Clinical Kidney Journal, 2021, vol. 14, no. 1, 245–254

doi: 10.1093/ckj/sfaa124
Advance Access Publication Date: 1 September 2020
Original Article

ORIGINAL ARTICLE

mHealth-based experience sampling method to identify fatigue in the context of daily life in haemodialysis patients

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ABSTRACT

Background. Fatigue in haemodialysis (HD) patients is a prevalent but complex symptom impacted by biological, behavioural, psychological and social variables. Conventional retrospective fatigue questionnaires cannot provide detailed insights into symptom variability in daily life and related factors. The experience sampling methodology (ESM) overcomes these limitations through repeated momentary assessments in patients' natural environments using digital questionnaires. This study aimed to gain in-depth understanding of HD patients' diurnal fatigue patterns and related variables using a mobile Health (mHealth) ESM application and sought to better understand the nature of their interrelationships.

Methods. Forty HD patients used the mHealth ESM application for 7 days to assess momentary fatigue and potentially related variables, including daily activities, self-reported physical activity, social company, location and mood.

Results. Multilevel regression analyses of momentary observations ($n = 1777$) revealed that fatigue varied between and within individuals. Fatigue was significantly related to HD treatment days, type of daily activity, mood and sleep quality. Time-lagged analyses showed that HD predicted higher fatigue scores at a later time point ($\beta = 0.22$, $P = 0.013$). Interestingly, higher momentary fatigue also significantly predicted more depressed feelings at a later time point ($\beta = 0.05$, $P = 0.019$) but not the other way around.

Received: 25.1.2020; Editorial decision: 18.5.2020

Conclusions. ESM offers novel insights into fatigue in chronic HD patients by capturing informative symptom variability in the flow of daily life. Electronic ESM as a clinical application may help us better understand fatigue in HD patients by providing personalized information about its course and relationship with other variables in daily life, paving the way towards personalized interventions.

Keywords: depressive symptoms, ESM, fatigue, haemodialysis, *mHealth*

INTRODUCTION

Fatigue is one of the most prioritized outcomes among haemodialysis (HD) patients, with great impact on their health-related quality of life [1, 2]. However, evidence-based interventions to improve fatigue in HD patients are lacking. This may be attributed to remaining gaps in the literature about its underlying aetiology and the lack of valid and reliable measuring methods to assess fatigue, hence the broad prevalence range of 40–80% [3–5]. A recently proposed biopsychosocial model to explain fatigue in HD patients posits that fatigue may initially be triggered by chemical imbalances but may eventually be perpetuated by other factors such as psychological (e.g. depression) and social factors (e.g. poor social support) [6]. Hence detailed insight into how behavioural, psychological and social variables may affect the course and severity of fatigue in HD patients is needed prior to the development of effective treatments.

Conventionally used measurement instruments for fatigue, such as the Fatigue Severity Scale (FSS) or the 36-item Short Form vitality subscale, may hamper an in-depth understanding of this symptom and the factors involved in its development. First, these instruments are often administered at one arbitrary moment in time and evaluate fatigue in general or retrospectively over a preceding period. As such, they rely on memory-based responses that may not provide reliable information about actual symptom experience [7]. Second, these conventional questionnaires only provide a general picture of fatigue, for instance, as an average fatigue severity score over a certain period. However, fatigue symptoms can vary across months, weeks, days and even within days [8, 9] and this variability may be causally related to diurnal variations in mood, daily activities or social context [10]. Conventional retrospective questionnaires do not allow assessing this symptom variability and related factors [11].

The experience sampling method (ESM) is a measuring method that overcomes these limitations. ESM is a structured, now digital, diary technique that allows investigating symptoms in daily life through their repeated real-time (here-and-now) assessment as well as potential contributing factors, including behavioural, psychological and social variables [11]. Importantly, ESM assesses symptoms in the patients' natural environments, which allow identifying informative variability in fatigue and factors related to that variability. Furthermore, repeated measurements provide insights into factors that may prospectively predict improvement or worsening of fatigue, paving the way towards personalized interventions targeting these factors. Finally, when incorporated into a mobile Health (mHealth) application, it can be flexibly integrated in the flow of daily life and may therefore reduce non-compliance [12]. To date, a limited number of studies have used ESM to identify fatigue in HD patients [8, 9, 13, 14]. However, they mainly queried fatigue without evaluating contextual variables related to fatigue and without the added benefits of using an mHealth application, such as random assessments throughout the day rather than at fixed time points. This limits the adaptation of daily life routines by participants to be more available for the questionnaires, thereby threatening reliable data collection (i.e. responsivity) [15].

Therefore we designed a study to gain in-depth insight into the diurnal variability of fatigue in HD patients using an mHealth ESM application. Second, we investigated whether momentary fatigue was related to variables in daily life, including current daily activity, location, social company, mood and self-reported physical activity. Finally, by investigating the temporal dynamics between fatigue and these variables, we sought to better understand the nature of their interrelationship.

MATERIALS AND METHODS

Study design and sample

We conducted a prospective observational study. Participants were recruited at the HD units of Zuyderland Medical Centre in Sittard-Geleen and Heerlen, The Netherlands, between July and August 2019. All prevalent patients on a chronic treatment for at least 6 months were screened for eligibility. Exclusion criteria were <18 years of age; insufficient understanding of the Dutch language compromising participation in the study based on clinical judgement; inability to handle the mHealth application independently because of hearing problems, vision problems or insufficient (cognitive) skills based on clinical judgement by the attending physician; diagnosed dementia; chronic fatigue syndrome; fibromyalgia or actual instability of clinical condition requiring hospitalization. The protocol was approved by the local medical ethics committee (METCZ20190078) and registered as NCT04049773 (ClinicalTrials.gov). Written informed consent was obtained from all patients prior to participation.

Data collection

PsyMate. PsyMate (smartHealth, Luxembourg City, Luxembourg) is a smartphone-based mHealth application developed by Maastricht University and Maastricht University Medical Center+ (www.psymate.eu) for momentary assessment of daily life experiences. It was specifically developed to implement ESM in clinical practice. Its user-friendly touch-screen interface makes it accessible for participants with limited technological experience [16].

The application was programmed to emit 10 auditory signals or 'beeps' throughout the day during 7 consecutive days at random moments in time between 6:30 AM and 10:30 PM. Beeps were separated by at least 15 min. Each beep was a prompt to complete a short self-report questionnaire of 25 items within the application, including statements about momentary fatigue, mood, activity, location and company. Completion of a questionnaire was possible until 15 min after the beep. Thereafter, it was closed and registered as missing data. Completion of each ESM questionnaire took 1–2 min.

First, participants were requested to respond to the general statement 'I feel tired' on a 7-point Likert scale, ranging from 1 (not at all) to 7 (very much). Whenever participants responded with ≥2, two additional statements were presented: 'I feel mentally tired' and 'I feel physically tired'. Next, questions about current activities (e.g. type of activity, self-reported physical or mental activity), mood and context (location and company) were presented. Questions with respect to mood and physical and mental activity were again answered on a 7-point Likert scale, whereas questions about location, company and type of activity were answered in a multiple-choice format (Figure 1 and Appendix 1). The same questions were repeated at every beep and were based on a preset questionnaire, the validity of which has been demonstrated in previous studies using the PsyMateapplication in several clinical populations [17–19].

Furthermore, the PsyMateapplication included a short self-report morning questionnaire containing statements about sleep quality during the previous night as well as an end-of-day questionnaire about retrospective evaluation of fatigue and mood during the preceding day (Appendix 2).

Baseline data and laboratory measurements. Demographic, clinical and laboratory information was obtained from computerized medical records at the hospital. The FSS and Hospital Anxiety and Depression Scale (HADS) were administered to assess average fatigue severity and depressive and anxiety symptoms in the sample. Blood results from routine monthly analysis pre- and post-dialysis included complete blood count, iron status, urea, creatinine, electrolytes, serum albumin, parathyroid hormone and C-reactive protein. Dialysis adequacy was calculated from urea clearance (K_t/V_{urea}).

HD treatment

Routine HD was performed according to the prescription of the clinic's nephrologist. Either low-flux (Polyflux 17 L, Gambro, Deerfield, IL, USA; Fresenius F6HPS, Fresenius, Bad Homburg vor der Höhe) or high-flux (Polyflux G210H, Gambro; FX100, Fresenius) dialysis membranes were used with a bicarbonate dialysate. The dialysis technique was conventional HD, except for four patients who were on haemodiafiltration. Patients in our sample received dialysis thrice weekly either during the day (3–4 h) or at night (6–7 h). Arterial blood flow was 300–400 mL/min during daytime HD and 150–200 mL/min during overnight dialysis. The dialysis flow rate was 400–600 mL/min for day treatment and 300 mL/min overnight. The desired ultrafiltration (UF) volume (mean 1.55 ± 0.72 L) was determined by the treating nephrologist. Most subjects were under regular treatment with recombinant human erythropoietin, antihypertensive medications and other commonly used drugs such as vitamin D analogues, phosphate and potassium binders.

Study procedure

Patients were screened by a researcher on the inclusion and exclusion criteria and received an information letter if considered eligible. After participants gave their written informed consent, the mHealth application PsyMate was installed on their personal smartphone or, in the absence thereof, a substitute iPod Touch (Apple, Cupertino, CA, USA) was provided. The use of the application was explained in detail in a briefing session that took place during the participants' regular treatment. Subsequently participants were requested to complete momentary assessments for 7 consecutive days. Importantly, participants were instructed to continue their normal daily routines. The FSS and HADS were completed on the last study day during regular HD, although one participant did not hand them in. Demographic and clinical information were obtained at the moment of inclusion. Blood results of monthly routine investigations were obtained closest to the last study day.

Data and statistical analysis

Statistical analysis was performed using SPSS software, version 25 (IBM, Armonk, NY, USA). Data are reported as mean ± standard deviation (SD) or median (range) as appropriate. ESM data have a multilevel structure, with observations (Level 1) nested within individuals (Level 2). The intraclass correlation coefficient (ICC) was calculated to assess fatigue variability between and within individuals. In this study, the ICC describes how strongly different observations from the same patient resemble each other. In the context of fatigue for instance, the higher the ICC, the more fatigue should be considered as a trait (i.e. low variability between observations from the same individual)

FIGURE 1: PsyMate interface representation of fatigue ESM questionnaire

rather than a state (i.e. high variability between observations). Multilevel regression analyses were conducted to investigate the relationship between momentary fatigue and variables of interest. Analyses were run in a random intercept and random slope model, except for the analyses with categorical variables, which employed a random intercept model. All Likert scales with a range of 1–7 were transformed to 0–6 scales to be able to meaningfully interpret the intercept. Categorical variables, that is, type of activity, location and social company, were recoded into dummy variables. Reference categories for type of activity, location and company were 'relaxing', 'at home' and 'no one', respectively. To investigate whether the type of daily activity, social company and location at a previous time point could predict currently experienced fatigue, time-lagged analyses were used while controlling for fatigue at those previous time points. To investigate the nature of the interrelationship between fatigue and depressed mood, two additional time-lagged analyses were run. In line with previous research, time-lagged analyses were carried out to two previous time points ($t - 1$ and $t - 2$) [20]. The richness of data obtained through ESM allows reliable statistical estimation in relatively small samples of participants (Level 2) because of multiple observations within individuals (Level 1).

RESULTS

Sample characteristics

Forty-two patients participated in this study. Two of them completed <30% of all PsyMatequestionnaires and were excluded from the analyses [21]. The remaining 40 patients (31 males) had a mean age of 64.35 years (SD 13.69). Their demographic and clinical characteristics are reported in Table 1. Participants completed 1777 ESM PsyMate questionnaires, 258 morning and 260 end-of-day ESM PsyMate questionnaires, for an average of 57 of 84 questionnaires per participant (68% compliance rate and 97% completion rate).

Momentary fatigue

At the level of the ESM questionnaires, the average momentary fatigue was 2.36 (SD 1.97) on a scale from 0 to 6. Participants responded ≥1 to the general statement 'I feel tired' in 1209 completed ESM questionnaires, which means that participants indicated experiencing at least some fatigue in 68% of all random momentary observations. The average physical fatigue was 3.26 (SD 1.61) and the average mental fatigue was 1.71 (SD 1.60). Concurrent daily activity patterns, location and social company patterns are shown in Figure 2. The average quality of sleep was 3.92 (SD 1.83).

Figure 3 illustrates that fatigue scores differed substantially within individuals and between individuals. The ICC was 0.65 [95% confidence interval (CI) 0.55–0.75], indicating moderate correlation in fatigue observations within individuals.

Table 2 provides a detailed overview of the fixed and random effects of the multilevel models with all of the included predictors of momentary fatigue in HD patients. In these multilevel models, the fixed effects reflect the overall association between a predictor (e.g. physical activity) and fatigue, whereas the random effects reflect individual differences in this association. For these analyses, responses to the multiple-choice questions about type of activity, social company and location were clustered together into meaningful categories (see Table 2).

Table 1. Participants' baseline characteristics ($n = 40$)

Characteristics	Values
Demographic and clinical characteristics	
Age (years), mean ± SD (range)	64.4 ± 13.7 (34–84)
Sex (male), n (%)	31 (77.5)
Body mass index (kg/m^2), mean ± SD (range)	27.9 ± 5.9
Charlson comorbidity index, mean ± SD (range)	2.7 ± 1.6 (0–6)
Primary kidney disease, n (%)	
Hypertension	8 (20)
Glomerulonefritis	2 (5)
Diabetes	13 (32.5)
Interstitial nefritis	0 (0)
Polycystic kidney disease	6 (15)
Other/unknown	11 (27.5)
Dialysis vintage (months), mean ± SD	49 ± 47
Diuresis/residual urine output, n (%)	14 (35)
Diuresis/residual urine output (mL/24 h),[a] mean ± SD	1044 ± 687
Interdialytic weight gain (kg),[b] mean ± SD	1.6 ± 0.7
UF rate (mL/h/kg) ($n = 34$),[c] mean ± SD	4.35 ± 2.23
Anuric patients ($n = 26$)	4.50 ± 2.34
Non-anuric patients ($n = 8$)	3.87 ± 1.93
Day HD treatment ($n = 25$)	4.82 ± 2.34
Night HD treatment ($n = 9$)	3.06 ± 1.28
Haemodialysis access, n (%)	
Arteriovenous fistula	30 (75)
Arteriovenous graft	3 (7.5)
Central venous catheter	7 (17.5)
Dialysis group (dialysis hours/treatment), n (%)	
Morning (3.5–5.0 h)	18 (45)
Afternoon (4.0 h)	8 (20)
Evening (4.0 h)	4 (10)
Night (7–7.25 h)	10 (25)
Laboratory characteristics, mean ± SD	
spK_t/V	1.6 ± 0.3
Haemoglobin (mmol/L)	7.0 ± 0.6
Serum albumin (g/L)	39.8 ± 3.4
Serum creatinine (μmol/L)	922.8 ± 260.8
Serum urea (mmol/L)	23.6 ± 4.9
Parathyroid hormone (pmol/L)	37.8 ± 26.6
Calcium (mmol/L)	2.3 ± 0.1
Phosphorus (mmol/L)	1.7 ± 0.5
C-reactive protein (mg/L)	9.4 ± 9.8
Conventional questionnaires ($n = 39$), mean ± SD (range)	
FSS	5.0 ± 1.2 (2.1–7.0)
HADS	
Anxiety subscale	4.5 ± 3.6 (0–14)
Depression subscale	4.2 ± 3.8 (0–16)

[a]Excluding anuric patients ($n = 26$).
[b]In patients with target weight ($n = 34$).
[c]Excluding patients without UF.
spK_t/V: urea clearance.

Fatigue scores were significantly higher on HD treatment days compared with non-HD treatment days. Fatigue ratings did not differ significantly between patients on day or night HD treatment. With respect to the type of daily activity, all activities were judged as significantly 'less' fatiguing than relaxing (reference category), except for receiving HD treatment, which did not differ significantly from the reference category. With respect to social company or location, no significant differences in fatigue were found between the respective categories, except

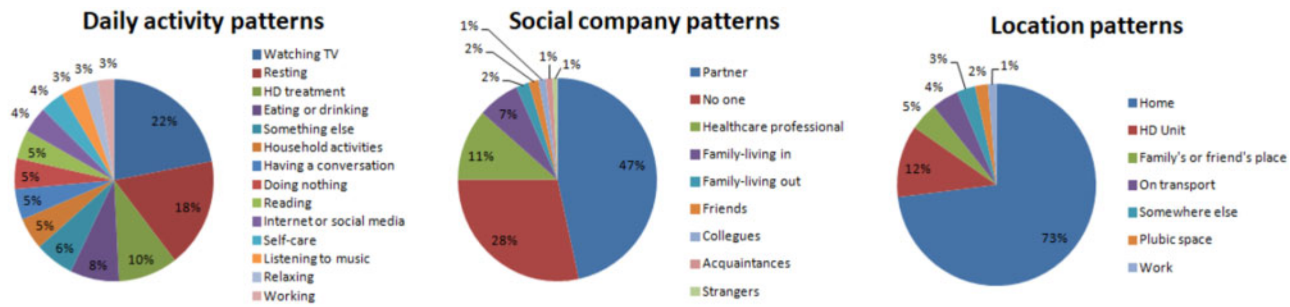

FIGURE 2: Percentages of daily activity ($n=1752$), social company ($n=1733$) and location ($n=1741$) during momentary assessments.

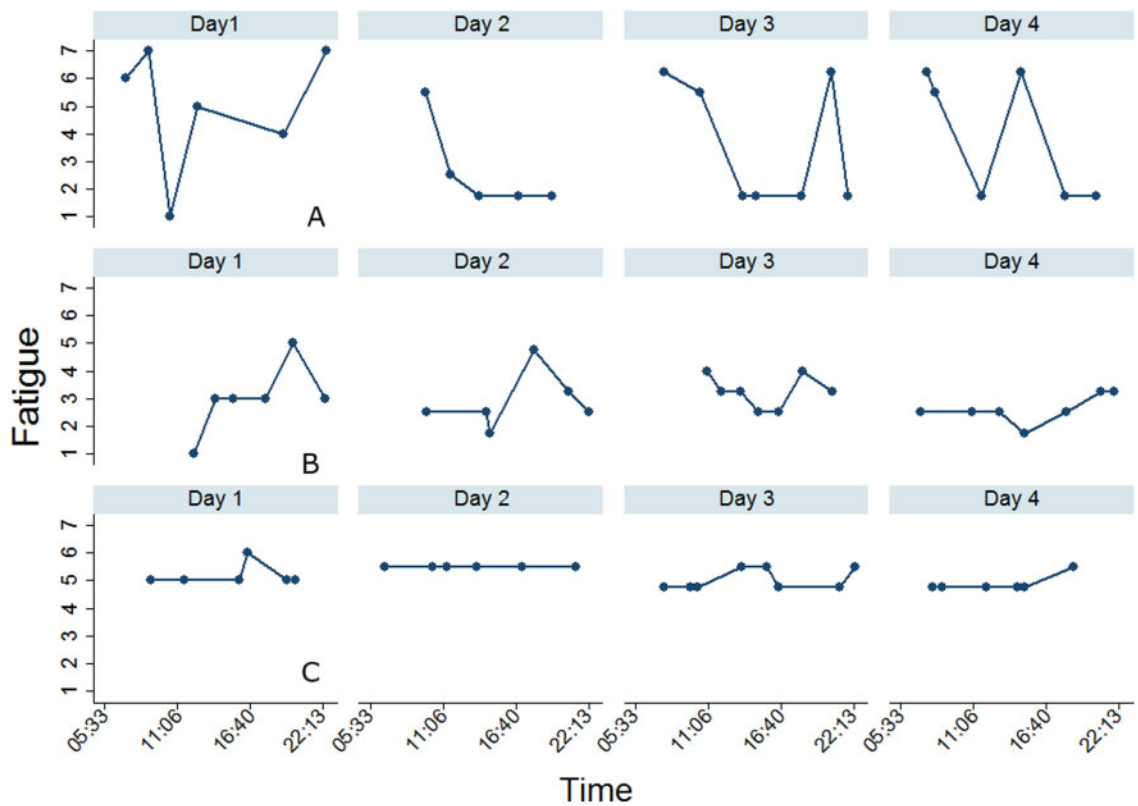

FIGURE 3: Diurnal patterns of momentary fatigue of three different HD patients (Patients A–C) during 4 consecutive study days, illustrating variability in fatigue between as well as within individuals.

for the category 'somewhere else' (public place, transport and somewhere else), which was significantly less fatiguing than being at home (reference category). With respect to physical or mental activity, we found no significant associations with fatigue measured at the same moment in time. In contrast, participants' mood was significantly correlated with momentary fatigue scores, with negative affect related to higher fatigue and positive affect to lower momentary fatigue ratings. Finally, all fatigue scores during the day were significantly lower if the quality of sleep during the previous night was higher.

Temporal relationship

HD treatment at previous time points ($t-1$ and $t-2$) predicted significantly higher current fatigue scores relative to the reference category (relaxing), while controlling for fatigue at those previous time points {$\beta=0.18$, standard error [SE] 0.08, $P=0.030$ (95% CI 0.17–0.35) for $t-1$ and $\beta=0.22$, SE 0.09, $P=0.013$ (95% CI 0.05–0.39) for $t-2$]. Subsequent analyses showed that this temporal relationship only applied to anuric patients [$n=26$; $\beta=0.23$, SE 0.10, $P=0.029$ (95% CI 0.23–0.43) for $t-1$ and $\beta=0.22$, SE 0.11, $P=0.042$ (95% CI 0.01–0.43) for $t-2$]. The UF volume and UF rate did not significantly predict this relationship. Other daily activities measured earlier in time ($t-1$ and $t-2$) did not differ significantly relative to the reference category in predicting current fatigue. Being in the company of a healthcare professional, being with a stranger and being at the HD unit (Appendix 1) at a previous time point ($t-1$) significantly predicted current fatigue ratings relative to the reference categories [i.e. $\beta=0.26$, SE 0.10, $P=0.015$ (95% CI 0.05–0.46) for being with a healthcare professional; $\beta=0.84$, SE 0.32, $P=0.008$ (95% CI 0.22–1.46) for being with a stranger and $\beta=0.35$, SE 0.09, $P<0.001$ (95% CI 0.18–0.53) for being at the HD unit]. All other

Table 2. Overview of multilevel model with momentary fatigue as a dependent variable

Model	Predictor	β	SE	95% CI	P-value
Fixed parameters					
HD versus non-HD day	Intercept	0.33	0.06	0.22–0.44	<0.001
Day versus night dialysis treatment	Intercept	0.47	0.58	−0.71–1.65	0.426
Type of daily activity[a]	Relaxing	2.42	0.25	1.91–2.93	<0.001
	Working	−0.35	0.11	−0.57 to −0.13	0.002
	Internet/talking	−0.33	0.10	−0.53 to −0.13	0.001
	HD treatment/self-care	−0.15	0.09	−0.32–0.02	0.081
	Eating/drinking	−0.26	0.11	−0.47 to −0.05	0.014
Social company[a]	No one	2.36	0.26	1.84–2.89	<0.001
	Family	−0.03	0.09	−0.21–0.15	0.747
	Friends/acquaintance	−0.15	0.19	−0.52–0.23	0.444
	Colleagues	−0.50	0.28	−1.05–0.04	0.071
	Health professionals	−0.11	0.12	−0.32–0.10	0.292
	Strangers	−0.51	0.32	−1.14–0.12	0.116
Location[a]	At home	2.37	0.25	1.86–2.88	0.003
	At family/friend's place	−0.19	0.15	−0.48–0.10	0.201
	At work	−0.39	0.25	−0.89–0.11	0.123
	At the HD unit	−0.10	0.09	−0.27–0.08	0.294
	Somewhere else	−0.24	0.10	−0.45 to −0.04	0.022
Positive affect[b]	Intercept	4.11	0.31	3.49–4.73	<0.001
	Positive affect	−0.40	0.05	−0.50 to −0.29	<0.001
Negative affect[b]	Intercept	2.16	0.24	1.67–2.64	<0.001
	Negative affect	0.23	0.07	0.08–0.38	0.004
Physically active	Intercept	2.34	0.26	1.82–2.87	<0.001
	Physically active	−0.00	0.03	−0.06–0.05	0.925
Mentally active	Intercept	2.27	0.26	1.75–2.79	<0.001
	Mentally active	0.03	0.03	−0.04–0.09	0.422
Quality of sleep	Intercept	2.87	0.27	2.32–3.42	<0.001
	Quality of sleep	−0.12	0.03	−0.18 to −0.06	<0.001
Random parameters					
HD versus non-HD day	Intercept	2.55	0.58	1.63–3.97	<0.001
Day versus night dialysis treatment	Intercept	2.51	0.57	1.61–3.91	<0.001
Type of daily activity	Intercept	2.53	0.57	1.63–3.95	<0.001
Social company	Intercept	2.54	0.58	1.63–3.97	<0.001
Location	Intercept	2.50	0.57	1.60–3.90	<0.001
Positive affect	Intercept	2.51	0.70	1.46–4.34	<0.001
	Positive affect	0.04	0.02	0.02–0.10	0.026
Negative affect	Intercept	2.24	0.52	1.42–3.54	<0.001
	Negative affect	0.05	0.04	0.01–0.25	0.197
Physically active	Intercept	2.53	0.59	1.61–3.99	<0.001
	Physically active	0.12	0.01	0.00–0.03	0.046
Mentally active	Intercept	2.52	0.58	1.61–3.96	<0.001
	Mentally active	0.01	0.01	0.00–0.04	0.159
Quality of sleep	Intercept	2.21	0.5	1.35–3.62	<0.001
	Quality of sleep	0.01	0.01	0.00–0.03	0.117

When the independent variable was dichotomous (i.e. HD day versus non-HD day, and day versus night dialysis treatment) or nominal (i.e. type of activity, social company and location), the intercept refers to the value of momentary fatigue (on a 7-point Likert scale from 0 to 6) when considering the reference situation (i.e. HD day, dialysis day treatment, relaxing, no one's company and at home, respectively). With respect to all the other variables (i.e. positive and negative affect, extent of mental or physical activity and sleep quality), the intercept refers to the value of momentary fatigue when the independent variable was 0 [on a 7-point Likert scale from 0 (e.g. meaning 'not at all' feeling cheerful, down or slept well) to 6 (e.g. meaning 'very much')].

[a]With respect to type of activity, 'doing nothing', 'resting', 'relaxing', 'listening to music', 'watching television' and 'reading' were combined in the (reference) category 'relaxing'. 'Work' and 'household activities' were clustered as 'working'. 'Undergoing HD treatment' and 'self-care' were also clustered. 'Talking', 'Internet' and 'social media' were put together as well. Social company selection options being 'with one's partner' and 'with a family member living in or living out' were combined into one single 'family' item. 'Friends and acquaintances' were put together. Location options of 'being in a public place', 'on transportation' or 'somewhere else' were also combined.

[b]PsyMateitems with respect to a positive state of mind (i.e. 'feeling cheerful', 'relaxed', 'satisfied' and 'confident') were combined to a single variable of 'positive affect' for these analyses. 'Feeling anxious', 'down', 'agitated' and 'powerless' were put together in a 'negative affect' variable.

social company and location items did not differ significantly from the reference categories in predicting current fatigue (not at $t-1$ or $t-2$).

To investigate the direction of the relationship between fatigue and depressed mood, two time-lagged analyses were run. In the first model, fatigue was the dependent variable and depressed mood earlier in time was the predictor variable (while controlling for fatigue earlier in time). In the second model, depressed mood was the dependent variable and fatigue earlier in time was the predictor variable (while controlling for depressed mood earlier in time). Momentary fatigue did not differ significantly when individuals reported feeling down at previous measured time points ($t-1$ or $t-2$) while controlling for their previously reported momentary fatigue scores. In contrast, momentary scores of depressed mood were significantly higher if participants reported more fatigue at the previous time point ($t-1$), controlling for depressed mood at that previous moment ($t-1$) [$\beta = 0.05$, SE 0.02, $P = 0.019$ (95% CI 0.01–0.10)]. No significant relationship was found at $t-2$.

DISCUSSION

This is the first study using an mHealth application for ESM to investigate fatigue in the flow of daily life in chronic HD patients. Moreover, it is the first study that extensively demonstrated variability in fatigue symptoms between and within HD patients and revealed several behavioural, social and psychological factors that were associated with momentary fatigue.

First, participants reported significantly less fatigue during daily activities such as work, household activities, eating, drinking, using the Internet or social media or having a conversation than when they reported relaxing. Time-lagged analysis further showed that relaxing did not predict significantly higher fatigue levels at a later moment in time relative to other daily activities. Together, these results suggest that relaxing should be considered as a behavioural response to fatigue that is already present rather than fatigue worsening as a consequence of prolonged resting. These findings are in line with previous studies, based on qualitative in-depth interviews, investigating how fatigue in HD patients relates to activities in daily life [10, 22]. In these interviews, HD patients retrospectively stated they adjusted their activities depending on their fatigue levels. Moreover, it may be possible that participants were more fatigue aware when they were not distracted by other activities. Interestingly, results also showed that undergoing HD was not significantly different from relaxing in terms of experienced fatigue. In addition, time-lagged analyses revealed that receiving HD predicted significantly higher fatigue levels at a later time point relative to the reference category. This is further corroborated by the finding that subjects reported more fatigue on HD treatment days relative to non-treatment days. These findings are in line with a previous study demonstrating fatigue increases significantly after HD treatment [8]. Moreover, it supports the concept of different fatigue patterns in HD patients (i.e. more general fatigue versus fatigue as a response to treatment) [14] and may suggest they should, at least partially, be distinguished in HD patients.

Furthermore, feelings of negative affect, including depressive mood, were associated with significantly higher momentary fatigue ratings. Extensive literature exists about the association between fatigue and low mood in HD patients [6, 8, 23–25]. However, due to cross-sectional study designs, the nature of their interrelationship remains unclear. In this study, time-lagged analysis revealed higher levels of depressive mood after feeling fatigued at an earlier point in time. The reverse relationship was not found, suggesting that low mood may be secondary to fatigue in HD patients. However, the small effect sizes indicate that other factors should be taken into consideration when trying to explain the relationship between fatigue and depressive symptoms (e.g. daily activity or physical activity).

Finally, the most important finding from a clinical point of view may be the extent of individual differences in fatigue between and within subjects as well as the factors related to fatigue. Therefore the potential effectiveness of a one-size-fits-all treatment for fatigue seems limited, a priori. Instead, a more personalized approach in treatment may be more beneficial. The advantage of ESM is precisely to obtain detailed and personalized insights in the relationship between symptoms and environmental variables, enabling interventions to be tailored to the needs of the individual.

A patient-reported outcome measure (PROM) for fatigue incorporated in an mHealth ESM may have the potential to become a valid and reliable measurement instrument to assess fatigue in the natural environment of HD patients. This resonates with the need for valid and reliable PROMs for fatigue in HD patients expressed in 2016 by the Fatigue Working Group of the International Standardized Outcomes in Nephrology (SONG) initiative [26]. Moreover, ESM may provide concrete entry points to develop and monitor personalized interventions to alleviate fatigue and improve HD patients' quality of life.

The major strengths of this study include using ESM measurements in daily life to obtain ecologically valid data about fatigue in HD patients, the use of time-lagged analyses to unveil temporal dynamics between symptoms and the inclusion of both patients receiving daytime HD and patients being treated overnight. Limitations include a potential selection bias due to a certain level of cognitive capacities needed to use the mHealth application. Furthermore, males were overrepresented in our study, notwithstanding a gender imbalance of 60% men receiving HD in European countries, including The Netherlands [27].

In conclusion, fatigue in HD patients is a prevalent but complex phenomenon that differs greatly between and within individuals over time. ESM measurement instruments allow for capturing informative symptom variability and enable linking this to patterns of daily life. By providing more detailed and personalized insights into fatigue symptoms and related factors, ESM paves the way towards personalized intervention. Furthermore, our results provide real-life evidence about the temporal dynamics of the interrelationship between fatigue and depressive symptoms. In our view, an important next step is to develop and implement a reliable and valid PROM for fatigue in HD patients in an electronic ESM measurement instrument. Moreover, investigating the effect of interdisciplinary interventions to improve HD patients' mood on their fatigue experience may be an interesting goal for further research.

ACKNOWLEDGEMENTS

The authors gratefully thank the patients involved in this study and the renal teams of the Zuyderland Medical Centre in Sittard-Geleen and Heerlen for assistance with recruitment and data collection.

AUTHORS' CONTRIBUTIONS

A.D.H.B., F.S. and B.L. conceived and designed the study. A.D.H.B. performed data acquisition. A.D.H.B. and B.L. performed data curation and formal analysis. F.S. and C.M.V.H. supervised the study. A.D.H.B. wrote the initial manuscript. B.L., F.S., M.B., G.G. and C.M.V.H. critically revised the manuscript for important intellectual content. All authors commented and approved the final manuscript.

CONFLICT OF INTEREST STATEMENT

All authors declare no conflicts of interest. There were no sources of financial support.

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Appendix 1: ESM PsyMate: questions

Domain	Item	Scale type
Mood	1. I feel cheerful	7-point Likert scale (1 'not at all' to 7 'very much')
	2. I feel relaxed	7-point Likert scale (1 'not at all' to 7 'very much')
	3. I feel satisfied	7-point Likert scale (1 'not at all' to 7 'very much')
	4. I feel anxious	7-point Likert scale (1 'not at all' to 7 'very much')
	5. I feel down	7-point Likert scale (1 'not at all' to 7 'very much')
	6. I feel confident	7-point Likert scale (1 'not at all' to 7 'very much')
	7. I feel irritable	7-point Likert scale (1 'not at all' to 7 'very much')
	8. I feel powerless	7-point Likert scale (1 'not at all' to 7 'very much')
	9. I am worrying	7-point Likert scale (1 'not at all' to 7 'very much')
Context activity	10. What am I doing (just before the beep)?	Doing nothing, resting, undergoing HD treatment, watching TV, reading, listening to music, Internet or social media, work, household, self-care, eating or drinking, having a conversation, relaxing, something else
	11. And also?	Resting, undergoing HD treatment, watching TV, reading, listening to music, Internet or social media, work, household, self-care, eating or drinking, having a conversation, relaxing, something else
	12. And. . .?	Resting, undergoing HD treatment, watching TV, reading, listening to music, Internet or social media, work, household, self-care, eating or drinking, having a conversation, relaxing, something else
	13. I can do this well	7-point Likert scale (1 'not at all' to 7 'very much')
	14. This is difficult for me	7-point Likert scale (1 'not at all' to 7 'very much')
	15. I would rather be doing something else	7-point Likert scale (1 'not at all' to 7 'very much')
Context location	16. Where am I?	At the HD unit, at home, at family's/friend's place, at work, public space, transport, somewhere else
Context social	17. Who am I with?	No one, healthcare professional, partner, family living in, family living out, friends, colleagues, acquaintances, strangers
	18. And also?	Healthcare professional, partner, family living in, family living out, friends, colleagues, acquaintances, strangers
	19. And. . .?	Healthcare professional, partner, family living in, family living out, friends, colleagues, acquaintances, strangers
Fatigue	20. I feel tired	7-point Likert scale (1 'not at all' to 7 'very much')
	Branched questions when feeling tired >1	
	20a. I feel mentally tired	7-point Likert scale (1 'not at all' to 7 'very much')
	20b. I feel physically tired	7-point Likert scale (1 'not at all' to 7 'very much')
Physical	21. I am suffering from a headache	7-point Likert scale (1 'not at all' to 7 'very much')
	22. I am suffering from muscle cramps	7-point Likert scale (1 'not at all' to 7 'very much')
	23. I am suffering from pain in bones or joints	7-point Likert scale (1 'not at all' to 7 'very much')
	24. I am suffering from itch	7-point Likert scale (1 'not at all' to 7 'very much')
	25. I am suffering from restless legs	7-point Likert scale (1 'not at all' to 7 'very much')
	26. I have been physically active before the beep	7-point Likert scale (1 'not at all' to 7 'very much')
	27. I have been mentally active before the beep	7-point Likert scale (1 'not at all' to 7 'very much')
General	28. This beep disturbed me	7-point Likert scale (1 'not at all' to 7 'very much')

Appendix 2: ESM PsyMate questionnaires

Morning questionnaire

Domain	Item	Scale type
Sleep—night rest	1. I slept well	7-point Likert scale (1 ‘not at all’ to 7 ‘very good’)
	2. How long did it take before I felt asleep yesterday evening?	0–5 min, 5–15 min, 15–30 min, 30–45 min, 45 min–1 h, 1–2 h, 2–4 h, >4 h
	3. How often did I wake up last night?	1 time, 2 times, 3 times, 4 times, 5 times, >5 times
	4. I feel rested	7-point Likert scale (1 ‘not at all’ to 7 ‘very much’)
Fatigue	5. I feel tired	7-point Likert scale (1 ‘not at all’ to 7 ‘very much’)
	Branched questions when feeling tired >1	
	5a. I feel mentally tired	7-point Likert scale (1 ‘not at all’ to 7 ‘very much’)
	5b. I feel physically tired	7-point Likert scale (1 ‘not at all’ to 7 ‘very much’)
	6. I do not look forward to this day	7-point Likert scale (1 ‘not at all’ to 7 ‘very much’)

Evening questionnaire

General	1. Today was an ordinary day	7-point Likert scale (1 ‘not at all’ to 7 ‘very much’)
	2. Without the application I would have done other things today	7-point Likert scale (1 ‘not at all’ to 7 ‘very much’)
Fatigue	3. Overall, I felt tired today	7-point Likert scale (1 ‘not at all’ to 7 ‘very much’)
	4. Overall, I felt mentally tired today	7-point Likert scale (1 ‘not at all’ to 7 ‘very much’)
	5. Overall, I felt physically tired today	7-point Likert scale (1 ‘not at all’ to 7 ‘very much’)
Mood	6. Overall, I felt good today	7-point Likert scale (1 ‘not at all’ to 7 ‘very much’)
	7. Overall, I felt tense today	7-point Likert scale (1 ‘not at all’ to 7 ‘very much’)
	8. Overall, I’ve been worrying today	7-point Likert scale (1 ‘not at all’ to 7 ‘very much’)
Medication	9. Today, I took my medication	7-point Likert scale (1 ‘nothing’ to 7 ‘everything’)