abbreviations:** CBT, Cognitive Behavioral Therapy; ESM, Experience Sampling Methodology; CFS/ME, Chronic Fatigue Syndrome/Myalgic Encephalomyelitis; (R) DSEM, (Residual) Dynamic Structural Equation Modeling; QFS, Q-Fever Fatigue Syndrome; JIA, Juvenile Idiopathic Arthritis; IRB, Institutional Review Board; SD, Standard deviation; CIS-8, Checklist Individual Strength-8; PedsQL-MFS, Pediatric Quality of Life-Multidimensional Fatigue Scale; RCADS, Revised Children's Anxiety and Depression Scale.

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Compared to peers without a chronic condition, persistent fatigue is four times more prevalent among children and adolescents with a chronic condition [5]. Fatigue has been conceptualized as a generic symptom present in chronic conditions, rather than a disease-specific symptom [6]. Accordingly, fatigue has been observed across all age, sex, and disease groups, regardless of disease activity [5–8].

The biopsychosocial framework considers persistent fatigue to be the result of a complex interaction between biological, psychological, and social factors [9,10]. The framework is supported by research showing that fatigue is indeed associated with biopsychosocial factors such as physical activity [11], fatigue-related cognitions [12], depressive symptoms [1] and social functioning [1,13,14]. As persistent fatigue can decrease daily functioning and quality of life [15–17], it is important to treat it adequately. By identifying modifiable biopsychosocial factors, treatment of persistent fatigue can be informed by the biopsychosocial framework [10].

Aligned with the biopsychosocial framework, treatments such as Cognitive Behavioral Therapy (CBT) address biological and psychosocial factors that are associated with fatigue and the consequences persistent fatigue has in daily life [10,18–20]. Although CBT is an effective treatment for persistent fatigue on the group level (i.e., for the average individual) [21–24], it is not successful for all individuals in the long term [25–27]. It is possible that a one-size-fits-all approach does not meet each individual's needs stemming from their complex interplay of biological and psychosocial factors. Therefore, it has been recommended to explore more patient-tailored treatment approaches [28].

The need for patient-tailored treatment has also been shown in a pilot study that used an intensive longitudinal diary method called Experience Sampling Methodology (ESM) [29–31] to explore associations between fatigue and cognitions, behaviors and affects in patients with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) after CBT [32]. These cognitions, behaviors and affects are associated with fatigue at the group level. However, investigation at the individual level with multi-level analyses showed that these associations were non-ergodic. That is, the strength and direction of associations between fatigue and cognitions, behaviors and affects varied across patients (i.e., random slopes and intercepts) [33]. As it is recognized that fatigue should be studied at the individual level while taking its dynamic nature into account, optimal ways to implement ESM and analyze its data are in development [29].

A novel technique to assess biopsychosocial factors associated with fatigue on the level of the individual patient is to compute single-case dynamic networks based on ESM data. This can be done with Dynamic Structural Equation Modeling (DSEM; or Residual-DSEM (RDSEM)) [31,34], as explained in further detail in the Methods section. The dynamic networks yield two types of associations between fatigue and biopsychosocial factors, namely cross-lagged and contemporaneous. The cross-lagged associations show what biopsychosocial factors precede or follow fatigue *over time*. The contemporaneous associations show which biopsychosocial factors are related to (and might maintain) fatigue *in the moment*. The combination of ESM and single-case dynamic networks has been shown feasible to study persistent fatigue in adolescents with a chronic condition [30], but a thorough investigation of which dynamic associations are related to fatigue is yet to be conducted. Studying the networks does not only improve our understanding of fatigue dynamics over time, but also our understanding of individual differences in persistent fatigue and the required tailoring of treatment.

In the present study, we derive dynamic single-case networks from the ESM data of 31 persistently fatigued young people living with a chronic condition (i.e., Q-Fever Fatigue Syndrome (QFS), Juvenile Idiopathic Arthritis (JIA), CFS/ME and long-COVID). Conceptualizing fatigue as a generic symptom, we expect no structural differences between chronic condition groups in dynamic associations. This, we will explore as supplementary material. The main focus of the present study will be to explore persistent fatigue and associated biopsychosocial factors at the individual level. Based on the biopsychosocial model of

fatigue, we expect to find a unique interplay of factors for each individual. In other words, we expect to observe large heterogeneity at the individual level regarding *which* biopsychosocial factors are associated with persistent fatigue and *how*.

## 2. Methods

### 2.1. Participants

Data was used from the PROfeel intervention arm of the QFS-study, a research project on identifying disrupted biological factors and patient-tailored interventions for 60 adolescents and young adults suffering from persistent fatigue (aged 12–29) [35]. The QFS-study was approved by the Institutional Review Board (IRB) of University Medical Center Utrecht (reference NL72103.41.20, IRB 20/166). Written informed consent was obtained from all participants before start. Eligibility criteria for participants were to be diagnosed with QFS, JIA, or CFS/ME. Within the CFS/ME group, we differentiate between participants who developed their symptoms after unknown or diverse triggers, and participants who developed their symptoms after COVID-19 infection. We refer to the latter as long-COVID. Participants with QFS or CFS/ME had to express severe fatigue, as measured with the Checklist Individual Strength-8 (CIS-8) questionnaire [4], as a major complaint in daily life for at least the last six months with CIS-8 total score > 39 [4]. The cut-off score for participants with JIA was a CIS-8 score of >34 as previous research has shown that these levels in rheumatic diseases correspond to fatigue levels in CFS/ME [36]. Exclusion criteria were 1) any concomitant (predominating psychiatric) diagnosis that may explain fatigue at baseline, such as major depressive disorder, or 2) cognitive impairment (i.e., estimated IQ of below 70). For more information on the QFS-study, see the published protocol paper [35].

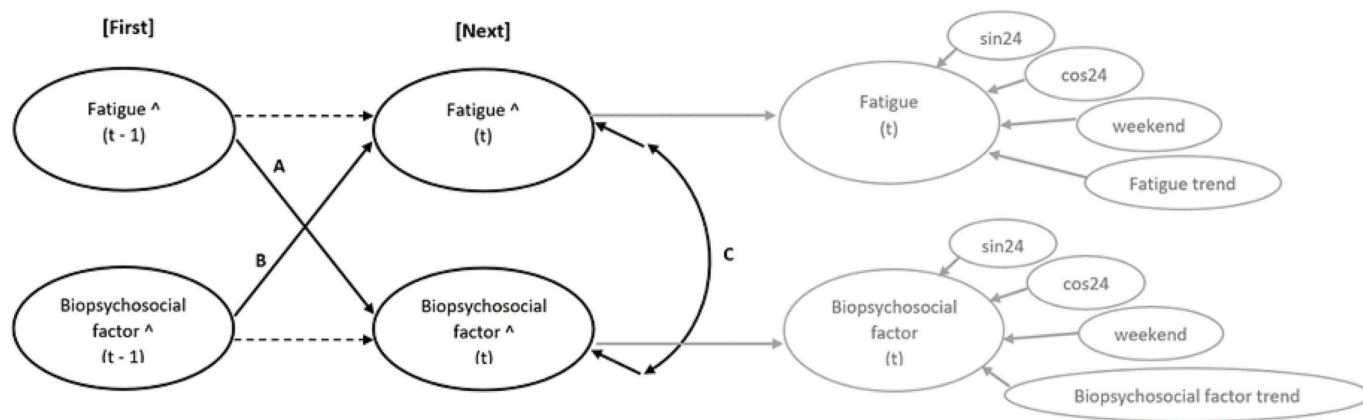
In line with Bos et al. [37], participants were included in the present study if ESM compliance was  $\geq 75\%$  to ensure reliable single-case analyses (i.e., at least 105 out of 140 ESM surveys completed). Ultimately, 31 participants from the QFS-study were included in the present study (see Supplement Table 1 for comparison of included versus excluded participants' characteristics).

### 2.2. Data collection

Data collection took place between October 2020 and April 2022. After completing the baseline visit and corresponding questionnaires, the following 28 days of the QFS-study consisted of ESM data collection. Participants received five ESM surveys per day on their smartphone with a three-hour time lag, through an application named *Ethica* (<https://ethicadata.com/>). On average, participants responded to at least 3 ESM surveys per day to achieve  $\geq 75\%$  ESM compliance. Completing an ESM survey took approximately one minute. All ESM items referred to the last three hours and were answered on a visual analogue scale ranging from 0 indicating "not at all" to 100 indicating "very much" (e.g., "In the last three hours, I felt fatigued"). Beside level of fatigue, the ESM surveys consisted of seven generic biopsychosocial items (e.g., amount of sleep, feeling hindered by symptoms, social contact), to which participants could add up to seven personalized biopsychosocial items during the baseline visit [35]. Instructions for choosing personalized items were provided in the *Ethica* app. The researcher was present to assist when necessary, for example if participants struggled to choose between two or more items. Additional information on the ESM measurement, including the selection procedure of personalized items, can be found in the QFS-protocol paper [35]. For an overview of all measured generic and personalized biopsychosocial factors, please see Table 2.

### 2.3. Computing the dynamic networks with RDSEM

The ESM data were used to derive multiple dynamic single-case networks for each participant: one separate network was derived for



**Fig. 1.** Structure of the Residual Dynamic Structural Equation Model in the present study.

Note. [first] and [next] refer to preceding (t-1) and following (t) three-hour time lag;  $\hat{\phantom{x}}$  = residual latent variable corrected for (amplitude and phase of) time of day effects (sin24 and cos24), weekend effects and low-frequency trends in the variables. Note that ‘physical activity’ is an example of one of the measured biopsychosocial factors in this study. Any other generic or personalized biopsychosocial factor could be assigned here.

each biopsychosocial factor, to estimate the dynamic associations between this specific factor and fatigue. Networks were computed with an extension of Dynamic Structural Equation Modeling (DSEM) named Residual Dynamic Structural Equation Modeling (RDSEM) in MPLUS version 8.6. [30,31,34,35] (see supplementary materials for an example MPLUS input and data file). An advantage of DSEM over other statistical methods is that it can deal with several statistical challenges such as imputation of missing values (e.g., when ESM surveys are not completed), standardization of the within-subject estimates, and observations with unequal spaced time-intervals (e.g., when ESM surveys are completed with a delay). RDSEM can additionally control for variance from time effects inherent to longitudinal data collection, such as circadian cycle, weekend-effects, and low-frequency trends derived from the observed variables [31]. In Fig. 1 we show an example of the used RDSEM model in the present study. We describe what goes in and out of the dynamic network models below.

### 2.3.1. Time of day, weekend, and trend effects

The grey elements on the right in Fig. 1 depict the control for variance stemming from time of day, weekend, and trend effects. *Sin24* and *cos24* stand for the amplitude and the ‘time of day’ phase effects (i.e., a 24-h cycle sine and cosine function). *Weekend* stands for the ‘weekend’ effect, for which we control because weekend days can be spent differently from work- or schooldays to a significant extent. *Fatigue trend* and *biopsychosocial factor trend* stand for the ‘low-frequency’ trends obtained by low-pass filtering the observed signals, yielding week-to-week fluctuations. We control for low-frequency trends because exploration of some of our datasets showed that cross-lagged estimates at lag 1 were influenced by these trends.

### 2.3.2. Latent (residual) variables

By controlling for the variance from the described time of day, weekend, and trend effects, latent variables remain in the model. The variables are not latent in meaning being derived from multiple variables. Instead, they are latent in meaning they are residual variables of one observed variable corrected for the described time of day, weekend, and trend effects. In our VAR1 model, one latent variable consistently represents fatigue, and the other latent variable represents a biopsychosocial factor. For illustrative purposes, the biopsychosocial factor in Fig. 1 is ‘physical activity’. The latent variables are printed in black and marked with symbol  $\hat{\phantom{x}}$  in Fig. 1. This results in a VAR1 model with a three-hour time lag between first and next (residual latent variable) measurements.

### 2.3.3. Types of associations

All associations in the RDSEM model are standardized and can have either a positive or negative direction (i.e., varying from  $-1$  to  $1$ ). Three types of associations are of interest in the present study. The first type is a cross-lagged association between *fatigue [first]* and the *biopsychosocial factor [next]*, indicated by arrow A from ‘fatigue’ towards ‘physical activity’ in Fig. 1. Here, fatigue precedes the level of physical activity three hours later. The second type is a cross-lagged association between the biopsychosocial factor [first] and fatigue [next], as represented by Arrow B from ‘physical activity’ towards ‘fatigue’. In this case, physical activity precedes fatigue three hours later. The third type is a contemporaneous association as indicated by Arrow C between ‘physical activity’ and ‘fatigue’, meaning that fatigue and physical activity are associated at the same time. Note that arrow C connects two separate arrows, indicating that the contemporaneous association is estimated with the residuals of the latent variables after correcting for their cross-lagged and autoregressive associations. Autoregressive associations are associations of a variable with levels of the same variable at the following time point. Fig. 1 depicts the autoregressive associations as dotted arrows, these are corrected for, but are otherwise beyond the scope of the present study.

### 2.3.4. Stationarity assumption

As VAR-models assume stationarity of the data (i.e., stable means, standard deviations (SDs), and network structures over time), RDSEM attempts to account for changes in the mean level over time through latent residual variables. By our knowledge, no statistical tests to evaluate the assumption of non-stationarity of network structures exist, hence we used visual inspection of the SDs to confirm there were no large changes in the fluctuations around the mean over time.

## 2.4. Statistical analyses and evaluation of dynamic associations

We used descriptive analyses to derive the participant characteristics of the total sample and the chronic condition groups. For each participant, cross-lagged and contemporaneous associations with fatigue were evaluated. Fatigue associations were deemed statistically significant if  $\alpha < 0.025$  and relevant for evaluation if the standardized estimate ( $\beta$ )  $\geq 0.20$ . Associations with a standardized estimate of 0.20–0.39 were considered small, 0.40–0.59 moderate, 0.60–0.79 moderate to large, and  $\geq 0.80$  large.

For our supplementary material, we explored group-level differences in dynamic associations with fatigue. We selected the biopsychosocial factors that were most often associated with fatigue and used Fisher’s

**Table 1**  
Participant characteristics of total sample (N=31) and per chronic condition group.

Participant characteristics	Total sample (N=31)	QFS (n=12)	Long-COVID (n=7)	CFS/ME (n=6)	JIA (n=6)	p-value
Female n (%)	28 (90%)	9 (75%)	7 (100%)	6 (100%)	6 (100%)	0.518
Age in years (SD)	20.2 (5.0)	22.8 (4.5)	21.4 (6.2)	16.3 (2.0)	17.3 (3.0)	<0.001*
Disease duration years (SD)	5.0 (4.2)	6.2 (3.5)	0.6 (0.5)	3.3 (4.2)	9.3 (1.8)	<0.001*
RCADS <sup>1</sup> total score (SD)	35.1 (19.6)	43.5 (18.4)	26.3 (9.5)	37.7 (29.2)	24.4 (12.4)	0.509
PedsQL-MFS <sup>2</sup> total score (SD)	123.9 (41.6)	103.5 (35.0)	108.9 (25.6)	137.0 (49.0)	169.2 (23.1)	0.002*
CIS-8 <sup>3</sup> total score (SD)	46.2 (6.5)	48.1 (4.2)	46.1 (5.6)	50.2 (4.0)	38.7 (8.0)	0.003*
ESM <sup>4</sup> Compliance in % (SD)	90.5 (6.0)	90.3 (6.5)	92.1 (5.8)	88.1 (3.2)	91.2 (7.9)	0.073
ESM Fatigue <sup>5</sup> (SD)	55.8 (19.1)	62.3 (11.2)	55.6 (19.7)	60.2 (24.0)	38.5 (11.4)	0.010*

Note. All characteristics are presented in mean (SD), unless stated otherwise. Kruskal-Wallis tests were performed to compare participant characteristics between chronic condition groups and significant if  $p < 0.05$  (indicated with \*).

<sup>1</sup> = Revised Children's Anxiety and Depression Scale, higher score indicates more anxiety and depressive complaints.

<sup>2</sup> = Pediatric Quality of Life Multidimensional Fatigue Scale, higher score indicates higher quality of life in relation to fatigue.

<sup>3</sup> = Checklist Individual Strength-8, higher score indicates higher severity of fatigue.

<sup>4</sup> = Experience Sampling Methodology.

<sup>5</sup> = Experience Sampling Methodology item "in the last three hours, I experienced fatigue", higher scores indicating more fatigue experienced.

Exact tests to compare the frequency of these associations. We used Kruskal-Wallis tests to compare the standardized estimates of these associations between groups.

To describe the extent of heterogeneity at the individual level, we reported the total number of fatigue associations across all monitored biopsychosocial factors, including their association type and direction. For the biopsychosocial factors most often associated with fatigue, we used a Forest plot to visualize the range in standardized estimates of significant and relevant associations per biopsychosocial factor, indicating the direction and size of the associations. Finally, we highlighted certain dynamic associations between fatigue and generic and personalized biopsychosocial factors for individual participants.

### 3. Results

#### 3.1. Participant characteristics

Table 1 presents the characteristics of all included participants stratified by chronic condition group ( $N = 31$ ). Participants with QFS or long-COVID were significantly older than participants with CFS/ME or JIA. Participants with JIA reported significantly longer disease duration, higher quality of life as measured with the PedsQL Multidimensional Fatigue Scale (PedsQL-MFS), and with a lower threshold for inclusion they did report lower fatigue severity as measured with the Checklist Individual Strength-8 (CIS-8) and the ESM surveys. Overall, the included sample was predominantly female (90%). Age ranged between 14 and 29 years. Compared to excluded participants, included participants had expectedly higher ESM compliance but were also significantly older (see Supplement Table 1 for additional information).

#### 3.2. All significant and relevant dynamic associations with fatigue

In total, 42 different personalized biopsychosocial factors were monitored in this study. The generic and personalized factors are listed in Table 2. Ultimately, 154 dynamic network associations with fatigue were observed across these factors. Most associations were contemporaneous (67.5%), followed by cross-lagged associations with fatigue first (17%), and cross-lagged associations with a biopsychosocial factor first (15.5%). The biopsychosocial factors most often associated with fatigue are reported in Supplement Table 2. The majority of cross-lagged associations with fatigue first, were with personalized biopsychosocial factors. Almost all cross-lagged associations with a biopsychosocial factor first, concerned a generic biopsychosocial factor (see Supplement Table 2). As we did not evaluate associations with a standardized estimate below 0.20, the strength of the observed fatigue associations ranged from small to moderate ( $\beta$ -range = 0.20–0.58).

#### 3.3. Group differences in the dynamic associations with fatigue

As part of our supplementary material, we explored differences in the significant and relevant dynamic associations with fatigue between the chronic condition groups. In Supplement Table 2, we reported how frequent the significant and relevant associations with fatigue were observed among the chronic condition groups. Fisher's Exact tests showed no significant group differences regarding the frequency of the associations. Supplement Table 3 shows the median of the associations' standardized estimates per group. With careful interpretation because of low power (due to small sample sizes), Kruskal-Wallis tests indicated that, except for physical activity, no significant group differences were found among the medians.

#### 3.4. Inter-individual differences in the dynamic associations with fatigue

In Table 3, we visualized the heterogeneity in strength and direction for the biopsychosocial factors most frequently associated with fatigue. It shows that the associations varied in strength and that the same biopsychosocial factor could have positive dynamic associations with fatigue for one participant, but negative dynamic associations with fatigue for another.

For some participants, multiple fatigue associations with the same biopsychosocial factor were found. In Supplement Table 4 these associations are marked with an asterisk (\*). For the generic biopsychosocial factor "feeling hindered by complaints", two participants had a contemporaneous and cross-lagged (fatigue first) or (factor first) association with fatigue. A third participant had all three types of associations between "feeling hindered by complaints" and fatigue. There was also a participant who had all three types of associations between "feeling happy" and fatigue. Sometimes, multiple fatigue associations with the same biopsychosocial factor were contradictory. For instance, for one participant, a negative cross-lagged but positive contemporaneous association between "daytime resting" and fatigue was found, which indicates that biopsychosocial factors can have different associations with fatigue in the short- versus long-term.

### 4. Discussion

The present study applied an innovative ESM combined with RDSEM technique to derive dynamic single-case networks for 31 persistently fatigued young people living with a chronic condition, to investigate fatigue associations with biopsychosocial factors at the individual level. In line with the biopsychosocial framework [9] and traditional group-level research [1,11–14], dynamic associations between biopsychosocial factors and fatigue were found. Building on previous research [33], the present study demonstrated that associations with



**Table 2**  
Overview of generic and personalized biopsychosocial factors measured with ESM.

Biopsychosocial factors	Total (N=31)	QFS (n=12)	Long-COVID (n=7)	CFS/ME (n=6)	JIA (n=6)
Daytime resting	31	12	7	6	6
Physical activity	31	12	7	6	6
Severity of symptoms	31	12	7	6	6
Feeling hindered by symptoms	31	12	7	6	6
Mental activity	31	12	7	6	6
Experiencing stress	20	6	6	4	4
Pain in whole body and/or joints	14	6	2	3	3
Avoiding activities	14	5	2	5	2
Headache	13	4	4	3	2
Ignoring symptoms	12	6	3	1	2
Feeling uncomfortable in own skin	12	2	4	2	4
Concentration issues	11	4	4	2	1
Feeling enthusiastic	10	4	5	0	1
Have a short fuse	9	3	2	2	2
Being occupied with what others think of me	7	2	2	2	1
Withdrawing from the social environment	6	1	3	0	2
Rumination (worrying)	5	3	0	1	1
Feeling happy	5	1	1	1	2
Feeling depressed	5	2	1	2	0
Pain in stomach	4	1	1	0	2
Backache	3	1	1	0	1
Dizziness	3	1	1	1	0
Feeling determined	3	2	0	0	1
Feeling loved	3	0	1	1	1
Feeling tense	3	1	0	1	1
Feeling strong	3	0	1	2	0
Feeling satisfied	3	2	0	1	0
Nausea	2	0	1	1	0
Feeling warm/cold	2	0	1	0	1
Memory issues	2	2	0	0	0
Feeling energetic	2	0	0	1	1
Feeling proud	2	2	0	0	0
Feeling nervous	2	1	1	0	0
Feeling anxious	2	2	0	0	0

Note. The frequency columns show how many participants per group selected the biopsychosocial factors. Generic biopsychosocial factors were monitored in all 31 participants (i.e., the total sample). Two generic factors are missing from this list, namely 'hours of sleep at night' and 'social contact'. These were categorical variables and therefore not added in the RDSEM dynamic single-case network models. The following personalized biopsychosocial factors were selected by only one participant and therefore not presented in the list: shortness of breath, stimulus sensitivity, feeling tired in whole body, fuzzy head, muscle ache, pain in throat, feeling sad, feeling pressure to function, feeling misunderstood, feeling angry, procrastination, changing weather conditions, work.

fatigue were non-ergodic. A large heterogeneity across participants was observed regarding which biopsychosocial factors were associated with fatigue and how, even in the generic biopsychosocial factors known as relevant for treatment from traditional group-level research. The findings imply that fatigue should be studied at the individual level while taking its dynamic nature into account, and that treatment may be more effective when tailored to the individual's unique interplay of involved biopsychosocial factors.

The heterogeneity observed in the present study manifested in various ways. For instance, the 31 participants chose 42 different personalized factors to be monitored with ESM. These were all factors which they thought to be related to their fatigue in some way. Furthermore, certain biopsychosocial factors were positively related to fatigue in some participants, but negatively in others. Moreover,

biopsychosocial factors could have cross-lagged associations with fatigue in some participants, yet contemporaneous associations in others. For a few participants, multiple types of associations with the same biopsychosocial factor were found, sometimes in opposite directions. For some biopsychosocial factors, such as factors related to social functioning and stress, few associations with fatigue were found, even though many participants selected these factors and previous research has indicated their relevance to fatigue [13,30,38]. This may be explained by the fact that ESM data was collected during the COVID-19 pandemic, when measures restricting social contact were often enforced by the Dutch government. Measures also included restrictions on going to school, work, and other obligations – all activities which were normally recognized as a growing source of stress and pressure among adolescents to young adults [39].

The majority of the observed associations with fatigue was contemporaneous (67.5%). Moreover, in the personalized factors, almost no cross-lagged associations with 'biopsychosocial factor first' were observed. Either the factors observed were indeed all contemporaneous or following after fatigue, or the lack of 'cross-lagged (factor first)' associations could be due to the three-hour time interval used in our ESM measurement. Shorter time intervals or longer assessment periods might disclose more factors eliciting fatigue. However, shorter time intervals or longer assessment periods may also increase burden on this fatigued population.<sup>1</sup> In the present study, the data of only 31 out of 60 potential participants could be used. This was partially the result of using a strict inclusion criterion of  $\geq 75\%$  ESM compliance, which was based on previous research [37]. Nevertheless, with the measurement period used in the QFS-study, at least 70% ESM compliance is required for computation of reliable dynamic single-case networks with RDSEM. It is therefore encouraged to consider ways to enhance ESM compliance in future studies.

To ensure that no relevant factors are missed in the dynamic single-case networks, it is recommended to guide participants in their choice of the personalized factors to be monitored. Regarding analyses, it is recommended to take into account the mean levels and variances of monitored ESM factors because dynamic network results reflect associations between fluctuations instead of mean levels. The reliability of dynamic network results may be hampered by consistently low or high mean levels (i.e., floor or ceiling effects). Due to floor or ceiling effects, it is possible that factors relevant for treatment are missed in the dynamic single-case networks. This risk is minimized by discussing the dynamic network results with the participant, inquiring after their own interpretation and context of the findings [30,35].

The findings of the present study show the added value of ESM combined with RDSEM, by providing a dynamic understanding of fatigue and revealing individual differences that are easily overlooked in group-level research. No significant group differences in the associations with fatigue were found in the present study as well, except for one group difference in the median beta of physical activity (although it should be noted that the group-level analyses were of exploratory nature and had relatively low statistical power). Previous research with persistently fatigued adolescents has already shown the feasibility of using the dynamic single-case network results as a conversation tool, as well as a shared-decision making tool [30]. The majority of the participants reported that discussion of the dynamic network results gave them good to very good insight into their fatigue and enabled them to take steps towards treatment options [30]. Currently, it is being investigated whether the dynamic single-case networks can help to derive effective personalized lifestyle advice to reduce fatigue and improve self-efficacy and quality of life [35]. Altogether, dynamic single-case networks derived from RDSEM hold potential to contribute to

<sup>1</sup> Research remains inconclusive about the effects of EMA schedules on compliance, as meta-analyses are limited by inconsistent reporting of compliance and key features within studies [40].

**Table 3**  
The standardized estimate range in fatigue associations.

Biopsychosocial factor	Number of associations		median $\beta$	median $\beta$ with range
	Positive direction	Negative direction		
Daytime resting (N = 31)	16	3	0.28	
Physical activity (N = 31)	7	7	-0.01	
Feeling hindered by symptoms (N = 31)	24	0	0.31	
Mental activity (N = 31)	6	5	-0.20	
Experiencing stress (N = 20)	3	1	0.28	
Pain in whole body or joints (N = 14)	6	0	0.29	
Avoiding activities (N = 14)	6	2	0.24	
Feeling uncomfortable in own skin (N = 12)	6	0	0.38	
Concentration issues (N = 11)	6	1	0.29	
Feeling enthusiastic (N = 10)	0	10	-0.26	
Feeling happy (N = 5)	2	2	-0.10	
<b>Total</b>	<b>69</b>	<b>31</b>	<b>0.14</b>	

Note. Not all participants had significant and relevant associations between the biopsychosocial factor and fatigue. Therefore, the number of presented associations does not add up to N. The depicted range shows the lowest through highest observed  $\beta$ -value, with the median  $\beta$ -value depicted as blue square. When there was an even number of associations, the median became the simple average of the two middle  $\beta$ -values. The vertical line through the range indicates 0.

treatment tailoring in various ways.

In conclusion, the large heterogeneity found across participants in dynamic single-case networks results makes it likely that persistent fatigue is the result of a complex interplay between biopsychosocial factors while growing up with a chronic condition. The present findings support the need for personalized treatment of persistent fatigue, possibly in addition to existing treatment protocols. Discussing the dynamic single-case networks with the participant can be a promising step towards tailoring treatment.

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### Declaration of Competing Interest

The authors have no competing interests to report.

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### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jpsychores.2023.111195>.

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