

ORIGINAL ARTICLE

# The dynamics in health-related quality of life of patients with stable coronary artery disease were revealed: a network analysis

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## Abstract

**Objective:** Health-related quality of life (HRQoL) is a dynamic construct. Experience sampling methods (ESM) are becoming increasingly popular to capture within-person fluctuations in HRQoL. An emerging approach to analyze such momentary data is network analysis. Our aim was to explore the use of network analysis for investigating the dynamics within individual's HRQoL.

**Study Design and Setting:** We analyzed ESM data of 30 patients with stable coronary artery disease (CAD). Patients completed eight HRQoL items representing four scales (i.e., positive mood, negative mood, CAD symptoms, and physical state) at nine times a day for seven consecutive days. Network analysis was used to analyze the data at group level to estimate the average HRQoL dynamics and at patient level to estimate HRQoL dynamics of individual patients.

**Results:** Group-level analysis showed that, on average, feeling “tired” and feeling “anxious” are the most central items in patients' HRQoL. Patient-level analysis revealed differences in patients' network structures, indicating within-person differences in HRQoL dynamics.

**Conclusion:** This study is one of the first to apply network analysis to momentary HRQoL data. To the extent that network models are meaningful representations of HRQoL dynamics, they may help deepening our insight into experienced HRQoL and provide targets for personalized treatment. © 2018 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

**Keywords:** Health-related quality of life; Network analysis; Experience sampling; Stable coronary artery disease; Personalized treatment; Psychometrics

## 1. Introduction

Health-related quality of life (HRQoL) is a dynamic construct [1]. In recent years, experience sampling methods (ESM) are becoming increasingly popular to capture within-person fluctuations in moods, symptoms, and other

domains subsumed under the umbrella term HRQoL [2–7]. In ESM studies, individuals are measured repeatedly within short-time intervals during daily life [8–11]. Such momentary measurements allow an ecologically valid examination of the *dynamics* within individual's HRQoL, that is, how different moods, symptoms, and other HRQoL domains influence each other or themselves over time [3,12–14]. For example, pain may result in insomnia, making the patient tired, eventually increasing his sensitivity to pain, which makes sleeping even more difficult [15]. An emerging approach to explore, visualize and analyze such dynamics is *network analysis* [16,17]. In network analysis a specific construct (e.g., HRQoL or major depressive disorder) is represented as a network of causally interacting

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**What is new?****Key findings**

- We illustrated the use of network analysis to examine momentary HRQoL data on group level and patient level.
- Group-level analysis revealed that, on average, feeling “tired” and “anxious” played the most central role in patients’ HRQoL.
- Patient-level analysis showed within-person differences in network structures, quantifying within-person differences in the dynamics among moods and symptoms.

**What this adds to what was known?**

- This study is one of the first to apply network analysis to momentary health-related quality of life (HRQoL) data.
- In network analysis, the potential dynamical relationships among observed variables are revealed, that is, how different moods, symptoms, and other HRQoL domains influence each other or themselves over time.

**What is the implication and what should change now?**

- Results suggest that network analysis can be used to highlight which moods, symptoms, and other HRQoL domains are more central and strongly connected with each other.
- Such analysis may deepen our insights into the HRQoL, exceeding static index scores, and provide targets for personalized treatment strategies.

variables [18–20]. By estimating network models on ESM data, potential dynamical relationships among observed variables can be revealed.

This study aims to illustrate network analysis for investigating the dynamics within patient’s HRQoL using ESM data of patients with stable coronary artery disease (CAD) who have multiple comorbidities and are scheduled for cardiac intervention. We will apply network analysis on group-level and patient-level data and illustrate how they can be used to study HRQoL dynamics.

## 2. Methods

### 2.1. Patient sample

All patients were recruited at the cardiology department of the Academic Medical Center Amsterdam and its

referring hospitals. Patients were eligible if they had stable CAD and were scheduled for elective coronary artery bypass graft (CABG) or elective percutaneous coronary intervention (PCI). Patients had to have at least one of the following comorbidities: diabetes mellitus, obesity (body mass index  $\geq 30$  kg/m<sup>2</sup>), joint disease (rheumatism, arthritis, osteoarthritis, and gout), pulmonary disease (asthma, chronic obstructive pulmonary disease, and bronchiectasis) or another chronic disease (chronic renal insufficiency, psoriasis, hypertension, HIV, peripheral facial paresis, thymoma with immunodeficiency, and hypothyroidism). In addition, patients needed to have experience with the use of smartphones (indicated at their own discretion) and a functional Wi-Fi connection at home.

### 2.2. ESM study

#### 2.2.1. Procedure

The week before the cardiac intervention, ESM was conducted over the course of 7 days. Patients received an iPod for the duration of the assessment period with the PsyMate application installed ([www.psymate.eu](http://www.psymate.eu)). PsyMate was programmed to give nine beeps at random moments within predefined time slots (maximally 2 hours apart) during daytime. After each beep, a set of items assessing HRQoL was presented. If patients did not respond within 15 minutes, the measurement was considered missing.

#### 2.2.2. HRQoL assessment

Patients rated a total of 14 items measuring four subscales of HRQoL. *Positive mood* was measured with four items (i.e., “I feel... ‘energetic’, ‘relaxed’, ‘cheerful’, and ‘happy’”). *Negative mood* was measured with four items (i.e., “I feel... ‘anxious’, ‘irritated’, ‘worried’, and ‘sad’”). *CAD symptoms* were measured with three items (i.e., “I feel... ‘pain on my chest’, ‘tightness on my chest’, and ‘an oppressive feeling on my chest’”). *Physical state* was measured with three items (i.e., “I feel... ‘shortness of breath’, ‘tired’, and ‘other pains’”). All items were rated on a 7-point scale, ranging from 1 (“not at all”) to 7 (“very much”).

### 2.3. Data preparation

#### 2.3.1. Item selection

A subset of eight items was selected to obtain interpretable network structures and to increase power; simulation studies have shown adequate performance of network estimation for eight-node networks using 50 momentary measurements [21]. Items were selected as follows: for each subscale, we calculated the reliability and selected the two items with the highest reliability.

### 2.4. Network estimation

To assess the dynamical relationships among HRQoL items, each patient’s momentary data were analyzed with vector autoregressive (VAR) models. In our VAR model,

each item was regressed on the values of all other items (including itself) at the previous time point [22–29]. The resulting regression coefficients represent the degree to which changes in one item predict changes in the other items and thus capture the dynamical relationships among HRQoL items at the time scale implemented in the ESM protocol and form the basis for our network models. Network models were estimated using a multilevel extension of the VAR model [30–32]. In the multilevel VAR, the average dynamical relationships are modeled as *fixed effects*, whereas regression coefficients are allowed to vary between patients as *random effects*. In doing so, data were analyzed at group level (group networks) and patient level (patient networks). In the *group networks*, average dynamical relationships between items are represented in a network structure in which items are represented as *nodes* that are connected by *edges* that correspond to the average regression coefficients (i.e., fixed effects), where the average is taken over the different patients. In the *patient networks*, patients' own dynamical relationships are represented in a unique network structure. Patient-level networks are based on the fixed and random effects of the group-level network. Items are also represented as nodes, but they are connected by edges that correspond to the patient's regression coefficients (i.e., random effects).

#### 2.4.1. Temporal networks

For both group- and patient-level analyses, we estimated *temporal networks*. Temporal networks allow us to examine how moods and symptoms influence each other at the next measurement (i.e., temporal relationship), potentially providing information about the direction of the effect [25,28,30,33]. In the temporal networks, edges (with arrowheads) indicate a temporal relationship between two nodes. The arrowhead indicates the direction of the effect. The color of the edge corresponds to the valence of the relationship; positive associations are blue, negative associations are red. Edge thickness and saturation represent the strength of the relationship [34].

#### 2.4.2. Contemporaneous networks

For both the group- and patient-level analyses, we estimated *contemporaneous networks*, which models the relationships occurring within consecutive measurements (i.e., contemporaneous relationships). Contemporaneous networks enable the examination of how moods and symptoms co-occur simultaneously [24,25,35]. In the contemporaneous networks, edges indicate a partial correlation between two nodes at the same time, after controlling for both temporal effects and all other variables within the same measurement. Contemporaneous relationships are computed by correlating the residuals of the temporal effects (i.e., the difference between the predicted value and the observed value) [36]. Edge colors indicate the valence of the relationship, and edge saturation and edge thickness represent the strength of the relationship [34]. Edges

have no arrowheads, as contemporaneous associations make no statement about the direction of the effect [24].

#### 2.4.3. Data preparation

VAR models assume stationarity of all variables, that is, they do not exhibit a trend in the mean or variance across time [22,37]. Following common practice to handle violations of stationarity in the means, we *removed the linear trend* by taking the residuals from items with a significant linear trend on time [35]. VAR models also assume equal time lags between consecutive measurements [38]. Because ESM was performed over 7 days, six pairs of consecutive measurements have nights between them. Given this increased time lag, we did not regress each first measurement of the day on the last measurement of the previous day, treating the latter as missing data [38].

#### 2.5. Network analysis

For group-level analyses we visually inspected the group networks to examine the average dynamical relationships. For patient-level analysis we performed network analysis to compare patients' global network structure (i.e., network connectivity) and specific parts of their network structure (i.e., node centrality).

##### 2.5.1. Network connectivity

*Network connectivity* indicates how strongly nodes in the network are interconnected [39]. Higher network connectivity

**Table 1.** Demographics and clinical characteristics of the final sample

Characteristics	Final sample (N = 30)
Demographics	
Mean age (SD), range	65 (8), 50–86
Number of males (%)	24 (80)
Mean number of observations (SD), range	44 (17), 10–74
Mean response rate (SD), range	70 (0.21), 0.26–0.94
Intervention (%)	
CABG	6 (20)
PCI	24 (30)
Number of comorbidities (%)	
1	13 (43)
2	8 (27)
3	5 (17)
4	4 (13)

*Abbreviations:* CABG, elective coronary artery bypass graft; PCI, percutaneous coronary intervention; SD, standard deviation.

*Demographics* gives the average age, gender, average number of observations, and the average number of responses to all beeps presented in the momentary measurement. *Mean response rate* gives the mean ratio of the total presented beeps and the number of beeps to which patients responded. *Intervention* gives the number of patients who had a CABG or PCI. *Number of comorbidities* gives the number of patients who had either one, two, three, or four comorbidities besides stable CAD.

**Table 2.** The average item scores and standard deviations over time of the items used in network analysis ( $N = 30$ )

Items	Mean	SD
Cheerful	4.82	1.17
Relaxed	4.78	1.08
Anxious	1.82	1.26
Worry	1.87	1.44
Tightness on chest	2.05	1.52
Oppressive feelings on chest	2.13	1.52
Tired	3.51	1.55
Shortness of breath	2.82	1.53

Abbreviation: SD, standard deviation.

indicates stronger interactions between moods and symptoms. Network connectivity was measured with *network density*, which is calculated by dividing the sum of all absolute edge strengths by the number of possible edges.

To illustrate network connectivity we compared the networks of a patient with high network connectivity with a patient with low network connectivity, that is, we selected the patients with the highest and lowest network density of temporal networks and compared their network structures for both temporal and contemporaneous networks.

### 2.5.2. Node centrality

*Node centrality* refers to the importance of a node within the network [40,41]. Node centrality was measured by *node strength*, indicating the summed absolute edge strengths connected to a specific node. For the temporal networks,

node strength is calculated by *out-strength* (the summed strengths of all outgoing edges) and *in-strength* (the summed strengths of all incoming edges). In the contemporaneous networks, node strength is calculated by the summed edge strengths.

We compared node strengths of a patient who reported high levels of anxiety with a patient who reported low levels of anxiety to illustrate node centrality at the patient level. For both temporal and contemporaneous networks, we visualized patients' node strengths in a centrality plot.

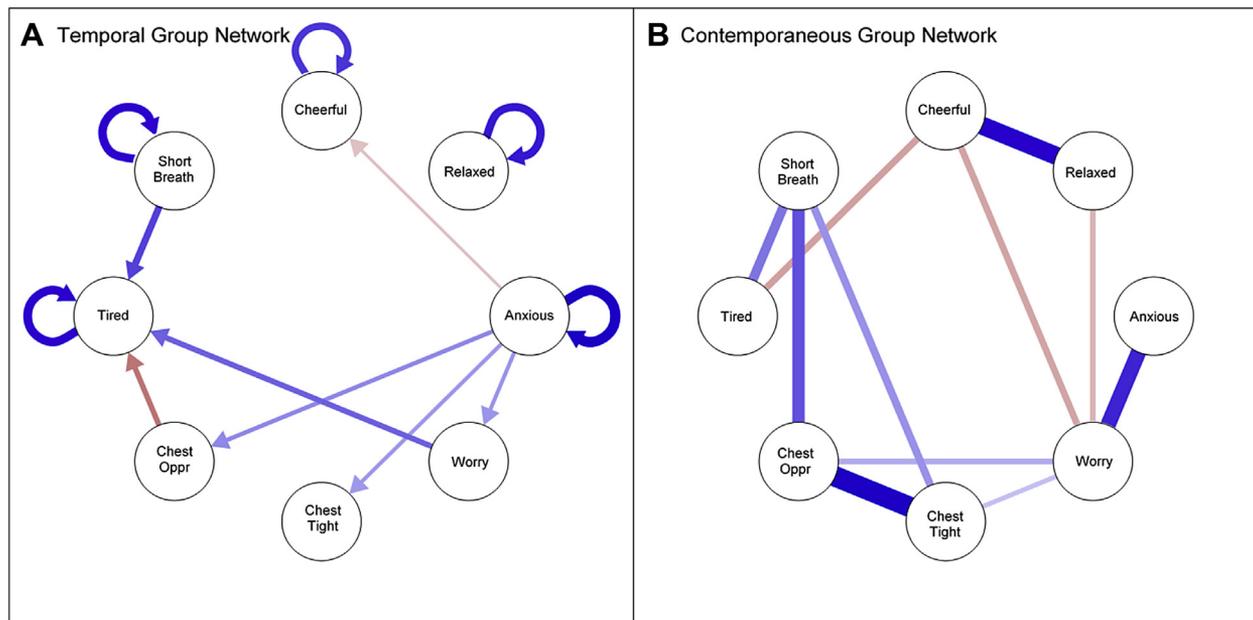
### 2.6. Software

All networks were estimated using the R-package mlVAR version 0.4.1 [42]. mlVAR estimates the model parameters using a two-step frequentist multilevel method [24,30]. In the first step temporal effects are estimated by sequentially estimating univariate multilevel regression models of one variable, given all lagged variables. In the second step contemporaneous effects are estimated by sequentially estimating univariate multilevel regression models to predict the residuals. Network connectivity and node centrality were computed and visualized with the R-package qgraph version 1.5 [34].

## 3. Results

### 3.1. Patients

Data collection took place from 2016 until 2018. From the 37 patients who agreed to participate, seven were



**Fig. 1.** The group networks. (A) temporal group network ( $N = 30$ ). (B) Contemporaneous group network connectivity ( $N = 30$ ). Circles (nodes) represent HRQoL items, edges (arrows) represent a temporal/contemporaneous relationship between another variable at the next measurement. Blue edges are positive associations, and red edges are negative associations. Saturation of the edge represents the strength of the relationship; the stronger, the more saturated. Only significant edges ( $\alpha = .05$ ) are shown [34]. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

excluded from analysis: five did not perform the momentary assessment before the intervention, and two did not receive a cardiac intervention (see Table 1 for the demographics and clinical characteristics).

### 3.2. Item selection

On the basis of the reliability analysis (see Table A1), we selected items “cheerful” and “relaxed” from the positive mood scale. From the negative mood scale, we selected “anxious” and “worry.” From the CAD symptom scale, we selected “oppressive feelings on chest” and “tightness on chest.” From the physical state scale, we selected “tired” and “shortness of breath.” Item descriptives are depicted in Table 2.

### 3.3. Group networks

#### 3.3.1. Temporal group network

The temporal group network in Fig. 1A shows that nodes “anxious” and “tired” play a central role in the network. “Anxious” has many outgoing edges; indicating that anxiety has a high influence on other moods and symptoms. “Tired” has many ingoing edges, indicating patients are susceptible to become more/less tired as other moods and symptoms are experienced. Furthermore, most nodes show self-loops (edges pointing toward themselves), indicating that current experiences are predictive of subsequent experiences. For example, when patients feel tired, they are likely to remain tired at the next measurement. CAD symptoms do not show self-loops, indicating that they are

experienced for a shorter time. Noteworthy are the positive edges between nodes of similar valence, indicating that moods and symptoms of similar valence tend to reinforce each other. Also noteworthy are the positive edges from “anxious” toward the CAD symptoms, indicating that increased anxiety may increase CAD symptoms.

#### 3.3.2. Contemporaneous group network

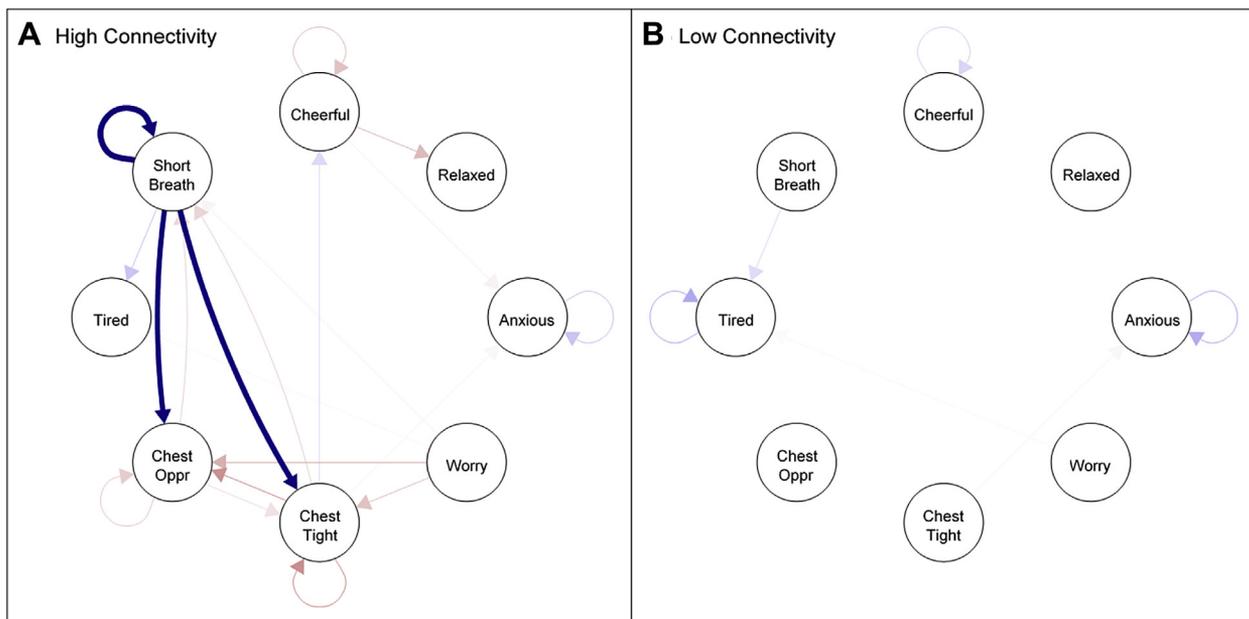
The contemporaneous group network in Fig. 1B also shows that nodes of similar valence have positive edges between them. In addition, we find negative edges between nodes of opposite valence. These results might indicate that moods and symptoms of similar valence co-activate, and moods and symptoms of opposite valence keep each other in check.

### 3.4. Patient networks

All temporal patient networks are depicted in Fig. A3. Corresponding node descriptives are found in Tables A2, A3 and A4.

#### 3.4.1. Temporal patient networks

3.4.1.1. Network connectivity. Fig. 2 depicts the temporal networks of the patient with the highest network connectivity (A) and the patient with the lowest network connectivity (B). The high connectivity patient is a 68-year-old male with one comorbidity scheduled for PCI. The low connectivity patient is a 70-year-old male with two comorbidities



**Fig. 2.** The temporal networks of the patients with the highest and lowest networks connectivity. (A) Patient 16 = high connectivity. (B) Patient 10 = low connectivity. Circles (nodes) represent HRQoL items, and edges (arrows) represent a temporal relationship between two variables at the next measurement. Blue edges are positive associations, and red edges are negative associations. Saturation of the edge represents the strength of the relationship; the stronger, the more saturated [34]. To make networks more comparable, only edges with an edge strength  $> .03$  are shown in the plots (edges are not omitted from analysis). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

scheduled for PCI. Network densities of all patients' temporal networks are shown in Table A2.

Self-evidently we find that for the high connectivity patient nodes are more strongly connected, indicating that his moods and symptoms tend to interact more strongly over time. Noteworthy are the positive edges from “shortness of breath” toward “tightness on chest” and “oppressive feelings on chest,” indicating that he is likely to experience CAD symptoms after feeling short of breath. The low connectivity patient shows fewer edges, indicating that his moods and symptoms barely interact over time.

**3.5.1.2. Node Centrality.** Tables A3 and A4 give the centrality measures of all patients' temporal networks. Fig. 3 depicts the temporal networks of the patient with the highest reported anxiety score (A; average anxiety = 5.64) and the patient with the lowest reported anxiety score (B; average anxiety = 1.00). The highly anxious patient is a 67-year-old male with four comorbidities who is scheduled for CABG. The low anxious patient is a 73-year-old male with two comorbidities who is scheduled for PCI. The centrality plots are depicted in Fig. A1.

Comparing the networks, we find that the highly anxious patient shows a higher centrality for “anxious,” indicating he is susceptible to become more/less anxious as other moods and symptoms are experienced. The low anxious patient shows a lower centrality for “anxious,” indicating he is less susceptible to become more anxious. A noteworthy feature of the high anxious patient is the positive feedback loop between “cheerful” and “relaxed”; feeling cheerful makes him more relaxed, which in turn makes him even more cheerful.

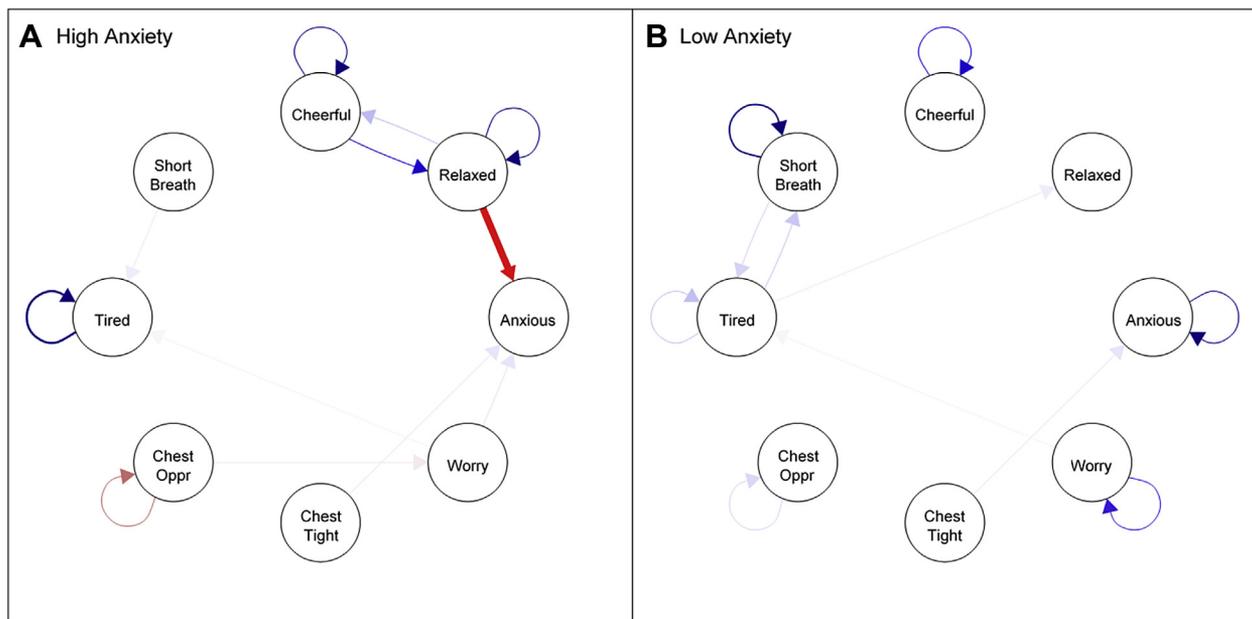
makes him more relaxed, which in turn makes him even more cheerful.

### 3.4.2. Contemporaneous patient networks

All patients' contemporaneous networks are depicted in Fig. A4 (See Tables A2 and A5 for corresponding densities and degree centralities). We compared the contemporaneous networks of the same pairs of patients from the temporal network analysis (see Fig. A2 for the centrality plot). When comparing the high and low anxious patients, we find a stronger negative edge between “cheerful” and “worry” for the low anxious patient. Whenever both patients became more cheerful, the low anxious patient felt less worried, whereas the high anxious patient remained as worried as before. This might indicate that the low anxious patient is better at suppressing feelings of worry. A more comprehensive description of the results is given in Figs. A5 and A6.

## 4. Discussion

This study is one of the first to apply network analysis on momentary HRQoL data. We illustrated the use of network models to examine HRQoL dynamics on group and patient levels. Group-level analysis indicated that, on average, “tired” and “anxious” played the most central role in patients' HRQoL. Patient-level analysis showed differences in patient's network structures, quantifying within-person differences in dynamical relationships among moods and symptoms. Our results suggest that network analysis can be used to examine which symptoms are more central and strongly



**Fig. 3.** The temporal networks of the patients with the highest and lowest reported anxiety. (A) Patient 2 = high anxious. (B) Patient 7 = low anxious. Circles (nodes) represent HRQoL items, and edges (arrows) represent a temporal relationship between another variable at the next measurement. Blue edges are positive associations, and red edges are negative associations. Saturation of the edge represents the strength of the relationship; the stronger, the more saturated [34]. To make networks more comparable, only edges with an edge strength  $> .03$  are shown in the plots (edges are not omitted from analysis). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

connected with each other. Such analysis may reveal insights into the HRQoL dynamics, exceeding static index scores, which may be useful for both patients and clinicians [43]. For example, degree centrality might be used to target symptoms that require additional treatment; treatment of a highly central symptom will likely improve other symptoms as well. Furthermore, network connectivity might be used to hypothesize how patients' HRQoL will respond to, for example, a physical setback. The well-known downward spiral of physical deterioration is more likely in patients whose symptoms are highly interconnected [44–46]. On the bright side, the same interconnectedness may also enhance a positive response. For example, cognitive behavioral therapy targeted at reducing fatigue may improve other symptoms, such as insomnia and cheerfulness, to the extent that these symptoms reinforce each other [47]. Network connectivity might be used to detect which patients are more likely to show such patterns and how to overcome or enforce such patterns. Finally, symptom dynamics such as those explored in network models may illuminate underlying physiological processes with diurnal variation. For instance, adrenal variation due to diurnal changes in cortisol levels could affect cardiac symptomatology, especially for those not taking beta blockers. Future research may be directed at the validation of these hypotheses.

#### 4.1. Limitations

Whereas the network approach offers promising implications for both researchers and clinicians, it should be noted that the methodology is still under development. A number of limitations of the method, in general, and this study, in particular, merit attention.

First, and foremost, it should be noted that our networks are exploratory, not confirmatory. Our networks should therefore be interpreted with caution. Edges cannot be interpreted as true causal relationships, as they can arise from different unobserved factors that might influence daily fluctuations in moods and symptoms.

Second, centrality measures of the temporal networks should be interpreted with caution. A high centrality at the contemporaneous level might not be revealed as such at the temporal level [25].

Third, a subset of eight items was selected to obtain interpretable network structures. Whereas this implies loss of information in itself, network structures may differ depending on the selected set of items. Moreover, there is currently no uniform methodology suited to guide the item selection process. In our study we used reliability estimates within each HRQoL domain. This method may lead to less informative network structures when items overlap in content (e.g., “tightness on chest” and “oppressive feelings on chest”), as we will automatically select the most similar nodes. Moreover, high intercorrelation between items will result in high centrality measures between nodes, thereby inflating centrality measures. Other approaches, with their own pros and cons, have been suggested and include item reduction by

dynamical factor analysis, and using sum scores. Of course, item selection needs to be guided by theoretical notions of the target construct, such as the domain structure of HRQoL.

Fourth, a patient-level network of one person is not generalizable to other persons; it only represents the idiosyncratic impressions of an individual. Moreover, validated methods for comparing individual networks are needed.

Fifth, in our study, time lags between beeps varied to avoid that patients would be able to anticipate the beeps. Multilevel VAR models assume that time lags between measurements are equal. How departure of this assumption would affect the network structure is still unknown. Multilevel methods for estimating network models on data with varying time lags are currently under development.

Finally, multilevel VAR model estimates patient-level networks using information from the group-level network. This method analyzes all data simultaneously, thereby increasing power. However, it is not well-suited to represent qualitative differences between individuals, as it assumes that all individuals' parameters originate from the same distribution [30]. This assumption may not always be realistic, for instance, when individuals do not only differ in edge strength but also in network structure. One could estimate networks only on individual's momentary data, and the self-evident disadvantage is a loss of power.

## 5. Conclusion

Network analysis of momentary HRQoL data offers a promising approach for investigating HRQoL dynamics. We illustrated that network models can deepen our insight into HRQoL at both group-level and individual-level analyses. Moreover, network analysis offers new hypotheses that may increase our understanding of HRQoL and allows for new possibilities in personalized treatment strategies. Although its implications are promising, it should be noted, however, that the network approach is still in its infancy, and work is in progress to advance this technique.

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## Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.jclinepi.2018.11.022>.

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