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 osteoarthritis, yet 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 osteoarthritis over 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 probability of acute changes (PACs) and standard deviations (SDs). 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 SDs of within-person daily fatigue fluctuations ranged from 0.00-0.80 and 0.35-2.95, respectively. Within-person associations of fatigue severity were moderate for positive affect (B=-0.57, 95%CI= -0.67;-0.47), weak for pain (B=0.41, 95%CI= 0.29;0.53) and negative affect (B=0.40, 95%CI= 0.21;0.58), and negligible for sleep (B=-0.13, 95%CI= -0.18;-0.08) and perceived exertion of physical activity (B=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.

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

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.
Lay summary

What does this mean for patients?

Pain is the most commonly experienced symptom in osteoarthritis. However, nearly half of the individuals report fatigue as well. The variable and unpredictable course of fatigue adds to the disease burden of osteoarthritis 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 osteoarthritis showed almost stable levels of fatigue severity. 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 together with 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.
Introduction

Osteoarthritis (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 as a significant contributor for disability as well (5).

In OA nearly half of the individuals report debilitating fatigue (6–9). Fatigue can be characterised as a feeling of physical or mental tiredness, or both (10). It is the enduring, subjective sensation of generalized tiredness or exhaustion. According to a recent qualitative meta-synthesis, the nature of fatigue in chronic diseases including OA comprises four distinct features: 1) it is a different fatigue than ever experienced before, 2) the intensity is overwhelming, 3) the trajectory is variable and unpredictable, and 4) the impact 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 itself. Further understanding of the link between modifiable physical and psychological determinants on one hand and fatigue fluctuations on the other hand, might provide clues on potential ways to improve the quality of life for 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 three consecutive months, living in the Netherlands with Dutch
language proficiency, and aged 40 years or over. This panel is used in several research studies to unravel mechanisms of pain and fatigue in osteoarthritis. 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 approximately 620 members. In order to participate in this study, participants had to 1) be clinically diagnosed with knee OA or have knee pain for most days of the month in the past three months, 2) be older than 40 years of age, and 3) 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, they could read and sign informed consent by following a personalised 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 given 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), length and weight (to calculate Body Mass Index (BMI)). Health status was measured using the EQ-5D visual analogue scale (EQ-VAS) (0: worst imaginable health – 100: best imaginable health) (16). Clinical characteristics were queried in terms of presence of self-reported OA in other joint groups (yes/no), including the number of other affected joint groups (0–9), and presence of comorbidities selected from a pre-defined 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 4 notifications per day at set times (9.00 a.m., 1.00 p.m., 5.00 p.m., and 9.00 p.m.) for a period of 14 consecutive days to fill in the ecological momentary assessments. Each notification included a 30-minute 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 (BRAF-MDQ), “how fatigued are you at this moment?” (numeric rating scale (NRS) 0: no fatigue – 10: totally exhausted) (17). Notifications took place at 9.00 a.m., 1.00 p.m., 5.00 p.m., and 9.00 p.m.

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 9.00 a.m., 1.00 p.m., 5.00 p.m., and 9.00 p.m.

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 9.00 a.m., 1.00 p.m., 5.00 p.m., and 9.00 p.m.

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 9.00 a.m.

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 1.00 p.m., 5.00 p.m., and 9.00 p.m.

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 9.00 p.m.

Data analyses – Descriptive statistics were used to describe the study sample (means and standard deviations for normally distributed continuous variables; median and interquartile ranges 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 for data analysis.

To describe the within-person fatigue fluctuations, an empty multilevel model (without determinants) was estimated with fatigue severity as dependent variable and participant ID as 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 standard deviations (SDs) as proposed by Jahng et al. (2008) (23). Briefly, the PAC examines the likelihood of clinical important changes between two consecutive time points and thus describes the frequency of either sudden elevations or decreases, whereas SDs 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 on -1.12 for improvement and 1.26 for worsening based on the minimal important clinical difference for fatigue visual analogue scale (VAS) in rheumatoid arthritis (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. Firstly, 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 dependent variable and participant ID as 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 at a particular day. These new determinants were added simultaneously as 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 $\geq 10\%$ 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, between 0.2 and $<0.5$ as weak, between 0.5 and $<0.8$ as moderate, and $\geq 0.8$ as strong (26). All analyses were performed using STATA (version 17.0, StataCorp LLC, College Station, Texas).

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 of 13 participants were excluded due to $<60\%$ completed scheduled assessments. This resulted in a final number of 49 participants included in the analysis. Forty-two (86%) participants were clinically diagnosed with knee osteoarthritis and seven...
1 (14%) participants had knee pain for most days of the month in the past three months. The mean (SD) age was 63.5 (8.5) years (range 41-80) and 40 (82%) participants were female. Median (IQR) Body Mass Index (BMI) was 27.0 (23.9-29.7). At baseline, the mean (SD) health status was 68.0 (13.8). The majority of participants (78%) indicated that they had OA in other joints than the knee, with median (IQR) 2 (1-3) other affected joints groups and almost every participant (96%) suffered from one or more comorbidities. Mean (SD) fatigue was 4.7 (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 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 mean (SD) 4.5 (2.2) day-to-day fluctuations that exceeded the minimal clinical important difference (Figure 1). One individual (2%) experienced a PAC equal to 0 and nine individuals (18%) experienced a PAC between 0 and 0.2. SDs ranged from 0.35 to 2.95 (Supplementary Figure S1. Available at Rheumatology Advances in Practice online).

**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 confounder in the model with sleep as determinant. This resulted in moderate associations of fatigue severity with pain (B=0.65, 95% confidence interval (CI)= 0.48;0.83), perceived exertion of physical activity (B=0.65, 95%CI= 0.32;0.98), and positive affect (B=-0.52, 95%CI= -0.90;-0.13) and in weak associations of fatigue severity with negative affect (B=0.49, 95%CI= 0.21;0.77) and sleep (B=-0.39, 95%CI= -0.70;-0.09) between-persons (Table 3 and Supplementary Tables S1-5. Available at Rheumatology Advances in Practice online). Within-persons associations of fatigue severity were moderate for positive affect (B=-0.57, 95%CI= -0.67;-0.47), weak for pain (B=-0.41, 95%CI= 0.29;0.53) and negative affect (B=0.40, 95%CI= 0.21;0.58), and negligible for sleep (B=-0.13, 95%CI= -0.18;-0.08), and perceived exertion of physical activity (B=0.18, 95%CI= 0.09;0.26) (Table 3 and Supplementary Tables S1-5). 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, although significant, negligible.

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. 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. Firstly, 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. Secondly, a considerable number of scheduled ecological momentary assessments was 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). Thirdly, the mean fatigue level in our study is somewhat higher as compared to 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 osteoarthritis 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 and negative affect. Addressing the potential modifiable determinants of fatigue have been proven clinical effective in patients with Rheumatoid Arthritis (30). Therefore, it might be interesting to explore whether participants with high skills in self-management experience less fatigue. It is additionally 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 directly be 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 together with positive and negative affect rather than sleep and perceived exertion of physical activity should be considered as potential targets.
No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

**Conflicts of interest**

The authors declare no conflicts of interest.

**Data availability**

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

**References**


### Table 1. Characteristics of participants (n=49).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (in years), mean (SD)</td>
<td>63.4 (8.5)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>40 (82)</td>
</tr>
<tr>
<td>BMI (kg/m²), median (IQR)</td>
<td>27.0 (23.9-29.7)</td>
</tr>
<tr>
<td>Presence of osteoarthritis in other joints, n (%)</td>
<td>38 (78)</td>
</tr>
<tr>
<td>Number of other joint groups with osteoarthritis (1–9), median (IQR)</td>
<td>2 (1-3)</td>
</tr>
<tr>
<td>Presence of comorbidities, n (%)</td>
<td>47 (96)</td>
</tr>
<tr>
<td>Number of comorbidities (1-20), median (IQR)</td>
<td>1 (1-2)</td>
</tr>
<tr>
<td>Health status (0-100), mean (SD)</td>
<td>68.0 (13.8)</td>
</tr>
<tr>
<td>NRS fatigue (0-10), mean (SD)</td>
<td>4.7 (1.7)</td>
</tr>
<tr>
<td>NRS pain (0-10), mean (SD)</td>
<td>4.1 (1.9)</td>
</tr>
<tr>
<td>NRS positive affect (0-10), mean (SD)</td>
<td>6.9 (1.2)</td>
</tr>
<tr>
<td>NRS negative affect (0-10), mean (SD)</td>
<td>1.6 (1.3)</td>
</tr>
<tr>
<td>NRS sleep (0-10), mean (SD)</td>
<td>5.9 (1.5)</td>
</tr>
<tr>
<td>Perceived exertion of physical activity (0-10), mean (SD)</td>
<td>4.9 (1.3)</td>
</tr>
<tr>
<td>Overwhelming fatigue, n (%)</td>
<td>34 (69%)</td>
</tr>
</tbody>
</table>

SD= standard deviations; BMI= body mass index; IQR= interquartile range; NRS= numeric rating scale. 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.

<table>
<thead>
<tr>
<th></th>
<th>Between-person variance</th>
<th>Within-person variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>66%</td>
<td>34%</td>
</tr>
<tr>
<td>Pain</td>
<td>77%</td>
<td>23%</td>
</tr>
<tr>
<td>Positive affect</td>
<td>64%</td>
<td>36%</td>
</tr>
<tr>
<td>Negative affect</td>
<td>73%</td>
<td>27%</td>
</tr>
<tr>
<td>Sleep</td>
<td>33%</td>
<td>67%</td>
</tr>
<tr>
<td>Perceived exertion of physical activity</td>
<td>38%</td>
<td>62%</td>
</tr>
</tbody>
</table>
### Table 3. Between- and within-person associations of five time-varying determinants with fatigue.

<table>
<thead>
<tr>
<th>Fixed effects</th>
<th>Estimate</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between-person</td>
<td>0.65</td>
<td>0.48;0.83</td>
</tr>
<tr>
<td>Within-person</td>
<td>0.41</td>
<td>0.29;0.53</td>
</tr>
<tr>
<td>Positive affect</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between-person</td>
<td>-0.52</td>
<td>-0.90;-0.13</td>
</tr>
<tr>
<td>Within-person</td>
<td>-0.57</td>
<td>-0.67;-0.47</td>
</tr>
<tr>
<td>Negative affect</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between-person</td>
<td>0.49</td>
<td>0.21;0.77</td>
</tr>
<tr>
<td>Within-person</td>
<td>0.40</td>
<td>0.21;0.58</td>
</tr>
<tr>
<td>Sleep</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between-person</td>
<td>-0.39</td>
<td>-0.70;-0.09</td>
</tr>
<tr>
<td>Within-person</td>
<td>-0.13</td>
<td>-0.18;-0.08</td>
</tr>
<tr>
<td>Physical activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between-person</td>
<td>0.65</td>
<td>0.32;0.98</td>
</tr>
<tr>
<td>Within-person</td>
<td>0.18</td>
<td>0.09;0.26</td>
</tr>
</tbody>
</table>

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 confounder in the model with sleep as determinant.
Figure 1. Probability of Acute Changes (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 clinical meaningful fluctuations of fatigue (PAC=0). Higher PACs indicate more clinical important fluctuations. Day-to-day fatigue scores of three participants are displayed at the top.
Figure 1. Probability of Acute Changes (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 clinical meaningful fluctuations of fatigue (PAC=0). Higher PACs indicate more clinical important fluctuations. Day-to-day fatigue scores of three participants are displayed at the top.