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# Day-to-day fluctuations of fatigue severity in individuals with knee osteoarthritis: an ecological momentary assessment approach

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## Abstract

**Objective:** The variable course of fatigue adds to the disease burden of patients with OA yet it has been poorly understood. This study aimed to describe within-person fluctuations of fatigue severity and explore its associations with pain, positive affect, negative affect, sleep, and perceived exertion of physical activity.

**Methods:** Individuals with chronic knee pain or a clinical diagnosis of knee OA ≥40 years of age completed daily assessments about fatigue, pain, positive affect, negative affect, sleep, perceived exertion of physical activity (numeric rating scale 0–10), and overwhelming fatigue (yes/no) on a smartphone over 14 days. Within-person fluctuations of fatigue severity were described by the probability of acute changes (PACs) and s.d.s. Associations with pain, positive affect, negative affect, sleep, and perceived exertion of physical activity were explored using multilevel models.

**Results:** Forty-nine individuals were included (mean age 63.4 years; 82% female). PACs and s.d.s of within-person daily fatigue fluctuations ranged from 0.00 to 0.80 and 0.35 to 2.95, respectively. Within-person associations of fatigue severity were moderate for positive affect [$\beta = -0.57$ (95% CI −0.67, −0.47)], weak for pain [$\beta = 0.41$ (95% CI 0.29, 0.53)] and negative affect [$\beta = 0.40$ (95% CI 0.21, 0.58)], and negligible for sleep [$\beta = -0.13$ (95% CI −0.18, −0.08)] and perceived exertion of physical activity [$\beta = 0.18$ (95% CI 0.09, 0.26)].

**Conclusion:** Some individuals showed almost stable day-to-day levels of fatigue severity, whereas others experienced a substantial number of clinically relevant fluctuations. To reduce the burden of daily fatigue fluctuations, our results suggest that pain, positive and negative affect rather than sleep and perceived exertion of physical activity should be considered as potential targets.

## Lay Summary

### What does this mean for patients?

Pain is the most commonly experienced symptom in OA. However, nearly half of the individuals report fatigue as well. The variable and unpredictable course of fatigue adds to the disease burden of OA, including pain, stiffness and functional limitations. Yet the ups and downs of fatigue severity have been poorly understood. For 14 days, individuals filled in daily questions about fatigue, pain, feeling happy and relaxed, feeling depressed and stressed, sleep and perceived exertion of physical activity on a smartphone. We found that some individuals with knee OA showed almost stable levels of fatigue severity, while others experienced many fatigue variations. When individuals reported more fatigue than usual, they also experienced more pain, felt less happy and relaxed or felt more depressed and stressed than usual. A night of worse sleep or a day of more perceived exertion of physical activity was not associated with more fatigue that same day. Thus pain, feeling happy and relaxed or depressed and stressed are likely to add to the daily variations of fatigue severity. Targeting these factors may help to lessen the burden of fatigue and its variable course.

**Keywords:** daily fluctuations, ecological momentary assessment, fatigue, knee osteoarthritis

**Key messages**

- The nature and extent of fatigue fluctuations differed per individual and from day to day.
- Fatigue fluctuations were moderately associated with positive affect and weakly associated with pain and negative affect.
- Sleep and perceived exertion of physical activity were not related to fatigue fluctuations within persons.

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## Introduction

OA is a chronic degenerative joint disease of the cartilage and surrounding tissues and a leading cause of disability worldwide [1]. In the Netherlands, 1.2 million individuals suffer from this disease, with the knee as most commonly affected site (≈60%) [2–4]. While pain, stiffness, and functional limitations have been considered the primary experienced symptoms leading to disability, research indicates fatigue is a significant contributor to disability as well [5].

In OA, nearly half of the individuals report debilitating fatigue [6–9]. Fatigue can be characterized as a feeling of physical and/or mental tiredness [10]. It is the enduring, subjective sensation of generalized tiredness or exhaustion. According to a recent qualitative metasynthesis, the nature of fatigue in chronic diseases, including OA, comprises four distinct features: it is a different fatigue than ever experienced before, the intensity is overwhelming, the trajectory is variable and unpredictable, and it impacts on sleep and sleep disturbances [11].

To date, the variable and unpredictable trajectory of fatigue in OA is poorly understood [10, 11]. Research on fatigue has traditionally adopted a rather static perspective by measuring fatigue as a single monotonous experience and investigating determinants of fatigue between individuals (i.e. interindividual). From these cross-sectional studies, it is already known that increased pain, decreased physical function, more sleep disturbances and decreased mental well-being are associated with higher levels of fatigue [8, 9]. Assessing variables at a single point in time, however, assumes them to be time-invariant, while this is often not the case [12]. Therefore, measuring fatigue longitudinally within individuals (i.e. intraindividual) in relation to time-varying variables may be more appropriate. So far, only a few studies have addressed these within-person fluctuations and their determinants in individuals with OA [7, 13]. However, these studies focused on similarities and differences across diseases rather than on the fluctuations. Further understanding of the link between modifiable physical and psychological determinants on the one hand and fatigue fluctuations on the other might provide clues on potential ways to improve the quality of life of individuals with OA [14].

Therefore, with this ecological momentary assessment study, we aimed to describe the nature and extent of within-person fluctuations of fatigue as well as the relationship with pain, positive affect, negative affect, sleep, and perceived exertion of physical activity in individuals with knee OA.

## Materials and methods

### Participants

Participants were recruited from the Knee Panel, founded by the Department of Rheumatology, Sint Maartenskliniek, Nijmegen, The Netherlands in 2018. The Knee Panel is a dynamic panel of people with a clinical diagnosis of knee OA or experiencing knee pain for most days of the month over a period of at least 3 consecutive months, living in the Netherlands, with Dutch language proficiency and ≥40 years of age. This panel is used in several research studies to unravel mechanisms of pain and fatigue in OA. Signing informed consent allowed researchers to invite participants for clinical trials and observational studies and to repurpose or combine data from various studies The Dutch Medical Research Committee of East Netherlands exempted ethical approval because this study was not subject to the Medical Research Involving Human Subjects Act (file number 2018-4832). At the time of recruitment, the panel consisted of ≈620 members. In order to participate in this study, participants had to be clinically diagnosed with knee OA or have knee pain for most days of the month in the past 3 months, be ≥40 years of age and be in possession of a smartphone with an internet connection.

### Procedure

Members from the Knee Panel received an e-mail with information concerning the research study. If an individual was interested in participating, he/she could read and sign the informed consent by following a personalized link to Castor, a web-based data collection and management system. After filling in the baseline questionnaire, an invitation with an instruction to download and install the Improve mobile app (Open HealthHub B.V., Utrecht, The Netherlands) was sent to the participant [15]. This allowed participants to fill in the ecological momentary assessments via their smartphone. Access to the application was provided with a unique code. If informed consent was not signed, participants did not receive the baseline questionnaire, were not able to download the electronic diary and no data was collected. The Dutch Medical Research Committee of East Netherlands exempted ethical approval because this study was not subject to the Medical Research Involving Human Subjects Act (file number 2019-5996).

### Measures

#### Baseline questionnaire

The baseline questionnaire consisted of questions regarding demographic details, health status and clinical characteristics. Demographic details included sex, age (in years), height and weight (to calculate BMI). Health status was measured using the European Quality of Life 5-Dimensions questionnaire visual analogue scale (0, worst imaginable health; 100, best imaginable health) [16]. Clinical characteristics were queried in terms of the presence of self-reported OA in other joint groups (yes/no), including the number of other affected joint groups (0–9), and the presence of comorbidities selected from a predefined list: lung diseases; cardiovascular diseases; stomach, intestinal and liver diseases; cancer; vision problems; hearing problems; dizziness and balance disorders; increased cholesterol; dementia; migraine or chronic headache; depression; anxiety disorders; fibromyalgia; kidney diseases; diabetes; thyroid problems; rheumatoid arthritis; osteoporosis; gout and other.

#### Ecological momentary assessments

Participants received four notifications per day at set times (09:00, 13:00, 17:00 and 21:00) for a period of 14 consecutive days to fill in the ecological momentary assessments. Each notification included a 30-min response period.

Fatigue severity was measured using a question with the highest factor loading in the physical domain from the Bristol Rheumatoid Arthritis Fatigue Multidimensional Questionnaire: 'How fatigued are you at this moment?' [numeric rating scale (NRS) 0, no fatigue–10, totally exhausted] [17]. Notifications took place at 09:00, 13:00, 17:00 and 21:00.

Pain was measured by asking, 'How much pain are you in right now?' (NRS: 0, no pain–10, worst imaginable pain possible) [18]. Notifications took place at 09:00, 13:00, 17:00 and 21:00.

Positive and negative affect were measured with items derived from the Circumplex Model of Affect [19, 20]. The two items 'I feel happy right now' (NRS 0, no, not at all–10, yes, very) and 'I feel relaxed right now' (NRS 0, no, not at all–10, yes, very) were averaged to get a single score for positive affect. The two items 'I feel depressed right now' (NRS 0, no, not at all–10, yes, very) and 'I feel stressed right now' (NRS 0, no, not at all–10, yes, very) were averaged to get a single score for negative affect. Notifications took place at 09:00, 13:00, 17:00 and 21:00.

Quality of sleep was measured using the question 'How well did you sleep last night?' (NRS 0, very poor–10, very good) from the Consensus Sleep Diary [21]. Notifications took place at 09:00.

Perceived exertion of physical activities was measured using the Borg scale by asking 'Since <time point last prompt>, how much difficulty were your activities causing you?' (NRS 0, no exertion–10, maximal exertion) [22]. Notifications took place at 13:00, 17:00 and 21:00.

Overwhelming fatigue was measured by asking 'Today, have you been overwhelmed by fatigue forcing you to stop your activities?' (yes/no). Notifications took place at 21:00.

### Data analyses

Descriptive statistics were used to describe the study sample [means and S.D.s for normally distributed continuous variables; medians and interquartile ranges (IQRs) for non-normally distributed continuous variables; absolute numbers and percentages for categorical or dichotomous variables]. In order to examine day-to-day variability, mean scores per participant per day were calculated for each variable. Accordingly, the percentage of completed scheduled assessments was computed by dividing the total number of days an assessment was completed by the total number of days an assessment was scheduled. If the percentage of completed scheduled assessments was <60%, participants were excluded from data analysis.

To describe the within-person fatigue fluctuations, an empty multilevel model (without determinants) was estimated with fatigue severity as a dependent variable and participant ID as a random effect. The percentage of fatigue severity variation attributed to between- and within-person differences was calculated by the intraclass correlation (ICC). Within-person differences were described by the Probability of Acute Changes (PAC) and S.D.s as proposed by Jahng *et al.* [23]. Briefly, the PAC examines the likelihood of clinically important changes between two consecutive time points and thus describes the frequency of either sudden elevations or decreases, whereas S.D.s show how dispersed the data are in relation to an individual's mean across a certain time span and thus show the amplitude of fluctuations [24]. The cut point for the PAC was set as −1.12 for improvement and 1.26 for worsening based on the minimal clinically important difference (MCID) for fatigue visual analogue scale in RA [25]. PACs equal to 0 were considered as stable and PACs between 0 and 0.2 as almost stable.

To explore the associations of fatigue fluctuations with the determinants pain, positive affect, negative affect, sleep and perceived exertion of physical activity, the following steps were undertaken. First, to examine whether a determinant has the potential to show a within-person relationship with fatigue severity, within-person variation over time needs to be present. Therefore, the ICC for each determinant was calculated in an empty multilevel model with the determinant as a dependent variable and participant ID as a random effect. For determinants with an ICC $\neq 1$, the determinant was separated in a between-person determinant, calculated by subtracting the grand mean (i.e. the mean of all individuals' average scores of the time-varying determinant) from the individual mean (i.e. an individual's mean of the time-varying determinant across 14 days), and a within-person determinant, calculated by subtracting the individual mean from an individual's time-varying determinant score on a particular day. These new determinants were added simultaneously as a fixed effect to the empty multilevel model. The within-person determinant was additionally tested for random slopes. The model was adjusted for age, BMI and/or sex if confounding was present (i.e. a difference ≥10% on the relationship fatigue severity and between-person determinant) and an unstructured covariance matrix was used. Restricted maximum likelihood estimation was used to handle missing data. Significance levels were set at $P < 0.05$. Separated models were estimated for each determinant. Associations <0.2 were considered as negligible, 0.2–0.5 as weak, 0.5–0.8 as moderate and ≥0.8 as strong [26]. All analyses were performed using Stata (version 17.0, StataCorp, College Station, TX, USA).

## Results

### Participant characteristics

A total of 156 participants signed informed consent, of which 72 completed the baseline questionnaire and downloaded the app. Eventually 62 participants started with the ecological momentary assessments. Data for 13 participants were excluded due to <60% completed scheduled assessments. This resulted in a final number of 49 participants included in the analysis. A total of 42 (86%) participants were clinically diagnosed with knee OA and 7 (14%) participants had knee pain for most days of the month in the past 3 months. The mean age was 63.4 years (S.D. 8.5; range 41–80) and 40 (82%) participants were female. The median BMI was 27.0 (IQR 23.9–29.7). At baseline, the mean health status was 68.0 (S.D. 13.8). The majority of participants (78%) indicated that they had OA in joints other than the knee, with a median of 2 (IQR 1–3) other affected joint groups, and almost every participant (96%) suffered from one or more comorbidities. The mean fatigue was 4.7 (S.D. 1.7) and 34 (69%) participants experienced overwhelming fatigue at least once in the 14-day period (range 1–11). Descriptive statistics are summarized in Table 1.

### Within-person fluctuations of fatigue severity

The empty multilevel model with fatigue severity as a dependent variable resulted in an ICC of 0.66. Put differently, of the total variance in fatigue severity, 66% was attributable to differences between persons and 34% to differences within persons (Table 2). During the observation period, PACs ranged from 0.00 to 0.80, with individuals experiencing a mean 4.5 (S.D. 2.2) day-to-day fluctuations that exceeded the MCID (Fig. 1). One individual (2%) experienced a PAC equal to 0 and nine individuals (18%) experienced a PAC of 0–0.2. The S.D.s ranged from 0.35 to 2.95 (Supplementary Fig. S1, available at *Rheumatology Advances in Practice* online).

**Table 1.** Characteristics of participants ($N = 49$)

| Characteristics | Values |
|---|---|
| Age, years, mean (S.D.) | 63.4 (8.5) |
| Female, *n* (%) | 40 (82) |
| BMI, kg/m2, median (IQR) | 27.0 (23.9–29.7) |
| Presence of OA in other joints, *n* (%) | 38 (78) |
| Number of other joint groups with OA (1–9), median (IQR) | 2 (1–3) |
| Presence of comorbidities, *n* (%) | 47 (96) |
| Number of comorbidities (1–20), median (IQR) | 1 (1–2) |
| Health status (0–100), mean (S.D.) | 68.0 (13.8) |
| NRS fatigue (0–10), mean (S.D.) | 4.7 (1.7) |
| NRS pain (0–10), mean (S.D.) | 4.1 (1.9) |
| NRS positive affect (0–10), mean (S.D.) | 6.9 (1.2) |
| NRS negative affect (0–10), mean (S.D.) | 1.6 (1.3) |
| NRS sleep (0–10), mean (S.D.) | 5.9 (1.5) |
| Perceived exertion of physical activity (0–10), mean (S.D.) | 4.9 (1.3) |
| Overwhelming fatigue, *n* (%) | 34 (69) |

For health status and sleep, higher scores reflect better outcomes; for fatigue, pain and positive affect, higher scores reflect higher levels; for negative affect and perceived exertion of physical activity, higher scores reflect more negative affect and perceived exertion of physical activity.

**Table 2.** Between- and within-person variance components of ecological momentary assessment variables

| Variables | Between-person variance, % | Within-person variance, % |
|---|---|---|
| Fatigue | 66 | 34 |
| Pain | 77 | 23 |
| Positive affect | 64 | 36 |
| Negative affect | 73 | 27 |
| Sleep | 33 | 67 |
| Perceived exertion of physical activity | 38 | 62 |

### Determinants of within-person fluctuations in fatigue severity

ICCs, as calculated in empty multilevel models, showed between-person as well as within-person differences for pain, positive affect, negative affect, sleep and perceived exertion of physical activity (Table 2). As such, within-person variation was present for all determinants. Random slopes were added for pain, negative affect and perceived exertion of physical activity, and age was added as a confounder in the model with sleep as a determinant. This resulted in moderate associations of fatigue severity with pain [$\beta = 0.65$ (95% CI 0.48, 0.83)], perceived exertion of physical activity [$\beta = 0.65$ (95% CI 0.32, 0.98)] and positive affect [$\beta = -0.52$ (95% CI $-0.90$, $-0.13$)] and in weak associations of fatigue severity with negative affect [$\beta = 0.49$ (95% CI 0.21, 0.77)] and sleep [$\beta = -0.39$ (95% CI $-0.70$, $-0.09$)] between persons (Table 3 and Supplementary Tables S1–S5, available at *Rheumatology Advances in Practice* online). Within-person associations of fatigue severity were moderate for positive affect [$\beta = -0.57$ (95% CI $-0.67$, $-0.47$)], weak for pain [$\beta = 0.41$ (95% CI 0.29, 0.53)] and negative affect [$\beta = 0.40$ (95% CI 0.21, 0.58)] and negligible for sleep [$\beta = -0.13$ (95% CI $-0.18$, $-0.08$)] and perceived exertion of physical activity [$\beta = 0.18$ (95% CI 0.09, 0.26)] (Table 3 and Supplementary Tables S1–S5, available at *Rheumatology Advances in Practice* online). All associations were statistically significant ($P < 0.05$).

## Discussion

In this ecological momentary assessment study, within-person fluctuations of fatigue severity and its associations with pain, positive affect, negative affect, sleep and perceived exertion of physical activity were examined in individuals with knee OA over a 14-day period. Although the nature and extent of day-to-day fluctuations of fatigue severity differed per person, the majority experienced a substantial number of clinically relevant fluctuations. These within-person fatigue fluctuations were associated with higher levels of pain and negative affect and with lower levels of positive affect. Associations with sleep and perceived exertion of physical activity were negligible, although significant.

To the best of our knowledge, this is the first time that the extent of within-person fluctuations of fatigue severity have been expressed in PACs and S.D.s in individuals with OA. While some individuals showed fairly stable day-to-day levels of fatigue, other individuals experienced a substantial number of clinically relevant fluctuations in the intensity of daily fatigue. Individual fluctuations in daily pain have been assessed before in a population with rheumatic diseases, including OA [27]. The extent of these pain fluctuations was similar to the extent of fatigue fluctuations found in our study.

Our data support the already existing evidence for the association of fatigue severity and pain [9]. As expected, this association was also found within persons, indicating that having more pain than usual increases levels of fatigue severity that same day. Between-person associations of fatigue severity and affect found cross-sectionally were also established within persons. Individuals reporting more positive affect than usual experienced significantly less fatigue, whereas individuals reporting more negative affect than usual were more fatigued. These findings are consistent with those found earlier in women with fibromyalgia, RA and OA [13]. More interesting is the discrepancy of between- and within-person associations of fatigue with sleep and perceived exertion of physical activity. Although we found between-person associations of fatigue severity with sleep and perceived exertion of physical activity, within-person associations of both determinants were negligible. This suggests that sleeping a night better than usual will not make individuals feel less fatigued that same day. Similarly, higher levels of perceived exertion of physical activity than usual do not make individuals more fatigued. According to a narrative literature review, it is often assumed that a night of worse sleep or a day of more physical activity is associated with more fatigue [5]. However, this is based on results between persons, while our results focused on within persons. Furthermore, we used perceived exertion of physical activity as a proxy for assessing whether someone had been physically active (i.e. how hard, heavy and strenuous the activity was), regardless of the activity per se [22]. Consequently, more ecological momentary assessment studies examining fatigue fluctuations are needed before our results can be confirmed or refuted.

## Strengths and limitations

A strength of our study was that we were able to quantify fatigue fluctuations in a population with OA for the first time.

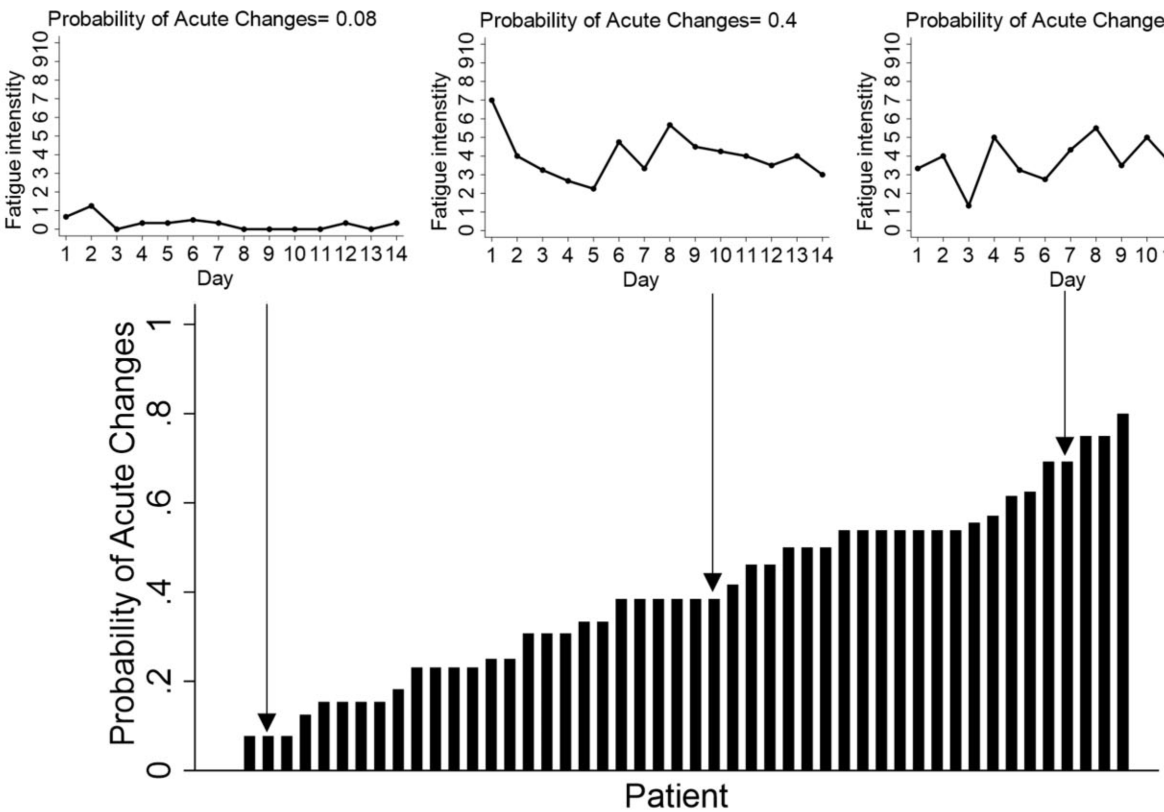


**Figure 1.** PACs of average fatigue severity over a period of 14 days per participant. Each bar represents one participant (*N* = 49). One bar graph cannot be seen, as this individual had no clinically meaningful fluctuations of fatigue (PAC = 0). Higher PACs indicate more clinically important fluctuations. Day-to-day fatigue scores of three participants are displayed at the top

**Table 3.** Between- and within-person associations of five time-varying determinants with fatigue

| Fixed effects | Estimate | 95% CI |
|---|---|---|
| Pain | | |
| Between person | 0.65 | 0.48, 0.83 |
| Within person | 0.41 | 0.29, 0.53 |
| Positive affect | | |
| Between person | −0.52 | −0.90, −0.13 |
| Within person | −0.57 | −0.67, −0.47 |
| Negative affect | | |
| Between person | 0.49 | 0.21, 0.77 |
| Within person | 0.40 | 0.21, 0.58 |
| Sleep | | |
| Between person | −0.39 | −0.70, −0.09 |
| Within person | −0.13 | −0.18, −0.08 |
| Physical activity | | |
| Between person | 0.65 | 0.32, 0.98 |
| Within person | 0.18 | 0.09, 0.26 |

Higher scores on pain, negative affect and perceived exertion of physical activity are associated with more fatigue. Higher scores on positive affect and sleep are associated with less fatigue. Age was added as a confounder in the model with sleep as a determinant.

Additionally, individuals were recruited from a community panel rather than from a hospital setting. This increases the generalizability of the findings.

There are also limitations to take into account when interpreting our findings. First, the total number of participants was relatively small, as a substantial number of patients signed informed consent but did not download the app. This may have to do with potential challenges accompanying the use of electronic data collection tools. Second, a considerable number of scheduled ecological momentary assessments were not completed, resulting in missing data. Accordingly, we could not investigate the within-day fluctuations of fatigue. A study investigating factors that affect ecological momentary assessment completion in patients with chronic pain did not show evidence to suggest that completion rates differ by medical diagnoses, gender or variations in pain levels [28]. Third, the mean fatigue level in our study is somewhat higher as compared with others [7]. This indicates that our data may represent an overestimation of the level of fatigue. Finally, the validity of Borg's perceived exertion construct is well established but has not been commonly used in OA ecological momentary assessment studies [29]. Therefore, the validity and usefulness of this construct in a daily dairy design should be further explored.

## Recommendations for future research

Future research in fatigue may focus on the effect of self-management on pain, positive affect, and negative affect. Addressing the potential modifiable determinants of fatigue has been proven clinically effective in patients with RA [30]. Therefore, it might be interesting to explore whether participants with high skills in self-management experience less fatigue. It is also important to investigate other determinants that might contribute to daily fluctuations of fatigue. Although the present study focused on determinants of which associations were already demonstrated cross-sectionally, determinants such as activity pacing and illness beliefs are less well studied in OA but may be directly related [5, 31].

## Conclusions

In conclusion, some individuals showed almost stable day-to-day levels of fatigue severity, whereas others experienced a substantial number of clinically relevant fluctuations. To reduce the burden of daily fluctuations in fatigue, our results suggest that pain, positive affect, and negative affect, rather than sleep and perceived exertion of physical activity, should be considered as potential targets.

## Supplementary material

Supplementary material is available at *Rheumatology Advances in Practice* online.

## Data availability

The data underlying this article will be shared upon reasonable request to the corresponding author.

## Authors' contributions

Conception and design: C. H. M. van den Ende, Y. A. S. Peters, J. E. Vriezekolk; Collection and assembly of data: Y. A. S. Peters; Analysis and interpretation of the data: M. W. J. Heijman, C. H. M. van den Ende, J. E. Vriezekolk; Drafting of the article: M. W. J. Heijman, C. H. M. van den Ende, Y. A. S. Peters, E. A. M. Mahler, C. D. Popa, J. E. Vriezekolk; Final approval of the article: M. W. J Heijman, C. H. M van den Ende, Y. A. S. Peters, E. A. M. Mahler, C. D. Popa, J. E. Vriezekolk.

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