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Co-morbidity of depression, anxiety and fatigue in cancer patients receiving psychological care

Lei Zhu[1,2], Adelita V. Ranchor[1], Marije van der Lee[3], Bert Garssen[3], Josué Almansa[4], Robbert Sanderman[1,5] and Maya J. Schroevers[1]*

[1]*Department of Health Psychology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands*
[2]*School of Psychology, Shaanxi Normal University, Xi'an, China*
[3]*Centre for Psycho-Oncology, Helen Dowling Institute, Bilthoven, The Netherlands*
[4]*Department of Health Sciences, Division of Community and Occupational Medicine, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands*
[5]*Department of Psychology, Health and Technology, University of Twente, Enschede, The Netherlands*

**Correspondence to: Department of Health Psychology, University Medical Center Groningen, University of Groningen, POB 196, A. Deusinglaan 1, 9700 AD Groningen, The Netherlands. E-mail: M.J.Schroevers@umcg.nl*

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Abstract

***Objectives*: This study aimed to examine (1) subgroups of cancer patients with distinct co-morbidity patterns of depression, anxiety and fatigue; (2) how individuals transitioned between these patterns; and (3) whether socio-demographic, clinical and psychological care characteristics distinguished patients' transitions.**

***Method*: This naturalistic, longitudinal study focused on 241 cancer patients receiving psycho-oncological care in the Netherlands. Data were collected before initiation of psychological care (T1), 3 months (T2), and 9 months thereafter (T3). Latent transition analysis was performed examining research questions.**

***Results*: Three distinct co-morbidity patterns were identified: class 1 ('mood disturbances and fatigue'), class 2 ('mood disturbances') and class 3 ('few symptoms of mood disturbances and fatigue'). Half of those in class 1 remained in this group from T1 to T3, a quarter transitioned to class 2 and another quarter to class 3. Baseline physical symptoms distinguished these transitions: those with more physical symptoms tended to remain stable. Half of patients in class 2 remained stable from T1 to T3, 46% moved into class 3 and 8% into class 1. Baseline physical symptoms and years after cancer diagnosis significantly distinguished these transitions: the 8% moving to class 1 had more physical symptoms and were longer after cancer diagnosis. Most patients in class 3 remained stable from T1 to T3, and predictors of transitions could not be examined.**

***Conclusions*: Three distinct co-morbidity patterns of depression, anxiety and fatigue were identified and exhibited different symptom courses longitudinally. Those with poor physical health tended to report elevated mood disturbances and fatigue during psychological care.**

Introduction

Cancer patients often report various physical and psychological disease-related and treatment-related symptoms. Regarding physical consequences, fatigue is one of the most common side effects of cancer and cancer-related treatment [1]. Fatigue is characterized by tiredness, weakness and lack of energy [2], affecting 45–74% of cancer patients [3,4]. Among psychological consequences, depression and anxiety are commonly reported by cancer patients, with prevalence rates of 8–24.6% [5,6] and 9.8–19% [6,7], respectively. Depression includes a depressed mood and/or loss of interest or pleasure in normal activities, with additional symptoms including worthlessness, guilt, concentration problems and changes in appetite, energy and sleep [8]. Anxiety is characterized by an emotional state consisting of feelings of apprehension and tension and arousal of the autonomic nervous system [9].

Several psychological interventions (e.g. psychosocial education and cognitive behavioural therapy) have been developed to reduce symptoms of depression, anxiety and fatigue in cancer patients. Reviews have demonstrated the effectiveness of these interventions in cancer patients, indicating moderate to large improvements in depression and anxiety [10,11] and small-sized improvements in fatigue [12], although some found less strong evidence to support the effectiveness of psychological care in treating depression and anxiety [13,14] or fatigue [15,16]. Additionally, evidence suggests that fatigue can be best treated by interventions specifically targeting at fatigue [15].

To test the efficacy of psychological interventions in cancer patients, most randomized controlled trials (RCTs) included multiple primary and secondary outcomes and examined changes in depression, anxiety and fatigue separately [17–20]. Consequently, these RCTs have not taken

into account that depression and anxiety were moderately to highly correlated [21–23] and that anxiety and depression were both strongly correlated to fatigue [24]. Cross-sectional studies in cancer patients have found a 'depression–anxiety' symptom cluster [22,23] and a 'depression–fatigue' cluster [25]. To our knowledge, no study in cancer patients has examined the possibility of clusters based on depression, anxiety and fatigue and the longitudinal transitions across different clusters. A better understanding of these clusters and how patients transition over time could help identify clinically relevant subgroups of cancer patients with distinct types of symptoms and the development of tailored psychological interventions that target a particular clustering of symptoms.

This naturalistic, longitudinal study focused on cancer patients seeking psychological care at specialized psycho-oncology institutions in the Netherlands over a 9-month period. Participants were assessed for depression, anxiety and fatigue before psychological care (T1) and at 3-month (T2) and 9-month (T3) follow-ups. First, we aimed to identify distinct co-morbidity patterns of depression, anxiety and fatigue. Second, we examined how patients transitioned between these co-morbidity patterns over time. To answer these research questions, latent transition analysis (LTA) was used to examine how individuals grouped together based on shared patterns of symptoms and how individuals transitioned between symptom patterns [26]. Third, we examined whether patients' socio-demographic, medical and psychological care characteristics distinguished those with different transitions.

Method

Sample and procedure

The current naturalistic study applied a consecutive sampling approach to recruit participants at all seven specialized psycho-oncology institutions in the Netherlands. Cancer patients seeking psychological care at one of these institutions between September 2008 and March 2010 were informed of our study. We did not do power analyses beforehand. Those patients who agreed to participate and signed the informed consent form were assessed before initiating psychological care. Follow-up questionnaires were sent to participants 3 and 9 months after baseline. The main reason to decide to follow up participants at fixed time points rather than at flexible time points (e.g. midst and at the end of psychosocial care) is the great diversity in the duration of psychological care. In a natural setting, we were not able to control at what time each participant would complete their therapy.

The inclusion criteria were as follows: (1) diagnosed with cancer and seeking psychological help at one of the seven psycho-oncology institutions, (2) >18 years and (3) able to complete questionnaires in Dutch. Patients were not screened for distress or any other psychosocial problem as prerequisites for care.

We approached 611 patients, and 524 agreed and gave written informed consent. The 87 non-participants did not differ from the 524 participants in age or gender (ps > 0.05). A total of 384 people were included (63% of 611) at T1. After 3 months, 278 people (72% of 384) completed the T2 assessment. After 9 months, 241 people (63% of 384) completed the T3 assessment. The study flow is shown in Figure 1.

Compared with the 143 dropouts, the 241 patients were more highly educated, perceived a favourable prognosis, were more likely to have received an operation and were more likely to be female ($ps < 0.05$). The 241 patients were not significantly different from the 143 dropouts in severity of depression, anxiety or fatigue at baseline (ps > 0.05). Of these 241 participants, 26 missed the second assessment. Because the analysis procedure can handle missing values, these 26 patients were included. The final sample included 241 patients, of whom 200 had complete data for depression, anxiety and fatigue at three measurements.

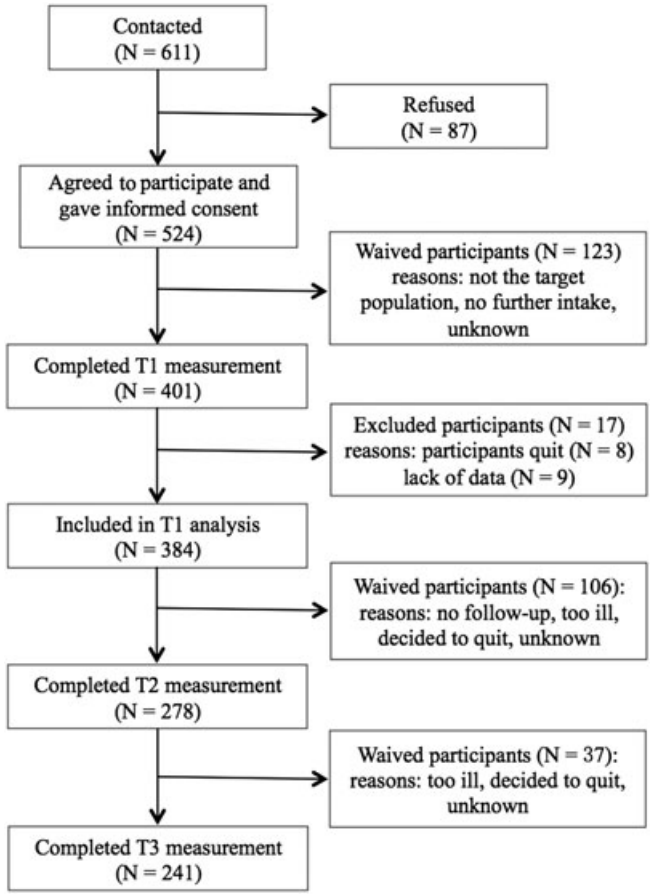

Figure 1. The study flow chart.

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Measures

Socio-demographic and clinical characteristics

Socio-demographic characteristics (e.g. age and gender) and clinical characteristics (e.g. cancer type and baseline physical symptoms) were obtained through a self-report questionnaire. Educational level was classified into three levels: low (i.e. primary schooling and lower vocational education), middle (i.e. secondary schooling and middle vocational education) and high (i.e. university education and higher vocational education). Physical symptoms were measured with a 10-item checklist (e.g. pain and nausea) using the physical symptom subscale of the Rotterdam Symptom Checklist [27]. None of these 10 symptoms related to somatic symptoms of depression. This subscale demonstrated good reliability and validity [27]. Questions were answered from 1 (*none*) to 4 (*very*). Total scores ranged from 10 to 40, with higher scores indicating more physical symptoms. Cronbach's alpha was 0.72 at baseline.

Psychological care characteristics

There was no standard treatment guideline in all seven psycho-oncology institutions. Based on patients' problems, patients were offered proper psychological care. Patients may have received more than one type of care. In T2 and T3, patients were asked to indicate whether they had received individual, group and other therapy (e.g. haptonomy). Psychological care was categorized as follows: individual, group, individual and group (all with/without other therapy) and only other therapy. Patients also indicated whether psychological care had been completed during the follow-up assessments.

Depression

The 16-item version of the Center for Epidemiological Studies Depression Scale was used to measure depression [28]. Each question is answered from 0 (*<1 day*) to 3 (*5–7 days*). Total scores range from 0 to 48, with higher scores indicating greater depression severity. The Center for Epidemiological Studies Depression Scale has been shown having good reliability and validity [29]. We found Cronbach's alpha coefficients of 0.88, 0.89 and 0.91 at T1, T2 and T3, respectively. A score ≥10 indicates clinical depression [30].

Anxiety

Anxiety was measured with the 6-item version of the State-Trait Anxiety Inventory [31,32]. Questions are answered from 1 (*not at all*) to 4 (*very much*). Total scores range from 6 to 24, with higher scores indicating greater anxiety. The State-Trait Anxiety Inventory has been shown to have good reliability and validity [32]. Cronbach's alpha coefficients were 0.85, 0.84 and 0.86 at T1, T2 and T3, respectively. A score ≥12 indicates significant anxiety [33].

Fatigue

The 8-item subscale of subjective fatigue of the checklist individual strength was used to measure fatigue [34]. Each statement is answered from 1 (*yes, that is true*) to 7 (*no, that is not true*). Total scores range from 8 to 56, with higher scores indicating more severe fatigue. The checklist individual strength has been shown to have good reliability and validity [34]. Cronbach's alpha coefficients were 0.92, 0.93 and 0.92 at T1, T2 and T3, respectively. A score ≥35 indicates severe fatigue [34].

Statistical analyses

Categorical variables were created to represent probable cases (≥cut-off) and non-cases (<cut-off) for depression, anxiety and fatigue at each time point.

Latent transition analysis was performed to identify distinct co-morbidity patterns and to examine how individuals transitioned between these patterns over time in Mplus 7.1 [35]. The LTAs were conducted on categorical variables indicating probable cases. On the basis of latent class analysis (LCA) and autoregressive modelling, LTA is a longitudinal extension of LCA with an additional examination of transitions between latent classes over time [26]. First, we identified cross-sectional subgroups with distinct co-morbidity patterns using separate LCAs at each time point. These LCAs were conducted across the three time points simultaneously, and thus, the estimated probabilities of elevated symptoms were calculated across all time points. Second, the longitudinal transitions between latent classes were examined longitudinally by the autoregressive modelling of LTA. This procedure estimated probabilities of individuals transitioning from one class at one time point to another class at the following time point (conditioned on the prior memberships). By using the full information maximum likelihood and expectation maximization algorithm, LTA assumed that missing values occurred at random and used only available data to examine models. To confirm that missing data did not influence results, LTA was repeated in 200 patients with complete data.

We examined separate LTA models ranging from two to four classes. First, several statistical criteria were used to select the best fitting model. We inspected the Bayesian information criterion (BIC) and the Akaike information criterion (AIC) of each model. The BIC and AIC are commonly used model fit indices, with lower values indicating better fit. Entropy was used to examine class separation. A model with entropy ≥0.6 is considered satisfactory [36]. Second, we used several non-statistical criteria to select the best model. The addition of one extra class should be conceptually meaningful and represent a co-morbidity

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pattern that is obviously different from patterns already present in a model with fewer classes. Each class should contain a substantial number of participants (≥5%) [36].

Based on the latent class posterior distribution from the best model, each individual was assigned into the most likely class at T1, T2 and T3, separately. These memberships were exported to SPSS 20.0 and used as indicators of co-morbidity patterns at each time point. First, patients were separated into distinct groups based on class memberships at T1. Second, within each group at T1, patients were separated into distinct subgroups according to their class memberships at T3. As such, within each class at T1, patients with distinct transitions from T1 to T3 could be separated. Chi-squared tests and one-way analyses of variance were performed to examine whether sociodemographic (e.g. age and gender), clinical (e.g. cancer type and baseline physical symptoms) and psychological care characteristics (e.g. type of care) differentiate participants with distinct transitions from T1 to T3. Characteristics that were significantly related to transition patterns were entered simultaneously in a multinomial logistic regression analyses.

Results

Sample characteristics

As shown in Table 1, majority were female and around 50 years old. Half were diagnosed with breast cancer. Most patients received individual psychological care. At baseline, 67.6% reported elevated depression, 54.3% had elevated anxiety and 52.3% had elevated fatigue. Of the 241 sample at baseline, 34.9% reported elevated concurrent depression, anxiety and fatigue; 14.5% concurrent depression and anxiety; 9.1% concurrent depression and fatigue; 1.2% concurrent anxiety and fatigue; 9.1% only elevated depression; 3.7% only anxiety and 7.1% only fatigue; 16.6% did not report elevated depression, anxiety and fatigue; and 3.8% had missing values on these symptoms.

Table 1. Characteristics of participants and means of depression, anxiety and fatigue ($n = 241$)

		Mean (SD)
Depression	T1	15.33 (8.17)
	T2	11.76 (7.72)
	T3	10.23 (7.85)
Anxiety	T1	14.33 (3.54)
	T2	12.70 (3.43)
	T3	12.31 (3.41)
Fatigue	T1	35.69 (12.39)
	T2	33.55 (12.48)
	T3	31.51 (12.46)
Physical symptoms at T1	Mean (SD)	5.87 (4.22)
Age (years)	Mean (SD)	51.39 (10.6)
	Range	25–79
Years after diagnosis	Mean (SD)	3.29 (5.72)
	Range	1–36
		% (*n*)
Gender	Male	19.9 (48)
Relationship status	Yes	79.7 (192)
	No	19.1 (46)
	Missing	1.2 (3)
Educational level	Low	17.4 (42)
	Middle	32.0 (77)
	High	49.0 (118)
	Missing	1.7 (4)
Cancer type	Breast	45.6 (110)
	Digestive system	7.1 (17)
	Lung	2.9 (7)
	Hematologic	8.7 (21)
	Head and neck	6.2 (15)
	Gynaecological	5.8 (14)
	Multiple malignant tumours	7.9 (19)
	Others	14.9 (36)
	Missing	0.8 (2)
Under medical treatment	Yes	49.8 (119)
Type of medical treatment	Operation	15.8 (38)
	Chemotherapy	8.3 (20)
	Radiotherapy	2.1 (5)
	Operation + chemotherapy	20.7 (50)
	Operation + radiotherapy	17.0 (41)
	Chemotherapy + radiotherapy	5.4 (13)
	Operation + chemotherapy + radiotherapy	24.5 (59)
	Other	6.2 (15)
Cancer recurrence	Yes	14.1 (34)
Cancer metastases	Yes	31.9 (77)
Co-morbid diseases	Yes	25.2 (61)
Type of psychosocial care	Individual	60.2 (145)
	Group	9.5 (23)
	Individual + group	22.8 (55)
	Other	1.2 (3)
	Missing	6.2 (15)
Psychosocial care finished at T2	Yes	22.4 (54)
Psychosocial care finished at T3	Yes	46.5 (112)

SD, standard deviation.

Identifying subgroups of cancer patients with distinct co-morbidity patterns

Fit indices of the examined models were as follows: two-class model (AIC = 2382.30, BIC = 2420.64, entropy = 0.76), three-class model (AIC = 2334.25, BIC = 2414.40, entropy = 0.76) and four-class model (AIC = 2329.67, BIC = 2465.58, entropy = 0.79). Entropy of the three models was all satisfactory and comparable with one another. The AIC indicated that the four-class model fitted best, whereas the BIC favoured the three-class model. Therefore, from a statistical perspective, both three-class and four-class models were acceptable. We compared these two models from a non-statistical perspective. One of the classes in the three-class model was divided into two classes with similar co-morbidity patterns in the four-class model. Thus, the three-class model exhibited better interpretability and was therefore selected. To check whether missing data influenced results, we repeated LTA using patients with complete data. The three-class model represented the sample most closely

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and reflected the same three co-morbidity patterns as in the full sample. Therefore, model selection was not affected by missing data.

Table 2 shows the estimated probabilities of having elevated depression, anxiety and fatigue for patients in each class of the three-class model. Patients in class 1 ('mood disturbances and fatigue') were expected to have high probabilities of depression, anxiety and fatigue. Patients in class 2 ('mood disturbances') were expected to have greater probabilities of elevated anxiety and, to a lesser extent, depression, but a low probability of fatigue. Patients in class 3 ('few symptoms of mood disturbances and fatigue') were expected to have low probabilities of depression, anxiety and fatigue.

To check the representativeness of the three-class model, we examined the observed prevalence of elevated depression, anxiety and fatigue within each class (Table 3). Class 1 showed an elevated prevalence of depression, anxiety and fatigue across time. Class 2 displayed mainly elevated prevalence of depression and anxiety and a lower prevalence of fatigue. Class 3 reported almost no depression and anxiety and very few fatigue. These observed cases fit the expected probabilities obtained from the three-class model. Therefore, the three-class model had satisfactory representativeness.

Transitions between co-morbidity patterns and their predictors

For patients in class 1 at T1, 54% remained stable at T3, 22% improved on fatigue (transitioning into class 2) and 24% improved on all three symptoms (transitioned into class 3). Of all socio-demographic, clinical and psychological care characteristics, baseline physical symptoms was the only factor distinguishing three transitions ($F(2, 112) = 7.30$, $p < 0.01$). *Post hoc* Bonferroni comparisons indicated that the 54% remaining stable reported significantly more physical symptoms before starting psychological care ($M = 8.78$) than the 22% transitioning into class 2 ($M = 5.85$) and the 24% moving to class 3 ($M = 5.52$). The most frequent physical symptoms for these 54% were pain elsewhere and shortness of breath.

For patients starting out in class 2 at T1, 46% remained stable at T3, 46% showed improvements (transitioning into class 3) and 8% developed additional fatigue (transitioning into class 1). Years after cancer diagnosis ($F(2, 85) = 5.76$, $p < 0.01$) and baseline physical symptoms ($F(2, 85) = 3.45$, $p < 0.05$) significantly distinguished these transitions. *Post hoc* Bonferroni comparisons suggested that the 8% who developed additional fatigue had more years since their cancer diagnosis ($M = 9.5$) and more physical symptoms ($M = 8.17$) than the 46% who transitioned into the class 3 (years after diagnosis: $M = 3.5$; physical symptoms: $M = 4.67$) and the 46% who remained in the same class (years after diagnosis: $M = 2.0$; physical symptoms: $M = 4.81$). For those 8%, the most prevalent physical symptoms were headache, pain elsewhere and shortness of breath. These two variables were included in the final multivariate logistic regression analysis: the pseudo R^2 (Cox and Snell's) was 0.58, with physical symptoms ($\chi^2 = 37.14$, $p < 0.05$) and years after diagnosis ($\chi^2 = 41.73$, $p < 0.05$) both significant predictors of patients' transition.

For patients in class 3 at T1, 88% remained stable, 7% transitioned into class 1 and 5% transitioned into class 2 at T3. As the majority remained stable, we could not examine predictors of transitional patterns.

Table 2. Estimated class sizes and probabilities of having elevated depression, anxiety and fatigue at each class

	Depression	Anxiety	Fatigue
Class 1 (class size: 42.3% at T1, 30% at T2, 27% at T3)	0.92	0.87	0.98
Class 2 (class size: 42.3% at T1, 34% at T2, 30% at T3)	0.65	0.90	0.24
Class 3 (class size: 15.4% at T1, 36% at T2, 43% at T3)	0.09	0.09	0.21

Table 3. Observed cases with elevated depression, anxiety and fatigue at each class

		Clinical cases *n* (%)		
		Depression	Anxiety	Fatigue
T1	Class 1 ($n = 115$)	108 (93.9)	100 (87.0)	114 (99.1)
	Class 2 ($n = 90$)	54 (60.0)	82 (91.1)	8 (8.9)
	Class 3 ($n = 36$)	4 (11.1)	1 (2.8)	7 (19.4)
T2	Class 1 ($n = 77$)	64 (83.1)	58 (75.3)	69 (89.6)
	Class 2 ($n = 78$)	42 (53.8)	66 (84.6)	14 (17.9)
	Class 3 ($n = 86$)	9 (10.5)	13 (15.1)	20 (23.3)
T3	Class 1 ($n = 68$)	58 (85.3)	60 (88.2)	68 (100)
	Class 2 ($n = 69$)	41 (59.4)	62 (89.9)	11 (15.9)
	Class 3 ($n = 104$)	7 (6.7)	10 (9.6)	19 (18.3)

Discussion

Most RCTs on the efficacy of psychological interventions to reduce symptoms of depression, anxiety or fatigue in cancer patients examined improvements in these outcomes separately, overlooking the strong associations among these symptoms. The current naturalistic study focused on cancer patients receiving psychological care and identified three distinct co-morbidity patterns of depression, anxiety and fatigue: class 1 ('mood disturbances and fatigue'), class 2 ('mood disturbances') and class 3 ('few symptoms of mood disturbances and fatigue'). Approximately half of patients in class 1 and class 2 at baseline remained stable up till 9 months after psychological care. Of those in class 1, approximately one-quarter improved to class 2 and another quarter to class 3. Of those in class 2, about half improved to class 3. Finally, regarding patients in class

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3, the majority retained low levels of depression, anxiety and fatigue over time. These findings underscore that depression, anxiety and fatigue tend to co-occur/cluster and that different patients may exhibit distinct symptom clusters.

When seeking psychological care, 67.6% of cancer patients reported elevated depression, 54.3% reported elevated anxiety and 52.3% reported fatigue before psychological care. Results showed that 35% of patients reported elevated depression, anxiety and fatigue and 15% reported elevated depression and anxiety. These findings corroborate previous findings showing strong correlations among depression, anxiety and fatigue in cancer patients [21–24] and are in line with previous cross-sectional research showing the 'depression–anxiety' cluster [22,23] and 'depression–fatigue' cluster [25] in cancer patients. This study is the first to examine symptom clusters based on depression, anxiety and fatigue and to identify a significant group of patients with elevated depression, anxiety and fatigue. Results also showed that the presence or absence of fatigue distinguished patients into distinct co-morbidity patterns: those patients primarily with depression and anxiety and those patients with depression, anxiety and additional fatigue.

Regarding the course of symptom clusters over time, of those patients who started out with elevated depression, anxiety and fatigue (class 1), half remained stable, a quarter improved in fatigue and transitioned into class 2 and another quarter improved in all three symptoms and moved to class 3. Patients with more physical symptoms (e.g. pain) when presenting themselves for psychological care were at a greater risk of reporting persistent mood disturbances and fatigue. Our findings are partly in line with results from a recent longitudinal study, showing that cancer patients reporting more impact of cancer reported stable high anxiety and depression in the year following diagnosis [37]. Our results suggest that an overall poorer physical health seems unfavourable for patients in terms of the likelihood to experience improvements in functioning over time.

Of the cancer patients reporting elevated depression and anxiety but no elevated fatigue (in the 'mood disturbances' class at baseline), about half remained stable and the other half improved. Only a small group of patients developed additional fatigue over time. Similar to those patients reporting persistent mood disturbances and fatigue over time, also the small group of patients who developed fatigue in addition to depression and anxiety was more likely to report elevated physical symptoms at the start than those patients who transitioned into the other two patterns. Together, these results indicate that patients starting psychological care with a poorer physical health are more likely to report persistent fatigue or develop elevated fatigue in addition to depression and anxiety.

The small group of patients who developed additional fatigue in addition to depression and anxiety was also more likely to have received their diagnosis of cancer longer ago, on average 10 years, than the patients maintaining elevated depression and anxiety and those improving in these mood symptoms. Given the small size of this group, we remain cautious with interpreting these finding and whether those with a poorer physical health and/or a longer time since cancer diagnosis are more at risk of developing fatigue. Future research is needed to further examine this issue.

When interpreting results, several limitations should be considered. First, this study was conducted in a naturalistic setting and lacked a control group. It remains unclear whether transitions could be associated with one specific psychological care patients received. Second, this study in cancer patients seeking psychological care included mostly women with breast cancer. This seems representative of cancer patients seeking psychological care in clinical practice [38], but not of general cancer population [39]. Third, as our participants differed in their disease trajectory and medical treatment, this might influence their response to self-reported questionnaires on depression, anxiety and fatigue. Fourth, our sample is insufficiently large to enable examining the co-morbidity classes and transitions within homogeneous subgroups of patients. This also holds for our group of breast cancer patients, which is the largest subgroup. Therefore, our results, obtained in a heterogeneous cancer sample differing in natural course, medical treatments and disease progression, cannot be generalized into distinct cancer populations. Future research on homogeneous cancer sample is needed to replicate our findings.

This study is the first using LTA to identify distinct co-morbidity patterns of depression, anxiety and fatigue during psychological care. Our findings add to previous literature on psychological and physical symptoms trajectories in cancer patients [40] and expand current understanding of cancer patients' symptom patterns by highlighting that the presence or absence of fatigue distinguishes patients into distinct co-morbid patterns. Clinicians should pay special attention to those patients at greater risk of persisting symptoms, such as those with poorer physical health.

Our results warrant further examination of co-morbidity patterns, as a more in-depth understanding of these co-morbidity patterns and distinct co-morbidity patterns may help the design of psychological interventions tailoring the specific patterns of symptoms. Findings suggest that a quarter of cancer patients maintain mood disturbances and another quarter maintain mood disturbances and fatigue, with patients benefiting insufficiently from receiving psychological care. More research is needed to explain this lack of

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improvement. Future RCTs could examine depression, anxiety and fatigue concurrently. For example, RCTs including multiple symptoms could identify possible symptom clusters and examine whether a psychological intervention is more or less effective for certain symptom clusters. Yet the relatively small sample size of RCTs might limit the examination of distinct symptoms clusters, because the analyses require larger sample size.

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Conflict of Interest

The authors have declared that there is no conflict of interest.

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