Developing e-health applications to promote a patient-centered approach to medically unexplained symptoms

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CHAPTER 10

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Exploring interrelationships among worrying, anxiety, and somatic symptoms using time-series analysis.

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ABSTRACT

Background: The aims of this study were 1) to explore interrelationships among daily worrying, anxiety, and somatic symptoms within subjects of the Dutch general population, and 2) to investigate the association between the overall level of functional somatic symptoms (FSS) and the interrelationships among daily worrying, anxiety, and somatic symptoms.

Methods: 444 participants were included in the study (82% females, mean age 40 years). Participants were recruited through an online crowdsourcing study in the Dutch general population. They used their smartphone to fill out an electronic diary three times a day for 30 days. Automated vector autoregressive modeling was used to explore interrelationships among worrying, anxiety, and somatic symptoms within individuals. Logistic regression analysis was used to investigate whether these interrelationships were associated with the level of FSS (PHQ-15, assessed at baseline), in a subset of 129 participants.

Results: 65% of subjects showed one or more relationships between symptoms of anxiety (worrying and/or feeling anxious) and somatic symptoms. Both contemporaneous (44% of subjects) as well as cross-lagged associations (40% of subjects) were found. The level of FSS predicted the simultaneous experience of anxiety and somatic symptoms.

Conclusions: Interrelationships among daily worrying, anxiety, and somatic symptoms are highly heterogeneous across individuals. Combining electronic diaries with (automated) time-series analysis might contribute to a patient-tailored explanatory model of FSS, which in turn may guide treatment.

INTRODUCTION

Somatic symptoms do not always result from disease. Experiencing somatic symptoms is part of normal life. In the general population, 95% of people report having experienced at least one somatic symptom in the past two weeks (1). Common symptoms include back pain, fatigue, and headache. When somatic symptoms are presented to a physician, between 25 and 50% cannot be explained by organic pathology (2). If persistent and causing distress and/or disabilities, these so-called functional somatic symptoms (FSS) can become very problematic. FSS are associated with reduced quality of life (3), functional limitations (4), increased use of healthcare services (5), and absenteeism from work (6).

The development of FSS is thought to be a multifactorial process in which biological, psychological, and social factors are involved (7). To date, many risk factors associated with FSS have been identified, yet not much is known about underlying mechanisms of FSS. In other words: although we know more about who gets FSS (8), we still know relatively little about how FSS develop and what causes them to fluctuate.

One of the most extensively researched psychological factors associated with FSS is anxiety. Previous studies have shown that FSS and anxiety disorders often co-occur (9, 10). Furthermore, individuals reporting high levels of anxiety are more likely to report high levels of FSS (11, 12). Yet the nature of the relationship between FSS and anxiety remains largely unclear. Does anxiety lead to somatic symptoms? Or do somatic symptoms lead to anxiety?

The reason for this uncertainty might be the approach taken in most previous studies. Previous research on FSS is characterized by a 'between-subjects' approach, in which a limited number of observations from a large number of subjects are analyzed at a group level. However, associations found at the group level do not necessarily exist at the level of the individual. Generalizing from the group level to the individual level is only justified under certain conditions, one of which is homogeneity, meaning that the same statistical model applies to each individual in the population (13). Since FSS is a diagnosis of exclusion, the population of patients with FSS is likely to be very heterogeneous. Furthermore, the temporal order of associations is difficult to establish when taking a 'between-subjects' approach.

In order to unravel the mechanisms underlying fluctuations in FSS and to clarify relationships between FSS and maintaining factors, we propose taking a 'within-subject' approach. This can be done by means of time-series analysis, in which a large number of observations from a limited number of subjects are analyzed at the level of the individual.

In the current study, we will use time-series analysis to explore interrelationships among daily worrying, anxiety, and somatic symptoms within subjects of the Dutch general population. Secondly, we will investigate the association between the overall level of FSS and the interrelationships among daily worrying, anxiety, and somatic symptoms. We hypothesize that individuals with FSS might be more sensitive to the influence of psychological factors on somatic symptoms and thereby experience an increase in somatic symptoms when worrying

or feeling anxious. Individuals with FSS might also be prone to experiencing negative emotions and cognitions (i.e. worrying and feeling anxious) when faced with somatic symptoms.

METHODS

Study Sample and Procedure

This study was conducted in a subsample of participants from 'HowNutsAreTheDutch' (HND). HND is an online crowdsourcing study in the Dutch general population (14). Starting in December 2013, Dutch inhabitants were invited through various national and local media to register to the website (www.hoegekis.nl) and take part in the research. Eligible participants were adults (age ≥18 years), consenting to their data being used for research. Informed consent was obtained online before entering the study. The study protocol was approved by the Medical Ethical Committee of the University Medical Center Groningen. The committee judged the protocol to be exempted from review by the Medical Research Involving Human Subjects Act, because it concerned a non-randomized open study, targeted at anonymous volunteers in the general population (registration number M13.147422 and M14.160855).

HND comprises two parts: a cross-sectional part, consisting of several online questionnaires, and a longitudinal part, consisting of an electronic diary. For the cross-sectional part, participants were invited to fill out questionnaires on socio-demographic variables, childhood adversities, personality, intelligence, wellbeing, psychological symptoms, and somatic symptoms. For the longitudinal part, starting in May 2014, participants were invited to take part in a diary study. In order to take part in this study, participants were required to have a mobile phone with internet connection. Persons working night shifts or anticipating a major disruption of daily routines (due to a planned trip abroad or hospitalization for example) were excluded from participation. Participants were instructed about the diary study through written information and a short movie on the HND website. The electronic diary questionnaire contained 43 items on wellbeing, affect, sleep, physical activity, somatic symptoms, and context (location, social company, activities). Participants filled out the diary questionnaire three times a day for 30 days using their mobile phone. Data entry was prompted by a text message containing a link to the diary questionnaire with 6-hour intervals during awakening time. The timing of these text messages could be configured by participants, depending on their bed times. The questionnaire had to be filled out within one hour after receiving the text message.

From all participants who took part in the diary study between the start of the HND study and January 2018 (N = 1255), we selected those with at least 75% valid observations (≥68) for the first study objective (N = 444, 35%). For the second study objective, we included participants who additionally filled out the cross-sectional questionnaire on somatic symptoms within one month of the start of the diary study. This selection procedure resulted in a subsample of 129 participants.

Measures

Cross-sectional Questionnaires. FSS were assessed using the Patient Health Questionnaire-15 (PHQ-15). The PHQ-15 is a validated self-report questionnaire, which is used to screen for FSS and somatoform disorder (15, 16). It inquires about 15 (clusters of) symptoms that account for more than 90% of the somatic complaints reported in the outpatient setting (excluding self-limited upper respiratory symptoms) (15). Two versions of the PHQ-15 were used during the study period, which differed in response scale and timeframe for the purpose of a parallel study on scale validity. In about half of the cases (N = 69, 53.5%) the original 3-point scale was used to rate symptom severity, ranging from "not at all" (0) to "very much" (2), resulting in a total score between 0 and 30. In this version, a 2-week timeframe was used. In the other half (N = 60, 46.5%), a 5-point scale was used, ranging from "not at all" (0) to "very much" (4), resulting in a total score between 0 and 60. In this version, the original timeframe of 4 weeks was used. In order to harmonize scores, scores from the 5-point scale were divided by 2. In order to account for these differences in questionnaires, the variable 'PHQ version' was included as a covariate in the statistical analyses.

Electronic Diary Measures. Three diary measures were used for the current study, each assessed with a single question: worrying ("I worry a lot"), anxiety ("I feel anxious"), and somatic symptoms ("I experience physical discomfort (headache, diarrhea, heavy legs, etc.)"). The items were rated on a visual analogue scale (VAS) ranging from "not at all" (0) to "very much" (100).

Statistical Analysis

To explore interrelationships among daily worrying, anxiety, and somatic symptoms within subjects, vector autoregressive (VAR) modeling was used (17, 18). In a VAR model, each variable is regressed on its own lagged (preceding) values as well as the lagged values of the other variable(s) in the model. This yields information on autoregressive and cross-lagged effects (preceding values of the one variable predicting current values of the other variable). Information of contemporaneous associations can be retrieved from correlations among the residuals of the VAR model. To automate the VAR-modeling procedure, we used *Autovar*, an open source R package that reads raw data and automatically fits and evaluates VAR models (19). Analyses were performed using R studio version 1.1.453. Data of each subject were analyzed separately. First, missing data were imputed using Amelia (20). The following variables were used in the imputation model: time ('measurement number'), day of the week, time of day (morning/ afternoon/ evening), worrying, anxiety, somatic symptoms, and the lagged values of the last three variables. Subsequently, a VAR model was estimated for each subject, including the three variables of interest: somatic symptoms, worrying, and anxiety. Autovar can estimate VAR models with different time lags. Models with a maximum of up to three time lags were tested and the optimal lag was chosen based on model fit. If the time series of one of the variables showed a linear or quadratic trend over time, this was accounted

for by including the variable 'measurement number' (and the square of it) as a predictor. To adjust for systematic daily cycles, dummy variables for the time of day (morning/ afternoon/ evening) were included. If the data showed a weekly pattern, dummy variables for the days of the week were included. To check whether all assumptions of VAR analyses were met, Autovar performs diagnostic tests on stability, serial independency, homoskedasticity (stability of variance) and normality of the residuals of each model. In case of violation of model assumptions, dummy variables for outliers were added, and the model was re-estimated. Also, models with logtransformed variables were estimated for this reason. After this process of estimating and evaluating models, the model with the best model fit based on the Bayesian Information Criterion (BIC) was selected. Further details on the automated VAR modeling procedure are available here (https://autovar.nl/docs/) and from the authors upon request.

To investigate the association between the overall level of FSS and the interrelationships among daily worrying, anxiety, and somatic symptoms, we used logistic regression analysis with FSS (PHQ-15) as a predictor and results of the VAR analyses as outcome variables. The variable 'PHQ version' was included as a covariate. For both symptoms of anxiety (worrying and feeling anxious), we explored three outcomes: 1) whether or not there was a significant positive contemporaneous relationship between this variable and somatic symptoms; 2) whether or not an increase in this variable predicted an increase in somatic symptoms (cross-lagged effect); and 3) whether or not an increase in somatic symptoms predicted an increase in this variable (cross-lagged effect).

RESULTS

Subject Characteristics

The study sample consisted of 444 subjects (82% females) aged 18-73 years (M = 40.4, SD = 13.6). 80.4% of the study sample had at least a bachelor's degree (International Standard Classification of Education ≥6). From the 90 diary assessments, the percentage of missing data varied between 0 and 24.4 (M = 13.7, SD = 6.2).

In the subsample of participants who filled out the cross-sectional questionnaire on somatic symptoms within one month of the start of the diary study (N = 129), the mean PHQ-15 score was 6.50 (SD 4.10). There were no missing PHQ-15 data.

Description of the Models

For each of the 444 subjects, a VAR model was estimated. Table 1 shows a summary of the model specifications. In 38 cases (8.6%), Autovar could not find a valid model (i.e. meeting all assumptions). This was likely due to aberrant distributions of the diary variables. If no valid model was found, the subject was excluded from further analysis.

Table 1. Specifications of Vector Autoregressive (VAR) Models (N = 444).

Valid model found, N (%)	406 (91.4)
Lags	
0, N (%)	50 (12.3)
1, N (%)	111 (27.3)
2, N (%)	111 (27.3)
3, N (%)	134 (33.0)
Trend variable included, N (%)	284 (70.0)
Dummies for days of the week included, N (%)	136 (33.5)
Logtransformation, N (%)	283 (69.7)

Note. VAR models including diary variables worrying, anxiety, and somatic symptoms.

Within-subject Associations between Worrying, Anxiety and Somatic Symptoms

In 142 subjects (35.0%), neither a significant contemporaneous nor a cross-lagged relationship was found between symptoms of anxiety (worrying or feeling anxious) and somatic symptoms. In 146 subjects (36.0%), one relationship between symptoms of anxiety and somatic symptoms was found. 118 subjects (29.0%) showed more than one relationship. Table 2 summarizes the results of the VAR models.

Table 2. Summary of Results from Vector Autoregressive Models (N = 406).

	Worrying	**Anxiety**
Significant contemporaneous association with somatic symptoms*, N (%)	137 (33.7)	83 (20.4)
Size significant contemporaneous association		
Mean (SD)	0.31 (0.11)	0.26 (0.17)
Range	-0.23 – 0.68	-0.38 – 0.57
Significant cross-lagged association with worrying or anxiety as a predictor*, N (%)	58 (14.3)	54 (13.3)
Positive, N	24 (41.4)	33 (61.1)
Negative, N	22 (37.9)	17 (31.5)
Mixed, N	12 (20.7)	4 (7.4)
Significant cross-lagged association with somatic symptoms as a predictor*, N (%)	50 (12.3)	51 (12.6)
Positive, N	24 (48.0)	29 (56.9)
Negative, N	13 (26.0)	18 (35.3)
Mixed, N	13 (26.0)	4 (7.8)

Note. * $p<.05$

180 subjects (44.3%), showed one or more contemporaneous associations between symptoms of anxiety and somatic symptoms. In 137 subjects (33.7%), this concerned a contemporaneous association between worrying and somatic symptoms. 99% of these contemporaneous associations between worrying and somatic symptoms were positive, meaning that an increase in worrying was associated with a simultaneous increase in somatic symptoms. The percentage of subjects with a significant contemporaneous association between anxiety and somatic symptoms was somewhat lower (20.4%). Of these contemporaneous associations, 93% were positive. Average effect sizes of the contemporaneous associations were moderate (0.31 and 0.26, respectively). Of the 180 individuals showing a contemporaneous association between symptoms of anxiety and somatic symptoms, 20.0% also showed a cross-lagged association.

In 165 subjects (40.6%), one or more cross-lagged associations were found between symptoms of anxiety and somatic symptoms. In 58 subjects (14.3%), changes in worrying predicted successive changes in somatic symptoms. We found positive, negative, and mixed associations (Table 2). For example, a positive association between worrying and somatic symptoms was found in 24 subjects, meaning that an increase in worrying was followed by an increase in somatic symptoms. A negative association between worrying and somatic symptoms was found in 22 subjects, meaning that an increase in worrying was followed by a decrease in somatic symptoms. A mixed association indicates mixed results on different lags; for example a positive coefficient at the first lag and a negative coefficient at the second lag. Similar results were found for anxiety. Changes in anxiety predicted successive changes in somatic symptoms in 54 subjects (13.3%). Most of these associations were positive (61.1%). Yet, negative and mixed associations were also found. When looking at the cross-lagged associations between symptoms of anxiety and somatic symptoms in the other direction, a similar pattern arises. Changes in somatic symptoms predicted successive changes in worrying and/or anxiety in 50 (12.3%) and 51 (12.6%) subjects. Again, most associations were positive, but we also found negative and mixed associations.

Association between FSS and Within-subject Relationships among Worrying, Anxiety and Somatic Symptoms

Table 3 shows the results of the logistic regression analyses. Valid models were found for 113 (87.6%) of the 129 subjects. The overall level of FSS predicted a contemporaneous association between anxiety and somatic symptoms (OR = 1.135). This means that individuals with FSS were more likely to experience anxiety and somatic symptoms simultaneously. The other effects were not significant.

Table 3. Results from Logistic Regression Analysis with functional somatic symptoms (PHQ-15) as a Predictor (N =113).

	Independent variable: functional somatic symptoms (PHQ-15)		
Dependent variables	***OR***	***95% CI (OR)***	***p***
contemporaneous association			
worrying and somatic symptoms	1.052	0.960 – 1.154	.26
anxiety and somatic symptoms	**1.135**	**1.008 – 1.278**	**.04**
cross-lagged association			
worrying predicting somatic symptoms	0.926	0.794 – 1.080	.33
anxiety predicting somatic symptoms	0.969	0.847 – 1.109	.65
somatic symptoms predicting worrying	0.926	0.785 – 1.092	.36
somatic symptoms predicting anxiety	1.000	0.877 – 1.139	.99

Note. All dependent variables are binary variables, indicating a significant association (yes/no) with p <.05

DISCUSSION

In our study, 65% of subjects showed one or more relationships between symptoms of anxiety (worrying and/or feeling anxious) and somatic symptoms. In 44% of subjects, one or more contemporaneous associations were found, meaning that changes in worrying and/or anxiety were associated with simultaneous changes in somatic symptoms. In 41% of subjects, one or more cross-lagged associations were found, meaning that changes in worrying and/or anxiety preceded changes in somatic symptoms or vice versa. Even though most of these cross-lagged associations were positive, we also found negative and mixed associations. In addition, we found that the level of FSS predicted the simultaneous experience of anxiety and somatic symptoms.

Strengths and Limitations

This study had a number of strengths. To our knowledge, this is the first study taking a 'within-subject' approach to investigate the relationship between symptoms of anxiety and somatic symptoms. The longitudinal design of the study with its many repeated assessments, and the use of VAR models allowed us to draw conclusions about the direction of effects. Important features of the VAR model are that variables can be both predictor and outcome at the same time, and that the contemporaneous part is separated from the dynamic part (Brandt & Williams, 2007). This yields valuable information about the temporal order of the relationships and potential bidirectional effects. The automation procedure we used enabled the analysis of a large number of time series. Another strength of the current study is the combined use of longitudinal and cross-sectional data for the secondary study aim. This enabled us to explore 'between-subject' differences in 'within-subject' processes.

There were also some limitations. Due to the nature of the participant recruitment (crowdsourcing), the study population was not an accurate reflection of the general population. Highly educated women were overrepresented, due to a self-selection bias. Two other limitations of the current study concern the use of the PHQ-15 questionnaire, which was used to represent the level of FSS. First, because this is a self-report questionnaire we cannot be sure that there is no underlying organic pathology for the reported symptoms. However, the PHQ-15 is a commonly used and validated instrument to assess FSS. Its sum score predicts the presence of somatoform disorders (16) and highly correlates with distress, functional limitations and use of healthcare resources (15). Second, different versions of the PHQ-15 questionnaire were used in this study. Differences in timeframe (2 weeks or 4 weeks) influence the PHQ-15 score (21). In order to account for this, the variable 'PHQ version' was included as a covariate in the logistic regression analyses. Finally, diary measures were assessed with only one item. However, previous studies suggest one-item VAS scales can be a reliable approach to measure mood states and other daily measures (22, 23).

Relationship to Previous Studies

Previous studies have shown that anxiety and FSS are associated with one another at a group level. Individuals reporting high levels of anxiety are more likely to report high levels of FSS compared to individuals with lower anxiety levels (11, 12). In addition, FSS are associated with anxiety disorders, such as panic disorder and generalized anxiety disorder (9, 10). A longitudinal cohort study, aiming to clarify this relationship in a large population cohort of adolescents, suggested that anxiety is a risk factor for FSS, yet FSS also influences the development of symptoms of anxiety (24). These findings are in line with the findings of the current study, showing that relationships between symptoms of anxiety and somatic symptoms occur in both directions.

We found that 44% of subjects showed a contemporaneous association, meaning that changes in symptoms of anxiety were associated with simultaneous changes in somatic symptoms. A possible explanation for this co-occurrence of symptoms of anxiety and somatic sensations might be found in the reactions of the autonomic nervous system. Anxiety as an emotional state is oftentimes accompanied by physiological signs of hyperarousal (tachycardia, tachypnea, increased muscle tension), which can be perceived and interpreted as somatic symptoms (palpitations, shortness of breath, pain, and trembling) (25).

Furthermore, we found that 40% of subjects showed a cross-lagged association. Associations in different directions and with different signs (positive/negative) were found. When looking at symptoms of anxiety as a predictor for somatic symptoms, we found that an increase in symptoms of anxiety was most often followed by an increase, but in some subjects by a decrease in somatic symptoms. This contradiction might be explained a differential focus of attention. Selective attention to bodily processes has been shown to increase the reporting of symptoms (26, 27). Thus, if the anxiety is health- or symptom related, it may lead to increased

attention to bodily signals, which in turn may increase awareness and reporting of somatic symptoms (25). If the anxiety is focused on another source, it might actually divert the attention from the somatic symptoms, and therefore reducing the somatic symptoms. When looking at somatic symptoms as a predictor for symptoms of anxiety, a similar pattern arises. Somatic symptoms can lead to an increase, but also to a decrease in symptoms of anxiety. The first option seems obvious. Experiencing somatic symptoms may lead to worries about their nature, cause, and/or course. Interpreting physical sensations or symptoms as a threat or a sign of serious disease naturally elicits anxiety. The same applies to the idea that the symptoms might never go away and mean that one is faced with a debilitating condition for the rest of one's life. The role of health anxiety, illness worry and catastrophizing has been researched extensively (26, 27). Yet our study shows that in some subjects, an increase in somatic symptoms is actually associated with a decrease in anxiety. Like the relationship in the opposite direction, this might be explained by the focus of the anxiety as well. When worrying about work, relationships or family, the occurrence of somatic symptoms may shift the attention away from these worries and towards the body, thus decreasing anxiety. Another explanation for the negative signs in some of the cross-lagged associations may be found in the measurement interval. An association may be positive contemporaneously or at shorter time intervals, but negative after a longer time interval, reflecting some kind of compensation mechanism.

The second aim of the current study was to investigate the association between the overall level of FSS and the interrelationships among daily worrying, anxiety, and somatic symptoms. We hypothesized that individuals with FSS might be more sensitive to the influences of psychological factors on somatic symptoms and might also be prone to experiencing negative emotions and cognitions when faced with somatic symptoms. We found that individuals with FSS were indeed more likely to experience anxiety and somatic symptoms simultaneously. However, no relationships between FSS and cross-lagged effects were found. Therefore, this finding does not allow drawing conclusions with regard to the direction of this effect.

Implications and Future Directions

The current study shows that the relationships between symptoms of anxiety and somatic symptoms are highly heterogeneous across individuals. For patients with FSS, this means that we cannot assume that the same explanatory model or underlying mechanism applies to all patients. Electronic diaries combined with automated time-series analysis might be used to provide patients with a personalized explanation. The information that arises from these analyses might also provide a useful starting point for treatment interventions.

The results of this study raise new questions and therefore provide us with directions for future research. First, more research is necessary to explore the practical use and value of diaries combined with time-series analysis in clinical care. Second, the diary measures used in the current study were rather nonspecific. In order to unravel the day-to-day dynamics of FSS, it

would be interesting to continue this line of research with more specific measures, such as specific types of somatic symptoms and health-related cognitions. Some symptoms might have a stronger association with worrying and anxiety than others. In order to explain why symptoms of anxiety can lead to an increase as well as a decrease in somatic symptoms, it would be interesting to take a closer look at the role of daily illness worries and health anxiety in relation to somatic symptoms. Furthermore, it must be taken into account that the timing of diary measures influences results. In this study, diaries were filled out three times a day. It is possible that relationships between anxiety and somatic symptoms, measured on an hourly or weekly basis, have a different character.

CONCLUSIONS

Interrelationships among daily worrying, anxiety, and somatic symptoms are highly heterogeneous across individuals. Combining electronic diaries with (automated) time-series analysis might contribute to a patient-tailored explanatory model of FSS, which in turn may guide treatment.

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