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Comparing depressive symptom representation between individuals with cancer, non-cancer controls and healthy individuals: A network approach

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ABSTRACT

Introduction: Individuals affected by cancer are vulnerable to depression, but prevalence rates vary greatly between studies. The preponderance of somatic rather than psychological symptoms, overlapping with cancer-related symptoms, has spurred controversy on depressive symptom assessment in cancer. This work moves beyond sum scores of symptoms and explores symptom interrelations in individuals affected by cancer (compared to non-cancer and healthy controls) to deepen the understanding of depressive symptom expression in the context of cancer. It also compares the symptom network of individuals with cancer to a) non-cancer and b) healthy controls.

Methods: Network analyses and comparisons were conducted on 3512 participants from the Gutenberg-Health-Study (1230 with cancer; 1230 non-cancer controls; 1230 healthy individuals). Gaussian graphical models were estimated for each group, and network structures were compared regarding symptom predictability and centrality of PHQ-9 items.

Results: Depressive symptoms were more frequent in individuals affected by cancer than in non-cancer controls (d = 0.131) and healthy individuals (d = 0.172), but network structures did not differ. Mean predictability (amount of symptom variance explained through all other symptoms) ranged between 25 % and 29 %; with *depressed mood* highest in individuals with cancer and *energy loss* highest in non-cancer and healthy controls. Both symptoms were the most central nodes in all groups.

Conclusion: Symptom structure did not differ between individuals affected by cancer, non-cancer controls and healthy individuals. While somatic symptoms were more frequent in individuals with cancer, they were as closely associated with other symptoms as in the control populations. Along with psychological symptoms, somatic symptoms should be considered in screening as well as targeted by interventions in those with cancer.

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1. Introduction

Cancer diagnosis and treatment impose significant mental and physical challenges. Every second person affected by cancer reports moderate to high psychological distress [1], with 24.8 % to 36.7 % suffering from clinically relevant symptoms [2]. Reported rates of clinically relevant symptoms vary greatly, not just due to disease-related characteristics (e.g. cancer site) [3], but also due to other factors such as data collection modality (e.g. self-report screening tools vs. diagnostic interviews). Assessing depressive symptoms with the most commonly used screening instrument, the Patient Health Questionnaire (PHQ-9) [4], 12.7 % [5] to 24 % [6] cancer patients report symptoms above the clinical cut-off. However, calculating prevalence rates based on clinical interviews, Mehnert et al. found a four-week prevalence of any mood disorder of 6.5 % in a sample of 4020 cancer patients [7]. A comprehensive meta-analysis by Krebber et al. corroborates these findings, highlighting the wide range in reported rates of clinically significant depressive symptoms (8 %–24 %) depending on methodological differences [3], and pointing to a potential *overestimation* of symptoms when using self-report instruments.

Importantly, questionnaire sum scores do not differentiate between somatic and psychological (i.e., affective and cognitive) symptoms. A large body of research consequently discusses the validity and effectiveness of established screening instruments (e.g. PHQ-9) in the oncological context [5,8]. Especially the overlap of somatic symptoms of major depression (e.g. Diagnostic and statistical manual for mental disorders, DSM-V) [9] with symptoms and side effects of cancer and its treatment – such as *sleep disturbances*, *fatigue*, and *lack of concentration* – may lead to a false-positive classification [10–12]. Some researchers thus called for a revision of the somatic symptom items [13] or even for an exclusion when assessing depressive symptoms in cancer patients; such as in the Hospital Anxiety and Depression Scale [14]. For example, Zimmermann et al. proposed to exclude somatic symptoms of the DSM-IV criteria and lower the cut-off (proposed: 3 out of 5, compared to 5 out of 9) [15], entailing a decrease in proportions of palliative care patients classified as suffering from clinically relevant symptoms (15 % compared to 19.3 %) [16]. Taking a closer look at the symptoms reported, Jones et al. found that particularly *fatigue* had a significant effect on screening positive for clinically relevant symptom burden [10]. Four months after treatment start, 8.3 % were only screened positive if *fatigue* was included in the symptom score (positive screening rates for the full PHQ-9: 14.9 %; if *fatigue* was removed: 6.6 %). The removal of the symptoms *sleep disturbances* and *appetite change* also implicated substantial reductions in cases (by 7 % fewer for each item). However, as most participants screened positive on both somatic *and* psychological symptoms, the authors concluded that somatic symptoms should still be included when screening for depressive disorders, but high scores on *fatigue* and *sleep disturbances* should be viewed with caution. In general, somatic symptoms were found to be more frequent in depressed than in nondepressed cancer patients [12], highlighting the importance of including somatic symptoms in diagnostic tools to detect potential comorbid depression in cancer patients [12].

Research generally indicates a good sensitivity and specificity of diagnostic and screening tools for depression within cancer patients [6,8,17]. Comparing all DSM-IV symptoms, somatic symptoms might even be the most sensitive and specific when screening for any depressive disorder [5]. In a large study of 4705 cancer patients, non-somatic symptoms had the best overall predictive performance, but all somatic symptoms had an adequate specificity [18]. Especially within individuals affected by a mild depressive episode, somatic symptoms might play an important role in sensitive comorbidity diagnostics [18,19]. Nevertheless, the evidence indicates that the general understanding of psychological disorders might not be easily transferable to the psychopathology of cancer patients, making a closer investigation of the underlying structure pertinent - not just for diagnostic reasons, but also to identify the most relevant symptoms for targeted psychosocial interventions.

While depression is conventionally understood as a latent factor, linked to a set of symptoms (e.g. *depressed mood, lack of motivation*), newer approaches consider psychological symptoms as networks and specific illnesses as symptom clusters. So-called network models display the interconnected symptom structure, wherein symptoms are considered to affect, interact with and reinforce each other [20,21]. Network models help to conceptualize and visualize the complex dynamical system of disease manifestations by analyzing the association ("edges"; regularized partial correlation coefficients) between each symptom variable ("nodes") [20]. This approach promises insights into the associations between somatic and psychological symptoms and their relevance for the development and maintenance of depressive disorders in those with cancer.

Only a few studies have investigated the interrelationships between depressive symptoms in cancer patients [22–25]. Psychological symptoms (e.g. *depressed mood, loss of interest*, and *worthlessness*) consistently were the most central variables and the most strongly connected to all other depressive symptoms [22,25]. Among somatic symptoms and other physical problems, *fatigue* was most closely connected [22,25]. To date, only two studies have compared the depressive network structure of cancer patients with the general population or non-cancer controls, yielding contradictory results: A network analysis of 559 Korean cancer patients showed *worthlessness* to be the most central symptom in the network, but also found no difference in the overall structure when comparing to a non-cancer sample (n = 599, age- and sex-matched controls) [24]. Results of a German study with 4020 cancer patients (vs. 4020 individuals from the general population), however, indicated a diverging network structure; in the sense that intercorrelations of depressive symptoms were less dense for cancer patients [23]. The interrelations between *energy loss – appetite change*, *depressed mood – suicidality*, *energy loss – suicidality* and *psychomotor issues – suicidality* were stronger than in the general population. While depressive symptoms were more frequent among cancer patients, the authors interpreted their reduced interconnectedness and predictability by other depressive symptoms that among cancer patients, a larger share of the variance in depressive symptoms is linked to external variables rather than the self-perpetuating effects of other depressive symptoms [23]. However, neither study reported on nor controlled for confounding variables within their comparison group (e.g. other chronic diseases). As replication studies are still lacking, it is unclear whether the presented studies' contradictory findings were due to cultural differences, different comparison samples, possible differences in the statistical approach (e.g. Ising vs. Gaussian Graphical models) or sample size (1198 vs. 8040). Consequently, empirical research using powerful statistical approaches and building on large samples of individuals with and without cancer, including high-quality, objective medical data, is needed to draw conclusions about the symptom structure of depressive disorders in individuals affected by cancer.

Therefore, this study aims to advance the understanding of depression in individuals affected by cancer and their differences to individuals without cancer or any other chronic illness. Regarding network analysis, specific goals are:

1. To explore the interrelations of depressive symptoms among individuals affected by cancer (overall network structure, predictability, centrality, and interrelations of depressive symptoms).
2. To compare the overall network structure, predictability, and centrality of depressive symptoms in individuals affected by cancer with non-cancer controls, and healthy individuals.

2. Methods

2.1. Procedure and study sample

The Gutenberg-Health-Study (GHS) is a population-based,

prospective, observational cohort study in the Rhine-Main-Region, Germany [26]. Its primary aim is to analyze cardiovascular risk factors and to foster health prevention in the community. At the baseline assessment (between 2007 and 2012; from which the present data were drawn), the study sample comprises 15010 participants (age range: 35–74 years). Participants were randomly drawn from the local registry; the response rate was 60.3 %. The study protocol was approved by the ethics committee of the Medical Chamber of Rhineland-Palatinate (reference no. 837.020.07) and the study was conducted in line with the Declaration of Helsinki. Written informed consent was retrieved from all participants before study inclusion.

Out of 15010 study participants, $N = 977$ were removed due to missing data on one or more PHQ-9 items, resulting in 14,033 potentially eligible study participants. Additionally, $N = 29$ were removed due to benign or unclear cancer diagnoses. In total, 1230 participants (out of 14033) had a self-reported malignant cancer diagnosis. This number differs from earlier examinations of this cohort [27] that relied on subjective morbidity and were not substantiated by matching information from Cancer Registry Data, such as the present work.

To ensure an adequate comparison of the depressive symptom network of individuals with cancer, two comparison groups were included: First, the *non-cancer control sample* consisted of participants without a cancer diagnosis. As no further exclusion criteria were applied, the included individuals may, however, have other chronic illnesses. Out of 12760 participants reporting either no cancer diagnosis or a current/past diagnosis, the comparison sample was drawn by a 1:1 matching process to ensure the best possible comparison. The following criteria were used for the matching process: sex, age ±3 years, socioeconomic status (SES; low = lowest 20 %, middle = mid 60 %, high = highest 20 %). To be able to reproduce the matching procedure, we set a seed at (129878). This initializes a pseudorandom number generator, enabling us to reproduce the matching procedure [28].

Second, the *healthy control sample* consisted of participants without a cancer diagnosis AND without any chronic illness (cardiovascular disease [CVD], COPD, pulmonary disease, chronic liver disease, chronic kidney disease, autoimmune disease, other cardiovascular risk factors). In total, 9845 participants reported neither a current/past cancer diagnosis nor any of the named chronic illnesses. Again, participants were matched 1:1 to the cancer sample by the criteria described above. It is important to note that participants included in the *healthy control sample* may also be part of the *non-cancer control sample*, as in the latter, only participants with cancer were excluded, and the comparison samples were drawn according to the best matching out of the overall sample. In total, 3512 participants were included in the comparison samples, resulting in 178 participants being in both the non-cancer control and the healthy individuals group.

2.2. Materials and assessment

The baseline examination was conducted at the study center (University Medical Center of the Johannes Gutenberg-University Mainz). It included the evaluation of cardiovascular risk factors and clinical variables assessed via highly standardized laboratory examinations (e.g. blood samples, anthropometric measurements) and a computer-assisted personal interview. All examinations were performed according to standard operating procedures by certified medical technical assistants.

2.2.1. Sociodemographic information

Sociodemographic variables were assessed by self-report: sex (self-reported as man/woman), age, employment (no/yes), income, living situation (with or without a partner), and SES. The SES index combines data based on education, profession and income and ranges from 3 (lowest SES) to 27 (highest SES).

2.2.2. Depressive symptoms

Depressive symptoms were assessed by the Patient-Health-Questionnaire depression module (PHQ-9) [4], a validated, reliable and widely used self-report measure [29]. Participants rated the occurrence of the nine depressive symptom criteria according to the DSM-IV (e.g., “Little interest or pleasure in doing things”) over the last two weeks. Ratings were conducted on a Likert scale (0 “Not at all” to 3 “Nearly every day”). The sum score of PHQ-9 ranges from 0 to 27. Internal consistency within the current study sample was good (McDonald’s ω: Combined sample: 0.84, cancer sample: 0.83; healthy controls: 0.83, non-cancer controls: 0.83).

2.2.3. Health and chronic diseases

Three questions inquired about individuals’ subjective health appraisal. Participants were asked to rate their general, physical, and psychological health on a four-point scale ranging from 1 “very good” to 4 “bad”. Chronic diseases were assessed via interview and self-report. Information contained whether (and if so, when) or not participants were diagnosed with cancer. Myocardial infarction, heart failure, stroke, deep vein thrombosis, pulmonary embolism, and peripheral arterial disease were summarized as cardiovascular disorder (CVD) in line with the established procedure of the GHS.

2.3. Statistical procedures

Statistical analyses were performed using R Version 4.3.0. To describe sociodemographic and health-related characteristics, descriptive statistics (e.g. mean, variance) were calculated. A cut-off ≥9 was applied to indicate clinically relevant depression [30]. For group comparisons, ANOVAs/Kruskal-Wallis-tests were conducted; when appropriate. In case of multiple comparisons Holm-Bonferroni correction was applied. Cohen’s d was used to indicate the effect size in group differences with 0.20, 0.50 and 0.80 indicating a small, medium and large effect, respectively [31].

For each group, we calculated Spearman’s correlation matrices estimating inter-item relationships as partial correlations. Given the large data sets, we did not apply regularization but conducted unregularized Gaussian Graphical models using the ggmModSelect-function from the qgraph-package (version 1.9.8) [32]. Within the procedure, 100 different network structures are obtained by executing the graphical least absolute shrinkage and selection operator (glasso) and then the best model is chosen according to the Bayesian Information Criterion (BIC), including testing all ways to improve BIC by omitting or adding edges. In the graphical depiction of the network models, items appear as nodes and partial correlation coefficients as edges, connecting the nodes. The network graphs were depicted using the Fruchterman-Rheingold algorithm („spring“layout, qgraph), placing highly correlated nodes more closely together at the center, and nodes with weak correlations at the periphery. The layout was averaged across the groups to facilitate visual comparison. We used the mgm-package [33] to calculate node predictability, which is the amount of variance of a node explained by all other nodes in the network. Predictability is visualized in the network plots as a ring-shaped pie chart around the nodes, whereby a ring filled completely would indicate that 100 % of the node’s variance of that node is explained by its correlations with the other symptoms of the network. We calculated node strength centrality [32], which is the sum of absolute edge weights a node shares with the other nodes included in the network. We compared the structural similarities between the networks using the network comparison test [34], a permutation test that randomly splits the data set and refits the network models repeatedly (1000 times in our analysis) to generate a reference distribution representing the null hypothesis that there is no difference between the networks estimated in two observed groups (in our case, individuals with cancer were compared to non-cancer controls and healthy individuals). The significance of group differences in three parameters can be tested in relation to the reference distribution (1) network structure, quantified as the maximum difference in any edge weight (Holm-Bonferroni corrected), (2) differences in individual edge

weights, and (3) difference of global network strength.

3. Results

Table 1 shows detailed sample characteristics for the total sample and separated by group (cancer, healthy control, non-cancer control). The sample affected by cancer differed significantly from the *non-cancer controls* by their general ($d = 0.302$, $p < .001$), physical ($d = 0.187$, $p < .001$) and psychological health status ($d = 0.082$, $p = .042$). In total, 130 cancer patients (10.6 %) reported depressive symptoms above cut-off, non-cancer controls also reporting higher rates of depression (x2(1) = 3.21, $p = .027$). Comparisons and test statistics are provided in Suppl. Table 1.

Compared to *healthy individuals*, persons affected by cancer reported significantly worse general health status ($d = 0.452$, $p < .001$), physical health status ($d = 0.338$, $p < .001$) and psychological health status ($d = 0.144$, $p < .001$), also reporting higher rates of depression ($x^2(1) = 4.97$, $p = .027$). For detailed comparisons and test statistics see Suppl. Table 2.

Cancer specific characteristics of individuals affected by cancer can be seen in Table 2.

3.1. PHQ-9 scores and correlations

Compared to *non-cancer controls*, participants with cancer reported more somatic depressive ($d = 0.166$, $p < .001$) as well as general depressive symptoms ($d = 0.131$, $p = .001$), but did not significantly differ regarding the total number of individuals reporting depression (cut-off ≥9; $x^2(1) = 3.21$, $p = .073$). Regarding single items significant differences in *depressed mood* ($d = 0.103$), *sleep disturbances* ($d = 0.142$), *energy loss* ($d = 0.147$), and *psychomotor issues* ($d = 0.100$) were found. Detailed test statistics are provided in Suppl. Table 3.

Compared to *healthy individuals*, those with cancer reported overall elevated depressive symptoms ($d = 0.172$, $p < .001$) as well as depression (cut-off ≥9; $x^2(1) = 4.97$, $p = .027$). This applied to cognitive ($d = 0.115$, $p = .004$) and somatic depressive symptoms ($d = 0.190$, $p < .001$). Persons affected by cancer reported more symptom burden on every single item ($d = 0.081$–0.192); except for *trouble concentrating* ($d = 0.044$, $p = .278$) and *suicidality* ($d = 0.037$, $p = .365$), which showed no differences. For detailed test statistics, see Suppl. Table 4.

All PHQ-9 symptoms were significantly associated with each other, with similar-sized associations in all three populations (cancer sample: median $r = 0.26$; non-cancer controls: median $r = 0.27$; healthy individuals: median $r = 0.25$). Detailed correlation matrices for all samples are provided in Suppl. Tables 5–8.

Table 2
Disease-specific characteristics of the cancer sample ($N = 1230$).

	M (SD)
Time since first cancer diagnosis [1]	9.7 (9.25)
Number cancer diagnoses per person	1.14 (0.43)
Cancer diagnosis [2]	
Bone Tumors and Soft Tissue Sarcomas	64 (4.81)
Breast Cancers	265 (19.92)
Central and Peripheral Nervous System Cancers	10 (0.75)
Dermatological Cancers	331 (24.89)
Endocrine Cancers	36 (2.71)
Gastrointestinal Cancers	144 (10.83)
Head and Neck Cancers	34 (2.56)
Hematological Cancers	18 (1.35)
Thoracic Cancers	18 (1.35)
Urogenital Cancers	400 (30.08)
Others	9 (0.68)

Note. M, Mean; SD, Standard deviation; [1] in years; [2] multiple diagnoses possible.

3.2. Network analysis

Fig. 1 depicts the PHQ-9 partial correlation symptom networks separated by groups. In individuals affected by cancer, 24/36 (66.66 %) possible edge weights differed from zero. This was true for 23/36 (63.88 %) in non-cancer controls and for 21/36 (58.33 %) in healthy individuals. In *individuals affected by cancer*, the strongest edges were *sleep – energy loss*, *interest loss – depressed mood*, and *depressed mood – worthlessness*. In *non-cancer controls,* the strongest edges emerged between *loss of interest – worthlessness*, *trouble concentrating – psychomotor issues*. In *healthy individuals*, the strongest edges were *depressed mood – worthlessness, sleep – energy loss, worthlessness – suicidality* (shown in Suppl. Fig. 1, 2). The average predictability (the extent to which a node's variance is explained by all other symptoms in the network) was 28 % in individuals affected cancer, 29 % in non-cancer controls, and 25 % in healthy individuals. *Depressed mood* had the highest predictability among individuals affected by cancer (40 %), while predictability was highest for *energy loss* among both non-cancer controls (44 %) and healthy individuals (40 %; shown in Fig. 1). We did not find evidence for substantial differences in standardized node strengths centrality (shown in Fig. 2) with *energy loss* and *depressed mood* appearing to be the most central nodes across groups.

3.3. Comparison of networks

The associations of adjacency matrices (cancer sample versus healthy individuals: rho = 0.75; cancer sample versus non-cancer

Table 1
Detailed characteristics of the combined and single samples.

	Combined sample ($N = 3512$)	Cancer Sample ($N = 1230$)	Non-Cancer Control ($N = 1230$)	Healthy Individuals ($N = 1230$)
Age (*M, SD*)	61.07 (9.59)	61.38 (9.57)	61.18 (9.51)	61.15 (9.54)
Sex (*N*, %)				
Men	1601 (45.6)	559 (45.4)	559 (45.4)	559 (45.4)
Women	1911 (54.4)	671 (54.6)	671 (54.6)	671 (54.6)
Married (*N*, %)				
Not married	772 (22.0)	272 (22.1)	267 (21.7)	266 (21.6)
Married	2739 (78.0)	957 (77.8)	963 (78.3)	964 (78.4)
Monthly income (equivalized; *M, SD*)	2239.65 (1502.40)	2204.81 (1446.66)	2282.75 (1607.54)	2203.57 (1387.19)
Employment status (*M, SD*)				
No	2066 (58.8)	773 (62.8)	733 (59.6)	691 (56.2)
Full time	921 (26.2)	292 (23.7)	321 (26.1)	333 (27.1)
Part time	379 (10.8)	116 (9.4)	128 (10.4)	145 (11.8)
Marg. Employed [1]	141 (4.0)	44 (3.6)	48 (3.9)	61 (5.0)
General health status (*M, SD*)	2.39 (0.80)	2.59 (0.84)	2.34 (0.77)	2.23 (0.73)
Physical health status (*M, SD*)	2.12 (0.64)	2.23 (0.66)	2.11 (0.65)	2.02 (0.59)
Psychological health status (*M, SD*)	2.00 (0.65)	2.05 (0.65)	2.00 (0.65)	1.96 (0.63)
Depression (*M, SD*) [2]	321 (9.1)	130 (10.6)	103 (8.4)	97 (7.9)

Note. Cancer Sample, Individuals affected by cancer; M, Mean; SD, Standard deviation; [1] Marginally employed (≥ 400€); [2] Cut-Off ≥9; Please note that the combined sample includes the cancer sample as well as participants who are included in the non-cancer control as well as in the healthy individuals sample.

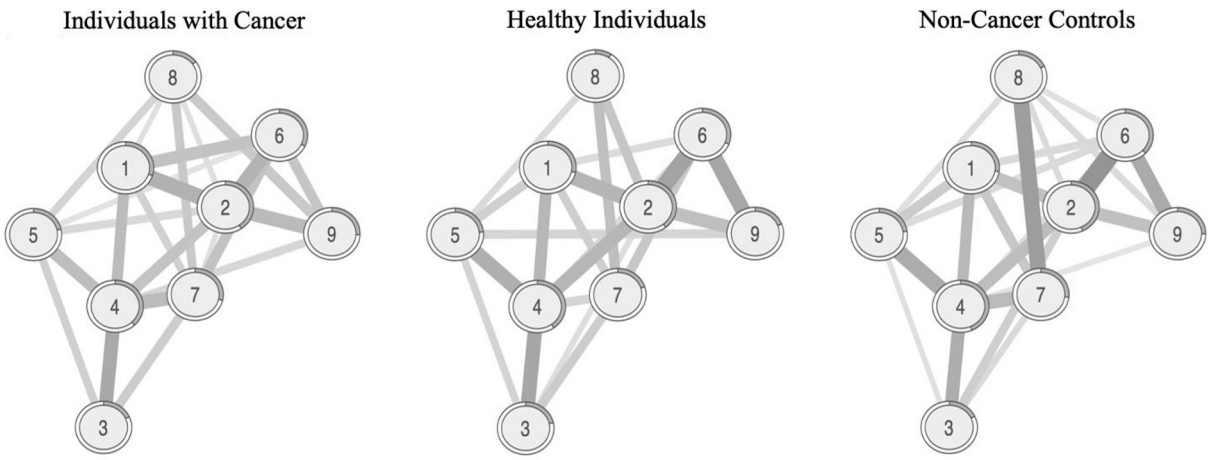

Fig. 1. Partial correlation networks of depressive symptoms (PHQ-9) in individuals affected by cancer, non-cancer controls, and healthy individuals' symptom predictability (i.e., symptoms amount of variance explained by all other symptoms in the network) is indicated by the ring-formed pie charts, a fully filled dark ring would imply 100 % predictability. 1, *loss of interest*; 2, d*epressed mood*; 3, *sleep disturbances*; 4, *energy loss*; 5, *appetite loss*; 6, w*orthlessness*; 7, *trouble concentrating*; 8, *psychomotor issues*; 9, *suicidality*.

controls: rho = 0.72) and node strength centralities (cancer sample versus healthy individuals: rho = 0.92; cancer sample versus non-cancer controls rho = 0.91) pointed to high similarities between the networks. The maximum difference in any edge weight was 0.085 ($p = .931$) when comparing those affected by cancer to healthy individuals, and 0.121 ($p = .304$) when comparing individuals affected by cancer to non-cancer controls. In post-hoc analyses, no statistically significant difference in edge weights was found between individuals affected by cancer and healthy individuals. Between individuals affected by cancer and non-cancer controls, we found a statistically significant difference in edge weights between *loss of interest* and *appetite change* ($p = .007$), however, when accounting for multiple testing, the difference was no longer statistically significant ($p = .252$). Global network strength did not differ statistically significantly between persons affected by cancer and healthy individuals ($S = 0.11$, 3.42 vs. 3.31, $p = .367$), or non-cancer controls ($S = 0.04$, 3.42 vs. 3.39, $p = .760$).

4. Discussion

The present work sought to shed light on the depressive symptom structure in persons affected by cancer to derive actionable insights for assessment and intervention premises. To this aim, we explored the interrelations of depressive symptoms among individuals affected by cancer. By an additional network comparison test, the depressive symptom structure of those affected by cancer was compared with that of persons not affected by cancer and healthy individuals.

4.1. General depressive symptom burden of individuals affected by cancer

Individuals affected by cancer reported significantly more depressive symptoms compared to non-cancer controls as well as to healthy individuals. These comparisons differ from previous investigations comparing unmatched individuals with versus without cancer that had not controlled for confounding effects of age and SES. Taking a closer look at the individual symptom level, however, a more nuanced picture emerges: The observation of more symptom burden only holds for somatic symptoms (i.e. significantly higher in those affected by cancer compared with non-cancer controls and healthy individuals). Psychological depressive symptoms, on the other hand, were only significantly stronger in those affected by cancer when compared to healthy individuals; not when compared to non-cancer controls. These observations are in line with previous research [23,35,36]. They indicate that even though non-cancer controls might be affected by other chronic diseases, cancer (treatment) seems to have a particular effect on the experience of somatic depressive symptoms. These findings support the notion of somatic depressive symptoms emerging not solely due to depressive disorder but also due to cancer (treatment) itself.

4.2. Depressive symptom network comparison

However, the mere increase in somatic depressive symptoms alone does not indicate that these symptoms are less specific for an underlying depressive disorder in this vulnerable population. Network analyses therefore aimed to gain a more in-depth understanding of somatic symptoms' role in the depressive symptom network structure in individuals affected by cancer by comparing it with the symptom structure of non-cancer controls and healthy individuals.

While descriptive comparisons indicated significant differences in the occurrence of somatic symptoms when comparing those affected by cancer and non-cancer controls, network comparison tests did not show significant differences in their depressive symptom *structure*. No differences were found regarding the global network strength nor for network connectivity. Also, no differences in edge weights were found between the three groups, except for the edge weight between *loss of interest* and *appetite change* when comparing those affected by cancer with non-cancer controls; in the sense that these symptoms were more strongly linked in non-cancer controls. This finding, however, must be interpreted carefully, as it was not robust to the correction for multiple comparisons.

The present findings thus provide no evidence for reduced connectivity between depressive symptom nodes in individuals affected by cancer vs. non-cancer controls or healthy individuals, respectively, as reported by Hartung et al. [23]. However, while the current analyses included individuals who were affected by cancer at any point in their lives, Hartung et al. included only individuals in acute treatment or the rehabilitation phase [23]. Further, Hartung et al. did not (report to) control for the control group's health status [23]. When comparing the predictability scores observed in the present study with those reported in Hartung et al.'s study, the respective comparison groups differ substantially (present control groups: 25–29 % vs. general population survey in Hartung et al. (2019): 43 %) [23]. Thus, it remains rather unclear whether the diverging results of the present study and Hartung et al. investigation emerged due to different sampling of the study participants affected by cancer or due to differences in the control group's health status (they did not undergo medical assessments as the control samples in the present investigation) [23]. Additionally, a recent study

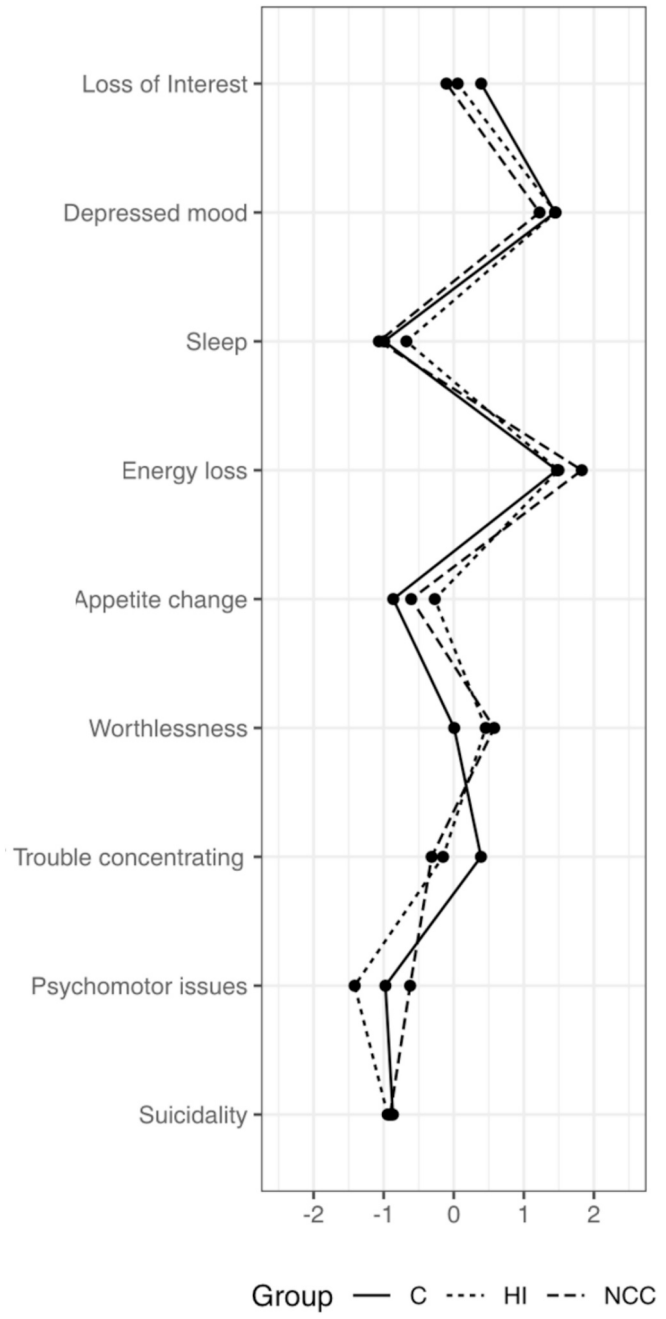

Fig. 2. Standardized node strength centrality of depressive symptoms (PHQ-9) in individuals affected by cancer (C), healthy individuals (HI), and non-cancer controls (NCC).

comparing Korean cancer patients with non-cancer controls did not find significant network differences in depressive symptoms either [24]. The present results thus (partly) align with previous research and, furthermore, do not point towards specific cultural differences in cancer patients' depressive symptoms' structure (as could have been hypothesized based on the diverging observations by Hartung et al. and Hwang et al. [23,24]). Rather they indicate that depressive symptom network do not differ between individuals affected by cancer, non-cancer controls and healthy individuals.

4.3. Implications for assessment and implementation premises

Somatic depressive symptoms were as strongly related to psychological symptoms in cancer as in non-cancer patients and in healthy controls. Thus, they should not be deleted from assessment of depression in cancer patients as suggested by Zimmermann et al. [15]. Instead, the present results underscore that somatic symptoms are an important and specific part of depressive symptoms within persons affected by cancer. Moreover, heightened somatic symptom burden might arise due to cancer and its treatment, but could then promote other depressive symptoms, resulting in the full clinical picture of severe physical and emotional burden. Hence, despite the potentially differing origin of somatic versus psychological depressive symptoms, somatic symptoms are still closely associated with the overall depressive symptomatology within those affected by cancer; potentially by reinforcing other (psychological) depressive symptoms [34]. Van Borkulo et al. even highlight somatic depressive symptoms (i.e. *fatigue, loss of energy*) as key symptoms determining the persistence or remission of major depression [34]. Thus, not only depressive somatic symptoms should be treated by psychosocial interventions, but also cancer-related somatic symptoms should be targeted in the oncological treatment (e.g. by pharmacological treatment, physiotherapy) to prevent and alleviate depressive symptoms in individuals affected by cancer.

4.4. Limitations and future directions

The presented findings must be interpreted in light of several limitations: first, the data used were derived from a cross-sectional assessment and thus do not allow for temporal or causal interpretations. While cross-sectional network approaches cannot inform within-subject processes, they offer valuable insights into the structure of psychopathology. Second, the present sample was drawn from a population-representative cohort study with high-quality data. As a consequence, the cancer sample could be very heterogenous in respect of cancer-related characteristics (e.g. time since diagnosis, current treatment/stage). While the data did not include information about the current stage of treatment, it did include time since cancer diagnosis. However, this information was not entered into the main analyses because it would have needed more detailed information to contextualize it, such as the total number of diagnoses, treatment received/treatment status, (current) stage, current symptom burden. In fact, existing evidence underscores a particularly high psychological burden closer in time to a cancer diagnosis [37–39], but the long-term (psychological) burden and health consequences of cancer are well-studied, too [40]. To better capture potential variations in depressive symptom structures of individuals affected by cancer, future research should compare the depressive symptom structure of individuals with cancer depending on specific cancer-related characteristics (e.g. prognosis, entity, current vs. past cancer diagnosis) in their analysis to make meaningful statements here. Third, while this study contributes to a deeper understanding of differences in depressive symptoms, it did not consider possible effects of multimorbidity, which is prevalent among individuals with cancer and constitutes an additional challenge for both clinical care and research. For instance, it was associated with a greater risk for depression [41]. Future studies should consider the potential influence of multimorbidity on depressive symptom networks in individuals with cancer. Fourth, while the replicability of network structures has been overall successful, detailed inferences might be more sensitive to variations across studies. Borsboom et al. therefore suggested to critically interrogate findings if differences might emerge due to failure to replication or failure to generalize across contexts [20]. Therefore, more replication studies are needed to be able to draw reliable conclusions.

5. Conclusions

The current work underlines the depressive symptom burden of individuals affected by cancer compared to non-cancer controls and healthy individuals. Those affected by cancer reported significantly higher cognitive as well as somatic depressive symptoms compared to healthy persons. However, when comparing with persons not affected

by cancer but possibly by other chronic diseases (non-cancer controls), results indicate that those affected by cancer are particularly affected by stronger somatic depressive symptoms (while the burden from psychological depressive symptoms remains comparably high).

Despite these differences, no depressive network structure differences emerged in the present analysis. Somatic symptoms appear to be equally integrated into the overall depressive symptom network structure as psychological symptoms when compared to the network structure of non-cancer controls and healthy individuals. These findings suggest that current screening and intervention strategies are largely suitable for individuals affected by cancer. Moreover, screening should be sensitive to somatic symptoms as well to then initiate targeted treatment.

Study approval statement

The study protocol was approved by the ethics committee of the Medical Chamber of Rhineland-Palatinate (Germany) and the study was conducted in line with the Declaration of Helsinki.

Consent to participate statement

Written informed consent was retrieved from all participants before study inclusion.

CRediT authorship contribution statement

Judith Hirschmiller: Writing – review & editing, Writing – original draft, Visualization, Methodology, Conceptualization. **Mareike Ernst:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Conceptualization. **Tamara Schwinn:** Writing – review & editing, Conceptualization. **Elmar Brähler:** Writing – review & editing, Resources. **Jörg Wiltink:** Writing – review & editing, Resources. **Rüdiger Zwerenz:** Writing – review & editing, Resources. **Philipp S. Wild:** Writing – review & editing, Project administration, Funding acquisition. **Thomas Münzel:** Writing – review & editing, Funding acquisition. **Jochem König:** Writing – review & editing, Funding acquisition. **Karl J. Lackner:** Writing – review & editing, Funding acquisition. **Norbert Pfeiffer:** Writing – review & editing, Funding acquisition. **Manfred E. Beutel:** Writing – review & editing, Supervision, Funding acquisition. **Lina Krakau:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration, Methodology, Formal analysis, Data curation, Conceptualization.

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Declaration of competing interest

The authors have no competing interest to report. The work is part of the first author's dissertation.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychores.2025.112376.

Data availability

Written informed consent from GHS study participants does not allow public access to the data. Access to the data in the local database is possible at any time upon request according to the ethics vote. This concept was developed with the local data protection officer and the ethics committee (local ethics committee of the Rhineland-Palatinate Medical Association, Germany). Interested scientists can make their requests to the Gutenberg Health Study Steering Committee (e-mail: info@ghs-mainz.de).

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