University of Groningen

Cancer survivors' experience with depressive symptoms and their (low) need for psychological care

van der Donk, Loek Joan

DOI:
[10.33612/diss.136048320](https://doi.org/10.33612/diss.136048320)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2020

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

van der Donk, L. J. (2020). *Cancer survivors' experience with depressive symptoms and their (low) need for psychological care: Lessons learned from a multi-center randomized controlled trial*. [Thesis fully internal (DIV), University of Groningen]. University of Groningen. <https://doi.org/10.33612/diss.136048320>

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Cancer survivors' experience with depressive symptoms and their (low) need for psychological care

Lessons learned from a multi-center randomized controlled trial

Proefschrift

ter verkrijging van de graad van doctor aan de
Rijksuniversiteit Groningen
op gezag van de
rector magnificus prof. dr. C. Wijmenga
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

maandag 02 november 2020 om 14:30 uur

door

Loek Joan van der Donk
geboren op 3 november 1989
te Loon op Zand

Promotoren

Dr. M. J. Schroevers

Dr. J. Fler

Prof. dr. R. Sanderman

Beoordelingscommissie

Prof. dr. J. B. Prins

Prof. dr. J. A. Langendijk

Prof. dr. M. Hagedoorn

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Chapter 1:

General Introduction

1.1 Cancer prevalence

Cancer is among the leading causes of death worldwide. Each year more than 18 million new cases are diagnosed and this number is expected to rise to 29.5 million in 2040 worldwide (1).

Yet, due to advances in early detection, diagnosis and targeted treatment, cancer mortality has decreased by 20% from 1960 to 2014 (2). In fact, about 70% of the cancer patients is estimated to live at least five years after diagnosis nowadays and cancer is therefore more commonly thought of as a chronic illness. Naturally, the prognosis is depending on the stage of cancer and the cancer site.

1.2 Psychological impact of cancer

With decreasing mortality rates, more people live with the psychological burden of having (had) cancer. Research has also put more emphasis on psychological well-being and quality of life after having had cancer. It was found that throughout the illness trajectory, cancer patients commonly report psychological complaints such as feelings of anxiety and depression (3). Rates of depressive symptoms among cancer patients vary between 8% and 24%, depending on type of depression instrument, cancer type and treatment phase (4), with studies using self-report questionnaires reporting higher rates of depressive symptoms compared to those using diagnostic interviews. In general, depressive symptoms reduce over time: in the acute phase of treatment (27%), within 1 year post-treatment (21%) and at least one year post-treatment (15%).

1.3 Depression treatment options in oncology

Due to the negative impact that depressive symptoms may have on patients' quality of life, treatment adherence, and cancer progression, research has focused on identifying effective

treatment options for reducing depressive symptoms. Given the bulk of studies, several meta-analyses and systematic reviews have investigated the efficacy of psychological interventions for reducing depressive symptoms among cancer patients (5–11). Overall, these reviews concluded that psychological interventions can effectively reduce depressive symptoms among cancer patients. Still, a major limitation of current research on the efficacy of psychological interventions in cancer patients is that most of these trials focus predominantly on women diagnosed with breast cancer (6,7,11), which makes it impossible to generalize findings to people with other types of cancer. A second main limitation of previous research on this topic is that few studies focus on patients having finished medical treatment that have entered the phase of survivorship, with the few studies that did investigate this only included breast cancer survivors (6,7,11).

1.4 The (initial) research plan

For these reasons, the Dutch Cancer Society released a call in 2013 for research providing evidence for the efficacy of psychological interventions among cancer survivors, hereby focusing on other types of cancer than breast cancer. The design and set-up of the trial had to meet strict methodological quality standards. Following these requirements, we set up a multi-center randomized controlled trial (RCT) to examine the efficacy of Cognitive Behavioral Therapy (CBT) (12) and Mindfulness-Based Cognitive Therapy (MBCT) (13,14) compared to Treatment As Usual (TAU) for treating depressive symptoms in cancer survivors. Cognitive Behavioral Therapy is an intervention that focuses on behavioral activation and changing negative thoughts, whereas Mindfulness-Based Cognitive Therapy focuses primarily on increasing (bodily) awareness and acceptance and learning to be more mindful: *“paying attention on purpose, in the*

present moment and nonjudgmentally”. Both CBT and MBCT encourage that an individual becomes aware of their thoughts and feelings and regulate them adequately. The major difference between the two interventions is that CBT focuses mainly on challenging and replacing negative thoughts, whereas MBCT focuses on observing thoughts and feelings in a nonjudgmental and accepting way, hereby creating space to respond wisely to these experiences.

For setting up the RCT, we followed the Cochrane criteria (15) in order to fulfill the high-quality standards, which is a list of criteria that are developed in order to minimize the risk of bias. Examples of this include the random allocation of participants to an intervention, monitoring therapists’ adherence to the treatment protocol and patients’ adherence to homework assignments, and the specification of a primary outcome.

For recruiting patients for the trial, we approached approximately 3,000 cancer survivors by means of screening (16,17). In research context, this involves the selection of eligible participants for study inclusion (in our case having elevated levels of depressive symptoms) and is referred to as sampling. Different forms of sampling can be used in order to recruit patients for a study. A common way to recruit patients in psychological trials is so-called *consecutive sampling*, which is a sampling technique in which every subject meeting the criteria of inclusion is selected until the required sample size is achieved. This strategy was also used in our trial and practically meant that cancer survivors received a letter from their department in the hospital, inviting them to fill in a short screening questionnaire. In case elevated scores were reported, they would be contacted by telephone to discuss this. For screening on depressive symptoms, the Patient Health Questionnaire 9 (PHQ-9) was used which is a validated and commonly used screening instrument in both the general population and cancer patients (18,19).

The initial plan for this thesis was to examine the efficacy of CBT and MBCT in reducing depressive symptoms, and moderators and mediators of change (i.e. for whom the interventions

are most effective and why the interventions are effective). However, due to the low uptake and participation of patients in the intervention study, we could not draw conclusions about the efficacy of the interventions.

This intriguing situation, that is, setting up an RCT that strictly follows high-quality methodological standards on the one hand, and the low number of patients participating in the trial on the other hand, has raised several fundamental questions about the utility and feasibility of screening in clinical practice, given that screening is currently recommended by clinical guidelines (20–23). We believe that our observations and encountered challenges are meaningful and insightful for future researchers who plan to set up an intervention trial or who want to implement and test the efficacy of psychological screening in the context of clinical practice or for trial recruitment.

We therefore shifted the focus of this thesis from the examination of interventions' efficacy, to possible pitfalls when conducting such research. In order to guide the reader, this thesis will first discuss the intervention trial and afterwards elaborate on major reasons for low uptake. Additionally, this thesis will focus on factors associated with psychological care needs among depressed cancer patients. Finally, this thesis will shed light upon the psychometric properties of the used screening instrument (PHQ-9) and discuss the utility of psychosocial screening in both research and clinical practice.

Throughout this thesis, the topic of depression will be central and terms such as 'depression' or 'depressive symptoms' are used interchangeable, but it should be noted that in our study this was measured by means of self-report so no official diagnosis of 'major depression' can be applied. Another remark should be made regarding depression assessment among chronic ill patients. The construct depression is very heterogeneous, as it consists of cognitive-affective symptoms, such as having a depressed mood, as well as somatic symptoms, such as fatigue and

concentration problems (24). A major difficulty in assessing depressive symptoms among cancer patients is that somatic symptoms of depression may overlap with somatic symptoms of cancer (treatment), the so-called somatic overlap. This may occur when screening for depressive symptoms is applied in the context of chronically ill patients (25), as most chronic illnesses (e.g. cancer, diabetes mellitus or cardiac disease) and their corresponding treatment are associated with similar somatic complaints (e.g. fatigue or reduced concentration) as a consequence of chemotherapy or poor HbA1c control. In the scenario of somatic overlap, somatic symptoms of the chronic illness are falsely attributed to being part of the depression. As a result, persons with symptoms that are related to their chronic condition or treatment are identified as being depressed, resulting in false-positive diagnoses.

1.5 Chapter Overview

First, we describe our efforts and results of the RCT, including a description of the trial design, the low uptake, and the reasons for low uptake of the intervention study in **Chapter 2**. As one of the interventions in the RCT was based on mindfulness (i.e. MBCT), we were at a more conceptual level interested in the relationship between mindfulness and psychological functioning in cancer patients. In **Chapter 3**, we therefore examined to what extent different facets of mindfulness and self-compassion (specifically focusing on awareness of unpleasant experiences and on holding an open and accepting attitude towards oneself) are related to cancer patients' report of depressive symptoms, negative and positive affect. In addition, we investigated whether the role of mindfulness and self-compassion for depressive symptoms and affect differs between cancer patients and healthy individuals.

In our trial, we encountered a low need for psychological care and we investigated whether this was related to heterogeneity in depressive symptoms (i.e. somatic, cognitive, affective symptoms). Specifically, we examined in **Chapter 4** to what extent a need for psychological care is related to the presence of cognitive-affective symptoms (e.g. feelings of worthlessness, depressed mood) or somatic symptoms (e.g. fatigue, problems with concentrations), using data collected in people with diabetes. It can be hypothesized that people with a somatic illness attribute somatic symptoms less to depression and for this reason, these persons may be less likely to seek psychological help.

In the next two chapters, we further examined the heterogeneity of depressive symptoms in cancer patients. First, **Chapter 5** addressed to what extent distinct depressive symptoms are related to overall severity of depression. In **Chapter 6** we examined to what extent different groups of cancer patients exist that differ in type of depressive symptoms. If distinct subtypes of depression exist, this warrants more targeted and personalized (i.e. symptom-based) treatment options that can be developed and tested in future research.

1.6 Summary

The main aim of this thesis was initially to conduct a multi-center randomized controlled trial to compare the efficacy of two different types of depression treatment in cancer survivors. However, as we encountered substantial challenges during participant recruitment for our trial resulting in low trial uptake, the focus of this thesis shifted to pitfalls and lessons learned when conducting a trial.

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Chapter 2:

Reasons for Low Uptake of a Psychological Intervention offered to Cancer Survivors with Elevated Depressive Symptoms

van der Donk, L. J., Tovote, K. A., Links, T. P., Roodenburg, J. L., Kluin-Nelemans, J. C., Arts, H. J., ... & Sanderman, R. (2019). Reasons for low uptake of a psychological intervention offered to cancer survivors with elevated depressive symptoms.

Psycho-oncology, 2019, 28(4), 830-838. <https://doi.org/10.1002/pon.5029>

Abstract

Objective

In line with screening guidelines, cancer survivors were consecutively screened on depressive symptoms (as part of standard care), with those reporting elevated levels of symptoms offered psychological care as part of a trial. Due to the low uptake, no conclusions could be drawn about the interventions' efficacy. Given the trial set-up (following screening guidelines and strict methodological quality criteria), we believe that this observational study reporting the flow of participation, reasons for and characteristics associated with non-participation, adds to the debate about the feasibility and efficiency of screening guidelines.

Methods

2,608 medium- to long-term cancer survivors were consecutively screened on depressive symptoms using the Patient Health Questionnaire-9 (PHQ-9). Those with moderate depressive symptoms (PHQ-9 ≥ 10) were contacted and informed about the trial. Patient flow and reasons for non-participation were carefully monitored.

Results

1,937 survivors (74.3%) returned the questionnaire, with 147 (7.6%) reporting moderate depressive symptoms. Of this group, 49 survivors (33.3%) were ineligible, including 26 survivors (17.7%) already receiving treatment and another 44 survivors (30.0%) reporting no need for treatment. Only 25 survivors (1.0%) participated in the trial.

Conclusion

Of the approached survivors for screening, only 1% was eligible and interested in receiving psychological care as part of our trial. Four reasons for non-participation were: non-response to screening, low levels of depressive symptoms, no need or already receiving care. Our findings question whether to spend the limited resources in psycho-oncological care on following screening guidelines and the efficiency of using consecutive screening for trial recruitment in cancer survivors.

Introduction

Depressive symptoms are common in cancer patients, not only shortly after diagnosis or during active treatment but also in cancer survivors (1,2). As effective psychological interventions exist to treat these symptoms (3–6), clinical guidelines currently recommend to routinely screen cancer patients on distress throughout the illness and treatment trajectory in order to detect distress and refer patients accordingly to additional care (7,8). These recommendations still hold, even though so far no well-conducted RCTs have demonstrated that mental health outcomes improve via these screening programs (9).

Evidence for the efficacy on interventions has mostly been confirmed in patients in the short-term phase and women with breast cancer, whereas less evidence is available for the efficacy of these interventions among cancer survivors (3–6,10–12). Therefore, the Dutch Cancer Foundation released a call in 2013 for more evidence regarding the efficacy of psychological interventions among (non-breast) cancer survivors. Following strict high-quality standards (13), including consecutively screening on depressive symptoms, we set up a multi-center randomized controlled trial (RCT) examining the efficacy of Cognitive Behavioral Therapy (CBT) and Mindfulness-Based Cognitive Therapy (MBCT) for treating depressive symptoms in cancer survivors. Due to the low trial participation, no conclusion could be drawn about the efficacy of the interventions. As a means to reflect on reasons why an RCT following high-quality methodological standards failed to work in clinical practice, this observational study examined the reasons for non-participation in the RCT and the demographic and medical characteristics of depressed survivors that did (not) participate. Cancer survivors in our trial were consecutively screened on depressive symptoms as a part of standard care, as recommended by the current clinical screening guidelines (7,8) and regarded as a quality standard in setting up an RCT

(14,15). Yet, the screening procedure was not efficient (i.e. resulting in low uptake). Findings of our study may therefore add to the debate regarding the feasibility and efficiency of current screening guidelines for identifying patients in need for care. Our aim is twofold: (1) to inform clinical practice about cancer survivors' levels of depressive symptoms and care needs and the use of consecutive screening; (2) to inform researchers in setting up future psychological RCTs in cancer survivors, to carefully reflect and make considerations regarding the use of consecutive and convenience sampling as a means for patient recruitment.

Method

Study Design

This observational study used data collected as part of a multi-center RCT comparing MBCT and CBT to Treatment As Usual (TAU). For the current study, only the screening data was used. Data were collected from February 2015 until May 2017.

Participants

Eligibility criteria for being approached for screening were: a cancer diagnosis (except breast cancer), age between 18 to 75 years at the time of diagnosis, currently no active cancer, and completion of curative treatment one to five years ago. For trial participation, an additional eligibility criterion was the report of moderate levels of depressive symptoms (PHQ-9 ≥ 10).

Exclusion criteria for trial participation were: not being able to read and write Dutch, having psychiatric comorbidity, receiving psychological treatment for depressive symptoms (currently or less than two months ago) and an instable anti-depressant regimen (i.e. starting/changing less than two months ago).

Screening procedure

Individuals were routinely screened for depressive symptoms at departments radiotherapy, surgery, oral and maxillofacial surgery, gynecology, hematology, endocrinology, medical oncology and colorectal surgery. Individuals received a letter from their department inviting them to complete a mood questionnaire (PHQ-9) on paper or online and in case this score was elevated they would be contacted. Individuals reporting elevated depressive symptoms ($\text{PHQ-9} \geq 10$) received feedback about their elevated levels and were informed that they would receive a telephone call to discuss the depressive symptoms and a possible need for psychological support. These telephonic interviews were executed by graduate clinical psychologists or research/student assistants who had received special training, in which they made a clinical assessment of the psychological problems. Subsequently, persons were selected on eligibility (using a standardized interview to check for exclusion criteria), interest in psychological support and willingness to participate. If this was the case, they received written information about the trial, a questionnaire, an informed consent form and pre-paid return envelope. They were asked to return a completed informed consent and questionnaire within two weeks. Individuals expressing interest in psychological support but who were ineligible or unwilling to participate, were given advice to discuss their care needs with their medical specialist or general practitioner.

Variables

For screening on depressive symptoms the Patient Health Questionnaire-9 (PHQ-9) was used (16), which is a self-report screening tool based on the nine depression criteria according to the Diagnostic and Statistical Manual of Mental Disorders. Each item can be scored from 0 (not at

all) to 3 (nearly every day), resulting in total scores ranging from 0 to 27 with higher scores indicating more depressive symptoms.

Statistical analyses

SPSS 25.0 was used for executing statistical analyses. Demographic (i.e. age, gender) and cancer-related characteristics (i.e. years since diagnosis, years since treatment, cancer type, treatment type, recurrence) were calculated. Chi-square tests and *t*-tests compared groups (i.e. respondents versus non-respondents; depressed versus not depressed; in trial versus not in trial) on demographic and cancer-related variables.

Results

Initially 2,608 cancer survivors were invited to complete a screening questionnaire (Figure 1). In total 25 individuals agreed to participate in the RCT, which was 1.0% of the approached individuals.

Of the 2,608 cancer survivors approached for routine screening, 1,937 returned a valid questionnaire. Table 1 describes demographic and cancer-related characteristics of 1,937 cancer survivors. Mean age was 63 years with 61% being male. Average time since diagnosis and time since treatment were both 3 years. Most common cancer type was gastro-intestinal cancer and only receiving surgery was the most common treatment. In total 166 individuals (8.6%) reported a cancer recurrence.

Those 1,937 persons who returned the questionnaire were compared to those who did not return it. Compared to those who did not return the questionnaire, cancer survivors returning the questionnaire were significantly older (63.3 years $\pm$ 10.3 versus 59.4 years $\pm$ 13.0), more often

Figure 1. Flowchart of participant recruitment and flow through the study.

PHQ = Patient Health Questionnaire

CBT = Cognitive Behavioral Therapy

MBCT = Mindfulness-Based Cognitive Therapy

TAU = Treatment As Usual

Table 1. Demographic and Medical Characteristics of 1937 Cancer Survivors.

Cancer Survivors		
Demographic variables		
N	1937	
Age (M, SD)	63.34	10.33
Gender, male (N, %)	1188	61.3
Cancer-related variables		
Years since diagnosis (M, SD)	3.40	1.31
Years since diagnosis (N, %)		
≤ 2 year	591	30.5
> 2 year	1346	69.5
Years since end treatment (M, SD)	3.07	1.24
Years since end treatment (N, %)		
1 year	218	11.3
2 year	523	27.0
3 year	468	24.2
4 year	397	20.5
5 year	330	17.0
Cancer type (N, %)		
Lung	70	3.6
Skin	35	1.8
Head and neck	235	12.1
Endocrine	59	3.0
Gastro-intestinal	789	40.7
Urological	358	18.5
Gynaecological	179	9.2
Bone & soft tissue	43	2.2
Hematological	160	8.3
Other / primary unknown	9	0.5
Received treatment (N, %)		
Surgery	429	22.2
Surgery + RT*	372	19.2
Surgery + Chemotherapy	180	9.3
Surgery + RT* + Chemotherapy	211	10.9
RT*	385	19.9
RT* + Chemotherapy	196	10.1
RT* + Hormone therapy	90	4.6
Chemotherapy	21	1.1
Other	52	2.7
Recurrence (N, %)		
No	1771	91.4
Yes	166	8.6

Numbers may slightly differ due to missing variables

*RT = Radiotherapy Treatment

male (61% versus 53%) and had more often a cancer recurrence (8.6% versus 4.8%). No significant differences were found in years since diagnosis or years since treatment. Concerning cancer site, highest response rates were found among survivors with bone and soft tissue (91.5%) and survivors with urological cancer (88.4%) with lowest response rates among lung cancer survivors (65.4%). A full overview regarding response rates and elevated depressive symptoms (PHQ-9 ≥ 10) according to demographic and cancer-related characteristics can be found in the Appendix.

In total 147 persons reported moderate levels of depressive symptoms (PHQ ≥ 10) and these persons were compared to those 1,790 persons not being depressed. Those depressed were significantly younger (63.7 ± 10.1 versus 59.3 ± 11.9) compared to those not depressed. No significant differences between those survivors with or without moderate levels of depressive symptoms were found for gender, year since diagnosis, year since treatment and cancer recurrence. Highest levels of depressive symptoms were found among lung cancer survivors (17.1%) and lowest levels of depressive symptoms among gastro-intestinal cancer survivors (3.9%).

Table 2 describes a comparison between 122 individuals with elevated levels of depressive symptoms not included in the trial versus 25 individuals with elevated levels of depressive symptoms who participated in the trial. No significant differences were found between these groups on age, gender, depressive symptoms, time since diagnosis, time since treatment or cancer recurrence.

Reasons for non-participation

Four major reasons for non-participation were identified. The first reason was not responding to the screening questionnaire, with 671 persons (25.7% of 2,608 cancer survivors) not returning a

Table 2. Characteristics of individuals participating in the RCT compared to those with elevated depressive symptoms that did not participate in the trial.

	Depressed, not in trial	Depressed, In trial	Total	<i>p</i> -value
N (%)	122 (83.0%)	25 (17.0%)	147 (100%)	
Age (M, SD)	59.93 ± 11.86	56.16 ± 11.71	59.29 ± 11.88	0.149
Gender (% male)	54.90	56.00	55.10	0.921
Depressive symptoms (M, SD)	14.42 ± 3.83	13.92 ± 3.67	14.33 ± 3.80	0.552
Time since diagnosis	3.38 ± 1.22	3.75 ± 1.25	3.45 ± 1.23	0.179
Time since treatment	3.03 ± 1.16	3.09 ± 1.07	3.04 ± 1.14	0.829
Recurrence (% yes)	10.70	20.00	12.20	0.194

valid questionnaire. Secondly, low rates of depressive symptoms were observed, with only 147 persons (i.e. 7.6% of those completing screening) scoring moderate levels of depressive symptoms. A third reason for non-participation involved low care needs, with 44 depressed persons (29.9% of 147) reporting no need or time for psychological care. A final reason for not being able to participate was already receiving treatment, reported by 26 depressed persons (17.7% of 147).

Discussion

As part of an RCT, we screened a large group of cancer survivors on depressive symptoms, with those reporting moderate or higher levels of depressive symptoms being contacted to discuss their need for care, and inform them about the possibility to receive psychological care, as part of an intervention study. We encountered a very low participation rate. The current paper examined the reasons for not participating, as we believe this will provide more insight into the feasibility of routinely screening for depressive symptoms in cancer survivors as well as of the use of consecutive screening for recruiting cancer survivors for a psychological RCT. Of the 2,608

survivors approached, only 7.6% reported moderate levels of depressive symptoms and of those, almost 50% reported no psychological care needs or already received treatment.

A key finding is that most cancer survivors reported no or only mild levels of depressive symptoms (taking into account that we excluded survivors of breast cancer who are known to be a group at risk for depressive symptoms (17,18)). Another main finding is that many survivors reporting elevated depressive symptoms were not interested in receiving psychological care. Our findings question whether consecutive screening on depressive symptoms as part of standard clinical practice (as recommended by clinical guidelines as well as research recommendations for recruiting trial participants) (7,8,14) is feasible among cancer survivors and an efficient way to detect those with a need for care and referral. Four major reasons for non-participation were identified: (1) one in four cancer survivors did not return the screening questionnaire, (2) rates of depressive symptoms were lower than expected according to literature, (3) one in three depressed cancer survivors did not wish to receive psychological care, and (4) a group of depressed cancer survivors already found psychological help themselves.

One in four cancer survivors could not be screened on depressive symptoms, a response rate of 75% that can be considered high when using a survey (19) and which is also somewhat higher than response rates in other screening studies (varying from 63% to 68%) among cancer patients using surveys (20–23). Research has shown that patients not responding to a screening questionnaire are also more likely to not show up for medical check-ups, suggesting that these patients may in general be difficult to reach (24). An explanation for the non-response to screening may be the information given in the accompanied letter, using words like ‘depressive symptoms’ and informing patients that they would be contacted in case an elevated score was reported (See Appendix).

The screening identified only a small group of cancer survivors (7.6 %) reporting moderate levels of depressive symptoms. This suggests that most cancer survivors are able to adapt and do not experience depressive symptoms in the years following curative treatment. When comparing rates of depressive symptoms in cancer patients, heterogeneity in prevalence rates can be observed, related, amongst others, to differences in cancer type, time since diagnosis and the specific screening instrument (1). Regarding cancer type, two reviews concluded that women with breast cancer are at risk for depressive symptoms (17,18) which could explain why rates in our study were lower than expected, as women with breast cancer were not approached. In fact, most cancer survivors in our study were diagnosed with gastro-intestinal or urological cancer, which have been associated with lower levels of depressive symptoms (17,20). Related to this, in contrast to most previous research focusing on female survivors (1,17,18,25), more than half (61%) of our sample were men that received only surgery. It has been shown that male cancer survivors have lower levels of depressive symptoms compared to women (21) and it can be argued that due to a good prognosis and advances in targeted cancer treatment, the impact of cancer treatment may have been reduced throughout the years, which could also have resulted in relatively low levels of depressive symptoms (26). Additionally, psychosocial support throughout the cancer trajectory has improved and cancer survivors in our study have possibly received intensive psychosocial support during cancer diagnosis and active treatment.

Concerning time since diagnosis, two meta-analyses among cancer patients found depressive symptoms to decrease over time, varying from 27% (in the acute phase), to 21% (within the first year post-treatment), to 15% (at least one year post-treatment), with similar levels as healthy controls after two years following diagnosis (1,27). This could also explain lower rates of depressive symptoms in our study, as cancer survivors were diagnosed and completed medical treatment on average more than three years ago. When interpreting above-

mentioned findings, it should be taken into account that both meta-analyses (like meta-analyses in general), have included a variety of screening instruments, which hampers drawing firm conclusions regarding rates of depressive symptoms. Generally, the efficacy of screening greatly depends on the timing of the screening (i.e. phase of the cancer trajectory). In our study, we targeted medium- to long-term cancer survivors for screening, but if recently diagnosed cancer patients or those in active treatment would have been approached, efficacy of screening may have been higher (due to higher rates of depressive symptoms and greater uptake).

Another factor that may explain variation in rates of depressive symptoms is the measurement of symptoms, which includes the use of a clinical diagnostic interview to classify major depressive disorder versus self-report screening questionnaires (1,28). Although screening questionnaires are often used because of their convenience (i.e. inexpensive and quick to administer to large groups), it should be noted that screening questionnaires overestimate the prevalence of depression (28). In addition, variation in rates of depressive symptoms may be explained by using different screening instruments but also using different cut-off thresholds within a distinct instrument for determining elevated depressive symptoms (1). Our study used the PHQ-9 which is commonly used in oncology for screening on depressive symptoms (16,20,21) and using a cut-off of ≥ 10 we found moderate levels of depressive symptoms rates of 7.6%. Other studies using the same criteria found similar, slightly higher percentages (9.3% - 11.3%) for a mixed group of survivors (20,25). On the other hand, some studies label mild depressive symptoms as being depressed. Therefore, caution is warranted when comparing different rates across studies and we recommend that future research includes a precise description of what their rates of depressive symptoms refer to.

A third reason was low need for professional psychological care among depressed cancer survivors. It is worth mentioning that in our trial, care need was distinguished from willingness to

participate in the trial by asking this in separate questions. In our study, almost one in three depressed persons reported no need or time for treatment. Several studies have drawn similar conclusions that cancer patients with elevated symptoms did not want a referral (29–32). Possible reasons that have been identified include patients' desire to manage problems on their own (31,33,34) or by means of informal social support (30,31,33), which may be related to fear of stigmatization for visiting a psychologist (30,33). Other reasons include that depressive symptoms are not perceived as a severe burden for which professional help is warranted (34) or the preference for receiving medication (e.g. anti-depressants) although there is evidence suggesting that patients with a medical diagnosis prefer psychological treatment to anti-depressant medication (35). More research is needed to examine cancer survivors' perceptions of and coping with depressive symptoms, their care needs and barriers to seek care in order to identify ways to improve psycho-oncological care.

A fourth reason was that cancer survivors already found professional psychological help themselves. In our study this was 17.7% and similar percentages were reported by another Dutch trial among cancer survivors one year after treatment (29) and somewhat higher numbers (24%) by an Australian study on care needs in distressed cancer patients (34). On the other hand, three Scottish high-quality RCTs found few depressed cancer patients to be already in treatment, varying from 0.8% to 7.0% (36–38). A possible explanation for the relatively high percentage of individuals already receiving treatment as well as the low care needs in our study, can be differences in healthcare policies between countries in terms of insurance and coverage of psychosocial aftercare for cancer survivors. For instance, in the Netherlands this is mostly covered by the insurance, making psychological care accessible for anyone irrespective of trial participation. This could explain why individuals in our trial reported low care needs and why the percentage of individuals already receiving treatment was substantial.

Currently, screening is recommended in clinical practice (7,8) as well as for trial recruitment (15), but in our trial screening (which was part of standard care) proved little effective in terms of detecting individuals with care needs. Only 1.0% of the approached individuals participated in the RCT. Several other trials on psychological outcomes in oncology also found low inclusion rates between 2.5% and 3.5% (29,36). Above-mentioned trials and our trial used consecutive sampling for patient recruitment, which encompasses systematically screening every individual who meets selection criteria (14). Another frequently used sampling method involves convenience sampling in which individuals are recruited by means of (self)referral, which has advantages in terms of cost, time and logistics, but may produce an unrepresentative sample (14). For this reason, consecutive sampling is generally seen as the golden standard and is favorable to convenience sampling, because the latter is more prone to selection bias (14). However, in practice this may not completely be the case, because a recent trial found that consecutive sampling still resulted in considerable selection bias in terms of enrolling predominantly young and highly educated patients (29). Moreover, consecutive sampling is not mandated in the CONSORT guidelines (recommendations for high-quality reporting of RCTs in order to maintain high internal validity (39)) implying that consecutive sampling is not a preferred method to convenience sampling for trial recruitment. Furthermore, convenience sampling may result in general in higher motivation among participants due to the self-referral method (40). Given these considerations and our finding that most cancer survivors were not depressed and those that were did not want or already found help, it can be debated whether the methodological advantages of consecutive sampling outweigh its time and resource consuming procedures (40). We do not presume either consecutive or convenience sampling to be a superior method, but instead recommend that in the future the trial's aims and objectives should be decisive for choosing the appropriate sampling method.

Study Limitations

Findings of our study need to be set in the context of several limitations. The first is that no information is available for non-responders regarding depression, so our findings can only be generalized to those returning the questionnaire. Possibly among non-responders there were depressed individuals, which would have influenced rates of depressive symptoms. Another limitation was the self-report measure of depressive symptoms, which may have resulted in not depressed individuals (i.e. false-positives) being contacted or that false-negatives were not approached for help.

Clinical Implications

Our findings suggest that screening cancer survivors consecutively on depressive symptoms as part of standard care was not effective for recruitment in a psychological trial. Of the initially approached cancer survivors, 99% was ineligible, unwilling to participate or could not be reached. Major reasons for non-participation included non-response to screening, low rates of depressive symptoms, low care needs or already receiving psychological treatment. Overall, given the minimal gain from routine screening as suggested by our findings as well as previous research (9), it can be questioned whether the required resources would seem better spent on providing inexpensive or free resources to those who need them or on providing psychological education to patients. These findings should be considered when designing future psychological trials in cancer survivors or when screening (for patient recruitment) is considered.

Acknowledgements

This study was supported by the Dutch Cancer Society (RUG 2013-6190).

Conflict of interest

The authors have no potential conflicts of interest to report.

Ethics Statement

The study was approved by the Medical Ethical Committee of the University Medical Center Groningen (METc 2014/214).

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Appendix

Appendix 1. Response rates and elevated depressive symptoms (PHQ-9 ≥ 10) according to demographic and cancer-related characteristics.

Characteristic	Response rate (%)	Elevated score* (%)
Age^a		
<57	62.6	12.2
57 to 66	75.8	9.4
66 to 70	80.4	4.6
>70	78.0	5.1
Gender		
Male	76.8	6.8
Female	70.5	8.8
Cancer type		
Lung	65.4	17.1
Skin	77.8	8.6
Head and neck	78.6	12.3
Endocrine	73.8	11.9
Gastro-intestinal	76.2	3.9
Urological	88.4	7.8
Gynaecological	68.6	8.9
Bone & soft tissue	91.5	7.0
Hematological	75.8	10.0
Other / primary unknown	81.8	22.2
Treatment Type		
Surgery	97.9	4.9
Surgery + RT*	81.6	7.0
Surgery + Chemotherapy	98.4	3.9
Surgery + RT* + Chemotherapy	81.5	4.7
RT*	79.1	12.2
RT* + Chemotherapy	74.0	11.2
RT* + Hormone therapy	85.7	7.8
Chemotherapy	100.0	19.0
Other	98.1	5.8
Time since diagnosis		
less than 2.5 years	88.5	6.4
more than 2.5 years	84.1	8.1
Time since treatment		
1 year	92.0	6.4
2 year	86.7	7.5
3 year	83.6	9.4
4 year	81.7	7.6
5 year	86.6	6.1
Cancer Recurrence		
No	84.9	7.3
Yes	91.2	10.8

*Determined by PHQ-9 ≥ 10 .

^a = Categories were based on quartiles.

Appendix 2. Screening letter for patients that was attached to the screening questionnaire.

Dear [MISS/SIR],

You are in follow-up at our department because you have had cancer in the past. Whenever you visit our hospital for a medical check-up, our main aim is to find out how you are doing in terms of medical health. Research, however, has shown that a diagnosis of cancer and treatment can cause feelings of tension, sadness and insecurity and that these emotional complaints can persist for a long while after cancer treatment has finished.

Questionnaire

Our department considers it important to also give attention to the emotional consequences of having had cancer. For this reason, a short questionnaire has been developed with questions regarding your current mood. You can fill in this questionnaire within five minutes at home via the internet. If you do not have internet access or if you encounter other problems when filling in the questionnaire, you can also make use of the attached paper questionnaire and send this back using the prepaid return envelope (a stamp is not required).

To fill in the online questionnaire at home, you can visit:

[WEBSITE]

In the questionnaire, you will be asked about your security code. Your personal security code is:

[SECURITY CODE]

Results

If the results from the questionnaire indicate that you have, for instance, depressed or tensed feelings, you will be contacted. The result of the questionnaire will also be in your medical records, making the information also accessible for your medical practitioner. Therefore, you can, if you want to, discuss the results of the questionnaire with your medical practitioner. You can call us as well if you have any questions. [PHONE NUMBER]

We would like to thank you in advance for your cooperation.

Kind regards,

[NAME]

Chapter 3:

The role of mindfulness and self-compassion in depressive symptoms and affect: A comparison between cancer patients and healthy controls

van der Donk, L. J., Fler, J., Tovote, K. A., Ranchor, A. V., Smink, J. G., Mul, V. E. M., Sanderman R., & Schroevers, M. J. The role of mindfulness and self-compassion in depressive symptoms and affect: A comparison between cancer patients and healthy controls.

Mindfulness **11**, 883–894 (2020). <https://doi.org/10.1007/s12671-019-01298-1>

Abstract

Objectives

Mindfulness and self-compassion are related to psychological well-being and can be regarded as personal resources. It is, however, unclear whether these resources are always beneficial (direct effect) or only in stressful circumstances (buffer effect). We therefore examined whether mindfulness and self-compassion are equally or more strongly related to depressive symptoms and affect in cancer patients, compared to healthy controls.

Methods

Using a case-control design, 245 cancer patients were matched to 245 healthy controls (without chronic somatic comorbidities). Both groups filled out questionnaires concerning mindfulness (Five Facet Mindfulness Questionnaire), self-compassion (Self-Compassion Scale), depressive symptoms (Center for Epidemiologic Studies Depression Scale) and affect (Positive and Negative Affect Scale). Using correlation and regression analyses, we examined within both groups the associations for mindfulness (i.e., total score and five facets) and self-compassion (i.e., total score, two factors and six facets) with depressive symptoms and affect.

Results

Mindfulness and self-compassion were equally strong related to depressive symptoms and affect in cancer patients versus healthy controls. Mindfulness facets Act with awareness and Non-judgment were strongly related to depressive symptoms, negative affect and the negative self-compassion factor. In contrast, mindfulness facets Describe and Observe were strongly related to positive affect and the positive self-compassion factor. When distinguishing the six self-compassion facets, Isolation and Mindfulness were strongly related to depressive symptoms, Over-identification to negative affect and Mindfulness to positive affect.

Conclusions

Results suggest that mindfulness and self-compassion are basic human personal resources associated with psychological functioning, regardless of the presence or absence of stressful life experiences.

Keywords

Stress, buffer, depressive symptoms, affect, case-control

Introduction

According to stress-coping models (Lazarus & Folkman, 1984; Moos & Schaefer, 1993), people have personal resources (e.g. internal traits or dispositions) and social resources (e.g. external support, time, money) that determine their psychological functioning and adaptation to stress. Some resources may always be beneficial and directly related to psychological functioning (regardless of the presence of stress) whereas others may be particularly important in stressful circumstances (so called ‘buffer effect’). Mindfulness and self-compassion have been related to psychological well-being and can be regarded as personal resources (Keng, Smoski, & Robins, 2011; Macbeth & Gumley, 2012; Sirois & Rowse, 2016). As personal resources, they have the ability to influence (i.e. moderate) the way in which stressors are perceived and coped with. So far, it is not clear whether these resources are always beneficial for psychological functioning or particularly in stressful circumstances.

Having had cancer has been shown to be greatly stressful to patients (Pinto-Gouveia, Duarte, Matos, & Fráguas, 2014; Schellekens et al., 2017) and this context provides a way to test the potential direct or buffer effects of mindfulness and self-compassion. That is, previous research in cancer patients has shown that some resources (e.g. self-esteem, perceived emotional support) had a direct effect on psychological functioning, whereas other resources (e.g. a lack of actual emotional supportive interactions) were more strongly related to depressive symptoms in cancer patients, suggesting a buffering effect (Schroevers, Ranchor, & Sanderman, 2003). Also studies comparing people with a chronic illness with healthy controls found that some resources had a direct effect, and some a buffer effect (e.g. mastery) (Bisschop, Kriegsman, Beekman, & Deeg, 2004; Penninx et al., 1998). Little is known about the possible beneficial direct and buffer effects of mindfulness and self-compassion.

Mindfulness has been defined as a state of being attentive to and aware of what is taking place in the present, with an open, accepting and non-judgmental attitude (Brown & Ryan, 2003). It can be regarded as a multi-dimensional concept, including facets related to attention regulation, non-elaborative awareness, as well as holding an attitude of non-judgment (Baer et al., 2008; Bishop et al., 2004). It has been hypothesized that mindfulness may help people to cope with stressful situations (i.e., buffer effect) (Bishop et al., 2004). However, it can also been hypothesized that being more open and fully aware in the present moment is in general important for psychological functioning (i.e., direct effect).

Previous research has shown a positive association in healthy individuals between mindfulness and psychological outcomes (such as depressive symptoms, negative affect, positive affect) (Bränström, Duncan, & Moskowitz, 2011; Cash & Whittingham, 2010; Nyklíček & Kuijpers, 2008; Snippe, Nyklíček, Schroevers, & Bos, 2015). Studies in people with cancer found somewhat stronger associations of mindfulness with lower depressive symptoms (Chambers et al., 2016; Schellekens et al., 2017), whereas others found associations of comparable strength as in the general population (Garland, Campbell, Samuels, & Carlson, 2013). Studies that have explicitly examined a buffering effect of mindfulness generally found weak support for this, as indicated by small and inconsistent interactions between stress (e.g. in terms of perceived stress, presence of life hassles) and mindfulness (Bergin & Pakenham, 2016; Bränström et al., 2011; Brown, Weinstein, & Creswell, 2012; Ciesla, Reilly, Dickson, Emanuel, & Updegraff, 2012; Garland, Campbell, et al., 2013; Marks, Sobanski, & Hine, 2010). Overall, these findings suggest that mindfulness is beneficial in a wide range of circumstances and populations (differing in demographics and health status), but given the conflicting findings and great differences between the studied populations, it is difficult to draw conclusions about the role of mindfulness for well-being in healthy versus chronically ill individuals.

Self-compassion can be described as compassion directed inward, relating to ourselves as the object of care and concern when faced with the experience of suffering (Neff, 2003). Given the definition of self-compassion, with a focus on being of importance when facing suffering, it can be hypothesized that self-compassion is particularly important when facing stressful life circumstances. Three meta-analyses (mainly including studies among students) found a strong inverse association of self-compassion with depressive symptoms (Macbeth & Gumley, 2012; Muris & Petrocchi, 2017; Zessin, Dickhäuser, & Garbade, 2015). Among cancer patients, similar relationships between self-compassion and psychological functioning have been found (Schellekens et al., 2017), also in the context of a self-compassion training (Campo et al., 2017), although one study found stronger associations of self-compassion with psychological functioning in cancer patients compared to those found in the general population (Pinto-Gouveia et al., 2014). As with research on mindfulness, it should be noted that there was also considerable variety in the strength of the associations of self-compassion with psychological functioning among the different samples. No studies were found that included a measure of stress and tested a potential buffering effect of self-compassion. So far, only one study compared cancer patients with healthy individuals (Pinto-Gouveia et al., 2014), but given the small sample size and differences in demographic characteristics of the two samples, it is difficult to draw conclusions about direct and buffer effects of self-compassion.

So far, no studies have investigated differences between cancer patients and healthy people in the relationships between mindfulness, self-compassion, and psychological functioning. Insight into these potential differences may indicate whether mindfulness and self-compassion based interventions need to be adapted to the context of cancer. In addition, it is important to distinguish positive and negative indicators of psychological functioning, as previous research found that associations of mindfulness and self-compassion with psychological functioning differ

when distinguishing positive and negative psychological outcomes (López, Sanderman, & Schroevers, 2016). Second, given the current debate about the number of facets of self-compassion (Coroiu et al., 2018; Kumlander, Lahtinen, Turunen, & Salmivalli, 2018; Muris, Otgaar, & Pfattheicher, 2018; Neff, Long, et al., 2018; Neff, Tóth-Király, et al., 2018; Neff, Whittaker, & Karl, 2017), self-compassion total scores as well as distinct facets need to be taken into account. That is, with respect to self-compassion, several studies have recently suggested a two factor model (instead of the original six facets), distinguishing a positive self-compassion factor (i.e., a combination of self-kindness, common humanity, mindfulness) and a negative self-compassion factor (i.e., a combination of self-judgment, isolation, mindfulness, over-identification) (Costa, Marôco, Pinto-Gouveia, Ferreira, & Castilho, 2016; López et al., 2015; Petrocchi, Ottaviani, & Couyoumdjian, 2014). Identifying which facets of mindfulness and self-compassion are most strongly related to positive and negative psychological outcomes, is a first step in clarifying possible mechanisms of change explaining how these interventions work. Such knowledge may be used to optimize future mindfulness and compassion-based interventions (Neff, 2016), although it should be taken into account that mindfulness and/or self-compassion based interventions may affect a range of mindfulness and self-compassion facets simultaneously.

So far, several studies have shown that certain facets of mindfulness and self-compassion are more strongly associated with health outcomes than others (Bränström et al., 2011; Cash & Whittingham, 2010; Christopher, Neuser, Michael, & Baitmangalkar, 2012; Garland, Campbell, et al., 2013; Körner et al., 2015; Pinto-Gouveia et al., 2014; Sirois & Rowse, 2016). Evidence from intervention research is mixed regarding which facets are cultivated and most strongly related to improved outcomes (Bränström, Kvillemo, Brandberg, & Moskowitz, 2010; Takahashi et al., 2019; Witek-Janusek, Tell, & Mathews, 2019). Distinguishing the positive and negative

facets of mindfulness and self-compassion may show whether improved outcomes are better explained by decreasing *negative* behaviors (e.g. self-criticism, functioning on automatic pilot) and/or increasing *positive* behaviors (e.g. acceptance, self-kindness, observing internal/external stimuli), and whether this depends on the type of population and outcome that is targeted by the intervention (e.g. increasing positive affect or reducing depression) (Muris & Petrocchi, 2017).

The present study aimed to examine whether mindfulness and self-compassion are equally or more strongly related to depressive symptoms and negative affect and positive affect under stressful circumstances (i.e., having received a cancer diagnosis), compared to healthy controls (i.e., without any chronic somatic condition). Based on the lack of previous studies and conflicting findings of those that did study such direct and buffer effects of mindfulness and self-compassion, no specific hypotheses were formulated.

Method

Participants

In this case-control study, a group of cancer patients was compared with a group of matched healthy controls, without a chronic somatic condition. Cancer patients met inclusion criteria if they were treated with curative intent, received a cancer diagnosis maximally 5 years ago and finished radiotherapy treatment for at least two months. Exclusion criteria were: age younger than 18, having breast cancer (excluded due to ongoing studies at the time), not being able to read Dutch and a serious psychiatric disorder. For healthy controls, exclusion criteria were: age younger than 18 and not being able to read Dutch. Among healthy controls there were cases reporting (a history of) presence of a malignity (171) or other somatic comorbidities (707) and these were therefore later excluded.

Mean age in both groups was 64.7 years, with 71.8% being male. The total group was evenly distributed regarding education, categorized into low (28.8%), middle (39.0%) and highly educated individuals (32.2%). Concerning the cancer patients, more than half of them (55.3%) received the diagnosis longer than 2 years ago. Most common cancer type was urological cancer (52.8%). Surgery with radiotherapy was the most frequently received therapy (30.2%). In total 39 out of 243 (16.0%) reported a recurrence of cancer.

Procedure

The institutional review board of the University Medical Center of Groningen (UMCG), the Netherlands, approved the study. Cancer patients were recruited through the department of radiation oncology of the UMCG from April 2011 until November 2011. In total, 762 eligible patients were approached by their radiation oncologist during a regular consult in which they were given information about the study and an informed consent with a return envelope. Those who consented received a questionnaire. In total, 252 cancer patients gave informed consent and returned the full questionnaires, of which seven individuals were excluded. One patient ID was invalid, one individual did not fill in educational level which was required for successful matching, one patient did not receive a cancer diagnosis but was under radio treatment for a benign condition and four patients received a diagnosis more than five years earlier, resulting in a total sample of 245 cancer patients.

Healthy controls were selected from the register office of the township in the same region as the cancer patients. A community-based sample was selected, based on age and gender distribution representative of the Dutch population. In total 7,492 adults were approached for this study. Healthy controls received an information letter explaining the aim of the study, an informed consent and were invited to complete and send back the informed consent form and

self-report questionnaire in a return envelope. The questionnaire used was similar to the one used for cancer patients as described above, apart from the cancer-related variables missing. In total, 1,736 individuals completed the full questionnaire. More information about the screening procedure can be found elsewhere (López et al., 2015). The final sample before matching involved in total 1,084 individuals, of which 839 healthy controls and 245 cancer patients.

Cancer patients were matched to healthy controls on variables age, gender and educational level by using Propensity Score Matching. If participants had missing values on any of these variables, they were excluded because matching was not possible. For this procedure R Studio 1.0.44 was used (utilizing the MatchIt plugin), entering variables in the order ‘gender’, ‘age’, ‘education’ and using method Nearest Neighbor Matching with a ratio of 1:1. This resulted in 245 cancer patients and 245 healthy controls. Successful matching (1:1) was obtained since age, gender and education were not significantly different for cancer patients compared to controls. Data were then exported to SPSS for further analyses.

Measures

Demographics and clinical variables

Information concerning socio-demographic variables including age, gender, education and chronic somatic comorbidities was gathered by means of self-report. Education level was divided into low, middle and highly educated. In case of lacking or peculiar data on cancer-related variables, patients’ medical records were used for checking authenticity.

Depressive symptoms

Depressive symptoms were measured with the Center of Epidemiologic Studies (CES-D) scale (Bouma, Ranchor, Sanderman, & Sonderen, 1995; Radloff, 1977). This is a 20-item

questionnaire, with each item ranging from 0 to 3. Sum score ranges from 0 to 60, with a higher score indicating more depressive symptoms. In general, a cut-off of ≥ 16 is used for determining elevated depressive symptoms. Internal consistency in this study was good ($\alpha = 0.84$ for cancer patients and $\alpha = 0.82$ for healthy controls).

Positive and negative affect

Positive and negative affect was measured by the 20-item Positive and Negative Affect Scale (PANAS) (Peeters et al., 1999; Watson, Clark, & Tellegen, 1988). This instrument involved two 10-item scales assessing feelings of activeness, enthusiasm and alertness (i.e., positive affect) versus subjective distress and unpleasant engagement (i.e., negative affect). Higher scores indicate more positive and negative affect. Participants were asked to indicate to what extent they perceived the particular emotion the previous week (i.e., 1 very slightly/not at all until 5 extremely). Cronbach's α was good with 0.89 – 0.90 for positive affect and 0.88 – 0.88 for negative affect.

Mindfulness

Mindfulness was assessed using the 39-item Five Facets of Mindfulness Questionnaire (FFMQ), consisting of five facets: Observe, Describe, Act with awareness, Non-judgment and Non-reactivity (Baer, Smith, Hopkins, Krietemeyer, & Toney, 2006; de Bruin, Topper, Muskens, Bogels, & Kamphuis, 2012). Each item involves a statement, which participants have to rate on a five-point Likert scale (1 indicates never/almost never and 5 very often/always). Scores for the five facets can be calculated by recoding negative items and subsequently summing the totality, with higher scores indicating higher levels of mindfulness. The facets Act with awareness and Non-judgment only consist of negatively formulated items and all items of these facets therefore

needed to be reversed. Cronbach's α for subscales in our study were acceptable: 0.76 – 0.75 (Observe), 0.82 – 0.84 (Describe), 0.87 – 0.85 (Act with awareness), 0.84 – 0.83 (Non-judgment) and 0.81 – 0.77 (Non-reactivity).

Self-compassion

Self-compassion was measured using the Self-Compassion Scale (SCS), with scores ranging from 24 to 120 (Neff, 2003; Neff & Vonk, 2009). The Dutch version of the SCS has been validated and contains 24 items instead of 26 items, due to difficulties in translation (Neff & Vonk, 2009). Items are rated on a five-point Likert scale (1 indicates seldom/never and 5 almost always), with higher scores indicating more self-compassion. Given the conflicting results in the literature concerning the amount of self-compassion facets (Coroiu et al., 2018; Muris et al., 2018; Neff, Long, et al., 2018; Neff, Tóth-Király, et al., 2018; Neff et al., 2017), we executed exploratory factor analysis (EFA), confirmatory factor analysis (CFA) and exploratory structural equation modeling (ESEM) to detect the underlying structure for the Dutch version of the SCS (Neff & Vonk, 2009). EFA suggested a two-factor model, whereas CFA results showed a non-sufficient fit of all models (i.e. one-factor, two-factor, six-factor, bifactor, two-bifactor. ESEM showed sufficient fit for a six-factor and bifactor (1 general factor, 6 subfactors) model (in line with findings from the original author (Neff, Tóth-Király, et al., 2018)), but these two models had poor factor loadings for facets Mindfulness (bifactor model) and Over-identification (both models). Given these results and those of previous research regarding the SCS factor structure, the current study presents results using a total SCS score, two factors and six facets. Internal consistency was acceptable and good for the total SCS score ($\alpha = 0.79 - 0.80$), excellent for the two self-compassion factors; the positive factor ($\alpha = 0.87 - 0.86$) and negative factor ($\alpha = 0.86 - 0.88$) and mostly acceptable for the six facets Self-kindness ($\alpha = 0.73 - 0.69$), Self-judgment ($\alpha =$

0.71 – 0.72), Common humanity ($\alpha = 0.64 - 0.75$), Isolation ($\alpha = 0.76 - 0.82$), Mindfulness ($\alpha = 0.78 - 0.74$) and Over-identification ($\alpha = 0.70 - 0.76$).

Data analyses

Further statistical analyses were executed using SPSS 23.0. A group variable was created for cancer patients and controls. First, baseline characteristics were compared between the groups (including the 3 matched variables to guarantee successful matching) using ANOVAs for continuous variables and chi-square tests for categorical variables to detect statistically significant differences. Cancer-related variables (e.g. time since diagnosis, cancer type) were also included for the cancer patients. Then descriptive characteristics for both groups were calculated for depressive symptoms, affect, mindfulness (with subscales Observe, Describe, Act with awareness, Non-judgment, Non-reactivity) and self-compassion (with the two factors: the positive factor and negative factor as well as the six facets Self-kindness, Self-judgment, Common humanity, Isolation, Mindfulness and Over-identification).

Subsequently, a correlation matrix was performed to reveal associations between mindfulness and self-compassion with depressive symptoms and positive and negative affect. Then, in total 15 regression analyses were performed: three analyses for mindfulness total scores and outcomes (i.e., depressive symptoms, positive affect, and negative affect as outcome respectively), three analyses distinguishing the five mindfulness facets, three analyses for self-compassion total scores, three analyses using the two self-compassion factors and three analyses including the six self-compassion facets. To check for multi-collinearity, bivariate correlations between all predictors and VIF values were examined. Neither the correlations (all below <0.80) or the VIF (all values below 2) indicated multi-collinearity. In order to detect whether the analyses were sufficiently powered for detecting a significant effect, we linked the sample size to

the amount of predictors in the analyses. A conservative criterion is that at least 10 to 15 subjects per predictor are required for detecting an effect (Harrell, 2001). Our study complied to this rule, since our regression analysis with the most predictors had 13 predictors and our sample size was 490 (i.e. 245 cancer patients and 245 healthy controls).

Results

Sample characteristics are shown in Table 1. We found significant differences between cancer patients and matched controls in levels of depressive symptoms ($p = .014$) and negative affect ($p = .018$) but not for levels of positive affect ($p = .106$). Regarding mindfulness, total scores did not significantly differ but facets Act with awareness ($p < .001$) and Non-judgment ($p < .001$) were higher in cancer patients, whereas Observe ($p < .001$) was higher in healthy controls (Table 2). For self-compassion, total scores did not significantly differ between the groups and neither did the two self-compassion factors, although cancer patients tended to score lower on the negative factor compared to matched controls ($p = .053$). Regarding the six facets of self-compassion, only Isolation was higher for controls compared to cancer patients ($p = .007$).

With respect to mindfulness, total scores were significantly related to depressive symptoms, negative and positive affect. Facets Describe, Act with awareness and Non-judgment were significantly associated with depressive symptoms in both cancer patients and healthy controls (Table 3), but facet Non-reactivity only in healthy controls. Partly similar results were found for Act with awareness and Non-judgment with negative affect, with Describe and Observe only significant in cancer patients and Non-reactivity not significant in either group. All facets of mindfulness, except for Non-judgment were significantly associated with positive affect in both

Table 1. Demographic and Medical Characteristics of Cancer Patients with Healthy Controls matched on age, gender and education.

	Cancer Patients		Matched Controls		<i>p</i> -value
Demographic variables					
N (%)	245	50	245	50	
Age (mean, sd)	65.35	12.01	64.11	12.11	.257
Gender (N, %)					
Male	184	75.1	168	68.6	.132
Education (N, %)					
Low	77	31.4	64	26.1	.353
Middle	89	36.3	102	41.6	
High	79	32.2	79	32.2	
Cancer-related variables					
Years since diagnosis (mean, sd)	2.39	1.39			
Years since diagnosis (N, %)					
≤ 2 year	110	44.9			
> 2 year	135	55.1			
Cancer type (N, %)					
Urological	124	52.8			
Lung	20	8.5			
Colorectal	15	6.4			
Haematological	16	6.8			
Gynaecological	20	8.5			
Bone & soft tissue	7	3.0			
Other	5	2.1			
Mixed	28	11.9			
Received treatment (N, %)					
RT	58	25.0			
RT + surgery	70	30.2			
RT + chemo	34	14.7			
RT + surgery + chemo	26	11.2			
RT + hormone	19	8.2			
RT + surgery + hormone	15	6.5			
Other	10	4.3			
Recurrence (N, %)					
No	204	84.0			
Yes	39	16.0			

*RT = Radiotherapy Treatment

Table 2. Descriptive characteristics (mean and standard deviation) of cancer patients and healthy controls matched on age, gender and education on depressive symptoms, affect, mindfulness and self-compassion (including facets).

	Cancer Patients		Matched Controls		Total		<i>p</i> -value
	M	SD	M	SD	M	SD	
Depressive symptoms	9.57	7.79	7.96	6.53	8.76	7.22	0.014
Negative affect	15.44	5.71	14.27	5.20	14.86	5.49	0.018
Positive affect	29.79	7.43	28.65	8.03	29.22	7.75	0.106
Mindfulness (total)	133.85	15.85	131.86	14.54	132.85	15.22	0.150
Observe	22.83	6.39	24.64	5.35	23.74	5.96	<0.001
Describe	27.65	5.93	27.32	5.39	27.49	5.66	0.520
Act with awareness	31.98	6.70	29.48	5.60	30.73	6.29	<0.001
Non-judgment	31.84	6.62	29.47	6.06	30.66	6.45	<0.001
Non-reactivity	20.46	5.72	21.21	4.81	20.84	5.28	0.122
Self-compassion (total)	82.56	11.18	81.65	10.95	82.10	11.06	0.366
Two factors							
Positive factor	35.77	8.99	36.41	8.06	36.09	8.53	0.412
Negative factor	25.42	8.08	26.90	8.58	26.17	8.36	0.053
Six facets							
Self-kindness	11.67	3.40	11.90	2.91	11.78	3.16	0.429
Self-judgment	10.07	3.36	10.19	3.39	10.13	3.37	0.702
Common humanity	11.38	3.49	11.80	3.42	11.59	3.46	0.187
Isolation	7.51	3.16	8.32	3.39	7.92	3.30	0.007
Mindfulness	12.67	3.55	12.71	3.08	12.69	3.32	0.881
Over-identification	7.84	3.05	8.37	3.20	8.11	3.14	0.067

Table 3. Inter-correlations between predictors mindfulness and self-compassion facets and outcomes depressive symptoms, negative and positive affect.

	Depressive symptoms		Negative affect		Positive affect	
	Cancer Patients	Matched Controls	Cancer Patients	Matched Controls	Cancer Patients	Matched Controls
Total Mindfulness	-0.471**	-0.463**	-0.399**	-0.349**	0.373**	0.512**
Observe	0.023	0.042	0.209**	0.120	0.304**	0.298**
Describe	-0.308**	-0.273**	-0.298**	-0.123	0.406**	0.310**
Act with awareness	-0.401**	-0.463**	-0.514**	-0.449**	0.197**	0.153*
Non-judgment	-0.414**	-0.387**	-0.461**	-0.417**	0.106	0.017
Non-reactivity	-0.057	-0.186**	0.049	-0.080	0.279**	0.271**
Total Self-compassion	-0.474**	-0.429**	-0.369**	-0.420**	0.169**	0.432**
Two factors						
Positive factor	-0.158*	-0.160*	-0.108	0.017	0.434**	0.237**
Negative factor	0.416**	0.450**	0.472**	0.489**	-0.103	0.006
Six facets						
Self-kindness	-0.120	-0.155*	-0.090	-0.022	0.217**	0.387**
Self-judgment	0.290**	0.272**	0.324**	0.348**	0.048	-0.021
Common humanity	-0.044	-0.023	-0.032	0.131*	0.126	0.242**
Isolation	0.432**	0.449**	0.447**	0.418**	-0.018	-0.176**
Mindfulness	-0.241**	-0.247**	-0.149*	-0.081	0.274**	0.482**
Over-identification	0.332**	0.438**	0.424**	0.508**	0.001	-0.063

* = correlation is significant at the 0.05 level

** = correlation is significant at the 0.01 level

groups. With respect to self-compassion, the total score was related to depressive symptoms, negative and positive affect. Regarding the two self-compassion factors, the negative factor was related to depressive symptoms and negative affect in both groups, whereas the positive factor was related to positive affect. The positive factor was somewhat stronger correlated to positive affect in cancer patients than in matched controls. For the six facets of self-compassion, Self-judgment, Isolation, Mindfulness and Over-identification were significantly associated with depressive symptoms for both groups and similar results were found for negative affect. Self-kindness and Mindfulness were strongest associated with positive affect in both groups and Common Humanity and Isolation only in controls.

Regression analyses revealed that after adjustment for ‘Group’, ‘Total Mindfulness’ inversely predicted depressive symptoms and negative affect but no interactions effects (i.e., total mindfulness*group) were found (Table 4). Regarding the five mindfulness facets, Non-judgment and Act with awareness significantly and mostly (inversely) predicted depressive symptoms and negative affect. Overall, we found no significant interaction effects between mindfulness facets and group (i.e., cancer patients versus healthy controls) except for a significant but weak interaction effect of Non-judgment on depressive symptoms. Observe and Describe mainly predicted positive affect. No significant interactions between mindfulness facets and group were found for positive affect.

After adjustment for ‘Group’, total self-compassion significantly predicted depressive symptoms, negative and positive affect (Table 5). A weak interaction effect was found for total self-compassion with group on positive affect, but not for depressive symptoms and negative affect. Concerning the two self-compassion factors, the negative factor mainly predicted depressive symptoms and negative affect, whereas the positive factor mainly predicted positive

Table 4. (Facets of) mindfulness as predictors of depressive symptoms, positive affect and negative affect.

	Depressive symptoms			Negative affect			Positive affect		
<i>Mindfulness (Total score)</i>	B	t	R ²	β	T	R ²	β	t	R ²
Step 1			.011			.011			.006
Group ^a	.105*	2.323		.107*	2.351		0.077	1.700	
Step 2			.226						.198
Total Mindfulness	-0.465***	-11.548		-0.375***	-8.897	.151	0.440***	10.722	
Step 3			.227						.200
Total Mindfulness*group	-0.028	-0.689		-0.027	-0.645	.152	0.035	0.852	
<i>Mindfulness (five facets)</i>									
Step 1			.012			.011			.006
Group ^a	0.109*	2.393		0.104*	2.292		0.075	1.634	
Step 2			.322			.338			.219
Observe	-0.060	-1.324		0.049	1.104		0.262***	5.409	
Describe	-0.096*	-2.158		-0.035	-0.801		0.200***	4.213	
Act with awareness	-0.292***	-6.078		-0.358***	-7.490		0.127*	2.466	
Non-judgment	-0.321***	-6.758		-0.280***	-5.936		0.094	1.841	
Non-reactivity	-0.124**	-2.856		-0.073	-1.703		0.123**	2.636	
Step 3			.332			.342			.224
Observe*group	-0.074	-1.631		0.003	0.066		-0.008	-0.164	
Describe*group	0.032	0.702		-0.036	-0.793		-0.023	-0.485	
Actaware*group	-0.002	-0.037		-0.035	-0.726		0.023	0.447	
Nonjudge*group	-0.105*	-2.233		-0.019	-0.409		0.063	1.250	
Nonreact*group	0.003	0.077		0.006	0.139		0.007	0.145	

* = $p < 0.05$

** = $p < 0.01$

*** = $p < 0.001$

^a = Group was coded as healthy controls (1) and cancer patients (2)

Table 5. (Facets of) self-compassion as predictors of depressive symptoms, positive affect and negative affect.

	Depressive symptoms			Negative affect			Positive affect		
<i>Self-compassion (Total score)</i>	β	t	R ²	β	t	R ²	β	t	R ²
Step 1			.013			.013			.004
Group ^a	0.114*	2.506		0.113*	2.494		0.064	1.407	
Step 2			.211			.167			.091
Total SCS	-0.445***	-10.930		-0.393***	-9.394		0.295***	6.745	
Step 3			.211			.169			.105
Total SCS*group	-0.014	-0.355		-0.042	-1.014		0.119**	2.744	
<i>Self-compassion (Two factors)</i>									
Step 1			.013			.013			.004
Group ^a	0.113*	2.492		0.116*	2.537		0.063	1.383	
Step 2			.246			.255			.125
Positive factor	-0.229***	-5.659		-0.125**	-3.110		0.349***	8.021	
Negative factor	0.464***	11.437		0.496***	12.324		-0.098*	-2.243	
Step 3			.248			.260			.136
Positive factor*group	-0.013	-0.314		-0.068	-1.698		0.082	1.890	
Negative factor*group	0.043	1.059		0.044	1.104		-0.077	-1.761	
<i>Self-compassion (Six facets)</i>									
Step 1			.013			.013			.004
Group ^a	0.113*	2.492		0.116*	2.537		0.063	1.383	
Step 2			.274			.269			.168
Self-kindness	-0.040	-0.709		-0.060	-1.050		0.124*	2.047	
Self-judgment	0.113*	2.231		0.113*	2.224		-0.028	-0.513	
Common humanity	0.059	1.125		0.051	0.967		-0.085	-1.512	
Isolation	0.286***	4.771		0.162**	2.695		-0.120	-1.870	
Mindfulness	-0.261***	-4.507		-0.122*	-2.105		0.350***	5.645	
Over-identification	0.105	1.785		0.282***	4.749		0.079	1.244	
Step 3			.279			.281			.178
Self-kindness*group	0.014	0.248		0.001	0.011		0.054	0.863	
Self-judgment*group	0.063	1.218		0.044	0.853		-0.004	-0.080	
Common humanity*group	0.008	0.143		-0.080	-1.517		-0.022	-0.396	
Isolation*group	0.054	0.900		0.087	1.449		-0.070	-1.081	
Mindfulness*group	-0.026	-0.441		-0.007	-0.119		0.037	0.572	
Over-identification*group	-0.066	-1.104		-0.070	-1.162		-0.006	-0.087	

* = $p < 0.05$

** = $p < 0.01$

*** = $p < 0.001$

^a = Group was coded as healthy controls (1) and cancer patients (2).

SCS = Self-Compassion Scale

affect. No significant interaction effects of the two self-compassion factors and group were found, suggesting no significant differences between cancer patients and healthy controls in the association of the two self-compassion factors with depressive symptoms, negative and positive affect. Regarding the six self-compassion facets, Isolation positively and Mindfulness negatively were strongest predictors of depressive symptoms, whereas mainly Over-identification predicted negative affect. Positive affect was mainly predicted by Mindfulness. Similar to findings from the two factors, no significant differences between cancer patients and healthy controls were found in the association of the six self-compassion facets with depressive symptoms, and negative and positive affect.

Discussion

Our study examined whether mindfulness and self-compassion are differently associated with depressive symptoms and affect for individuals with cancer compared to healthy controls, in order to test whether these resources are always related to psychological well-being (i.e., a *direct* effect) or in particular when being in stressful circumstances, such as having had cancer (i.e., a *buffer* effect). Results showed that the strength of the associations of mindfulness and self-compassion with psychological functioning is about equally strong in cancer patients and healthy controls, suggesting that these resources are beneficial for psychological functioning irrespective of the presence of stressful circumstances (in our case a diagnosis of cancer). In both groups, we found that mindfulness and self-compassion were inversely associated with depressive symptoms and negative affect, in particular the mindfulness facets Non-judgment and Act with awareness and for self-compassion the negative factor and facets Isolation, Mindfulness and Over-

identification. Strongest associations with positive affect were found for the mindfulness facets Observe and Describe and the positive self-compassion factor and the facet Mindfulness.

Our findings suggest that mindfulness and self-compassion are basic resources and that having these resources available is always beneficial for psychological functioning, not only in the presence of stressful life circumstances. Findings are in line with results of studies in distinct samples in the general population (Brown & Ryan, 2003; Macbeth & Gumley, 2012; Muris & Petrocchi, 2017; Nyklíček & Kuijpers, 2008; Snippe et al., 2015) and cancer patients (Brown & Ryan, 2003; Chambers et al., 2016; Garland, Campbell, et al., 2013; Pinto-Gouveia et al., 2014; Schellekens et al., 2017). When interpreting these results, it should be noted that there are different ways to examine the direct and buffer effects of resources. Based on previous literature that being diagnosed with cancer is associated with higher levels of depressive symptoms and negative affect (Mozaffarieh, Sacu, Benesch, & Wedrich, 2007; Pinto-Gouveia et al., 2014; Schellekens et al., 2017), we assumed that having had cancer can be used as an indicator of stress. In line with this reasoning, we indeed found that cancer patients reported higher levels of depressive symptoms and negative affect compared to the healthy controls. We did not, however, include a direct measure of stress such as the report of amount of daily hassles (Ciesla et al., 2012; Marks et al., 2010) or perceived stress (Bränström et al., 2011). It can be argued that not only cancer patients but also controls were confronted with stress in their daily life, which we did not take into account in our analyses. Also, the time since cancer diagnosis varied greatly between cancer patients, making it possible that the impact of the diagnosis for some individuals was no longer greatly stressful.

Regarding the facets of mindfulness, especially Non-judgment and Act with awareness were inversely associated with depressive symptoms and negative affect in our study. This is consistent with previous research showing that these facets are strongly related to psychological

symptoms, both in healthy individuals (Baer, Lykins, & Peters, 2012; Barnhofer, Duggan, & Griffith, 2011; Bränström et al., 2011; Cash & Whittingham, 2010; Christopher et al., 2012) and in cancer patients (Garland, Campbell, et al., 2013; Garland, Tamagawa, Todd, Specia, & Carlson, 2013). One possibility for this finding is that items of these two mindfulness facets (i.e. Non-judgment and Act with awareness) are all comprised of negatively worded items and previous research has shown that such negative facets tend to predict negative outcomes (e.g. depressive symptoms) (Neff, Long, et al., 2018). The report of positive affect was in our study most strongly related to the mindfulness facets of Observe and Describe. Findings in the literature regarding these facets are mixed, with studies that found associations with positive outcomes (Bergin & Pakenham, 2016), no associations with positive outcomes (Cash & Whittingham, 2010) or only for facet Describe (Bränström et al., 2011; Christopher et al., 2012).

When distinguishing the two factors of self-compassion, depressive symptoms were significantly associated with higher levels of the negative factor of self-compassion, whereas positive affect was predominantly related to the positive factor. This suggests that these two factors of self-compassion play a different role in psychological functioning. Most research so far has focused on the total level of self-compassion hereby overlooking the differences between the positive and the negative self-compassion factors. Our results add to the recent body of knowledge that the negative self-compassion factor is in general more strongly related to negative indicators of psychological functioning and the positive factor of self-compassion to positive indicators (López et al., 2015; Muris & Petrocchi, 2017). Regarding the six facets of self-compassion, depressive symptoms were significantly associated with higher levels of Isolation and reduced levels of Mindfulness which is in line with research among the general population (Körner et al., 2015), whereas for chronic ill patients only the latter may foster adaptive responses to adverse events (Sirois & Rowse, 2016).

Limitations and Future Research

Several limitations need to be taken into account when interpreting our findings. First, we *assumed* that cancer patients experience more stress than healthy controls, but we did not include a direct measure of stress. Therefore, the data does not allow to test directly the interaction between stress and mindfulness/self-compassion. It should be noted, however, that, as assumed and in line with previous research, we found that cancer patients reported more depressive symptoms and more negative affect than controls (Mozaffarieh et al., 2007; Pinto-Gouveia et al., 2014; Schellekens et al., 2017). Second, the cross-sectional design hampers drawing conclusions about the causal direction among the study variables (i.e., mindfulness, self-compassion, and psychological functioning). We assumed that higher levels of mindfulness and self-compassion result in reduced depressive symptoms and negative affect and higher levels of positive affect, but it is plausible that depressed individuals become more judgmental and more critical towards themselves. However, previous studies investigating the temporal order of these constructs found that mindfulness as well as self-compassion reduced depressive symptoms, but not the other way around (Krieger, Berger, & Holtforth, 2016; Snippe et al., 2015). Third, as our sample included mainly male urological cancer patients and no women with breast cancer, results may not be representative and cannot be generalized to other types of cancer patients. A final remark is that as a consequence of the many tests we conducted, the chances of multiple testing problem have substantially increased (i.e. incorrectly rejecting the null hypothesis). For this reason, caution is warranted when interpreting our results. In total, we conducted 15 tests for testing our hypotheses (i.e. 6 for mindfulness and 9 for self-compassion). Most associations that we found had significance levels of <0.001 , so when adjusting for multiple testing (i.e. $\alpha=0.05/15=0.0033$), the majority of effects that we found would still remain significant.

Future research is needed to further examine the differential associations of distinct facets of mindfulness and self-compassion with a range of positive and negative indicators of psychological functioning in different populations (including somatically and mentally healthy persons, somatically ill persons, persons with psychopathological symptoms) and which facets are most likely to be cultivated by interventions and are likely to be beneficial for health outcomes in these different populations.

Author Contributions: **LJD:** designed and executed the study and data analysis, and wrote the paper. **JF:** collaborated with the design, execution, data analysis and writing of the study. **KAT:** collaborated with the design and writing the study. **AVR:** collaborated with the design and writing the study. **JGS:** collaborated with data collection and writing the study. **VEMM:** collaborated with data collection and writing the study. **RS:** collaborated with the design and writing the study. **MJS:** collaborated with the design, execution, data analysis and writing and editing of the final manuscript. All authors approved the final version of the manuscript for submission.

Compliance with Ethical Standards

Conflict of Interest

The authors declare that they have no conflicts of interest.

Ethical Approval

The institutional review board of the University Medical Center of Groningen (UMCG), the Netherlands, approved the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent

Informed consent was obtained from all participants.

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Chapter 4:

Is type of depressive symptoms associated with patient-perceived need for professional psychological care in depressed individuals with diabetes?

van der Donk, L. J., Flier, J., Sanderman, R., Emmelkamp, P. M. G., Links, T. P., Tovote, K. A., & Schroevers, M. J. (2019). Is type of depressive symptoms associated with patient-perceived need for professional psychological care in depressed individuals with diabetes?.

PloS one, 14(2), e0212304. <https://doi.org/10.1371/journal.pone.0212304>

Abstract

Aims The objective of this study is to investigate whether type of depressive symptoms (i.e. cognitive-affective or somatic) is related to a patient-perceived need for professional psychological care in individuals with diabetes.

Methods In total 2,266 participants were recruited as part of the screening procedure for a multi-center randomized controlled trial on the treatment of depressive symptoms among individuals with diabetes. Individuals were invited to complete Beck Depression Inventory-II (BDI-II). Patients with elevated depressive symptoms ($\text{BDI-II} \geq 14$) were interviewed about their psychological care need. Based on their care needs patients were categorized into: unmet need, no need, met need and unclear need. These groups were compared on type of depressive symptoms, as categorized into cognitive-affective symptoms and somatic symptoms.

Results 568 eligible individuals had elevated depressive symptoms, of whom 519 were reached. Among these depressed individuals, 19.7% (102 of 519) had an unmet need for psychological care. Participants with an unmet need were younger ($p < 0.001$) and had higher total depression scores compared to the group with no need ($p < 0.001$). They also scored higher on cognitive-affective symptoms ($p < 0.001$), whereas somatic symptoms did not significantly differ ($p = 0.232$). Logistic regression revealed that cognitive-affective symptoms predicted an unmet need ($p = 0.001$). However, overall predictive capacity of type of depressive symptoms on care needs was weak.

Conclusions Cognitive-affective symptoms of depression - but not somatic symptoms - were associated with an unmet need for psychological care among depressed individuals with diabetes. Future research is needed to reveal better predictors explaining the discrepancy between distress and low care needs in order to optimize screening procedures.

Introduction

Depressive symptoms are a common comorbidity in diabetes mellitus type 1 and 2, with a prevalence as high as 31% [1] which is two to three times higher compared to individuals without diabetes [2,3]. This comorbidity is associated with poorer health outcomes in terms of medication and diet regimen nonadherence, poorer glycemic control, increased morbidity, increased mortality rates and increased healthcare costs [4–6]. Psychological interventions have been found to be effective in the treatment of depressive symptoms in persons with diabetes [7], with respect to both psychological outcomes (i.e. reduced levels of depressive symptoms and anxiety) and diabetes-related outcomes (i.e. HbA1c). Improvement of psychological outcomes and recovery is associated with significant reductions in work disability and healthcare costs [8] and has been found to be cost-effective [9]. These findings stress the importance of early detection and treatment of depressive symptoms among individuals with diabetes.

International guidelines advocate routine screening in order to identify people in need of psychological help [10,11] and refer them for effective treatment [5]. Frequently used screening instruments for detecting distress or elevated depressive symptoms among chronically ill patients include the Distress Thermometer (DT), Beck Depression Inventory-II (BDI-II) and Centre for Epidemiologic Studies Depression Scale (CES-D) [12,13]. Screening is however only effective when followed by uptake of treatment [5]. Currently, there are three usual ways regarding depression management for patients with diabetes [14]. In primary care settings, the majority of patients receive antidepressant medication, which have been found to be effective in reducing depressive symptoms [14]. Another effective treatment option is psychotherapy, which includes a variety of treatments such as cognitive behavioral therapy and problem-solving therapy. A final

depression treatment option involves collaborative care, which combines antidepressant medication and psychotherapy.

Screening may be a useful tool for identifying depressed persons with diabetes, because previous research has shown that the uptake of depression care is low, due to poor depression recognition by healthcare professionals in standard care [15–17]. Another possibility for the low uptake of depression care is that many depressed persons with diabetes do not have a need for psychological care. One study that investigated care needs in individuals with diabetes [18] showed that only a minority (34.6% of 104 participants) of depressed or distressed persons desired referral for psychosocial care. The main self-reported reasons for these participants to refuse referral were lack of interest and no time. Another recent study among persons with diabetes screened for participation in a trial and found that only 21% of the 130 individuals with elevated scores was willing to participate [19]. Main reported reasons for non-participation included not being interested in receiving help and finding it too strenuous. These findings resemble results from several studies in individuals with cancer, in which an increasing number of researchers have been examining perceived need for psychosocial services. Findings showed that despite elevated levels of distress, only a minority (ranging from 14% to 35%) perceived an unmet need for professional psychological care [12,20–24]. The most commonly reported reasons for not perceiving a need for care involve the preference for doing it themselves [20,23–26] and the reliance on (informal) social support [20,22,23]. It should be noted in all the above-mentioned studies that the reasons for declining help were self-reported by patients during the intake. It is therefore possible that there were underlying reasons for reporting ‘lack of interest’ that were not further discussed by the interviewer. Possible underlying reasons, of which patients may be aware or not, may include a lack of perceived benefit of depression care, stigmatization for receiving psychological care, a low burden of symptoms, or perceiving sufficient coping and social resources to manage the symptoms

on their own [20,23–26]. These results suggest that despite elevated levels of distress or depressive symptoms, only a minority of individuals with chronic somatic diseases (including diabetes) perceive a need for professional psychological care.

One of the reasons for a low need for care might be that individuals with diabetes do not recognize that (some of) their symptoms are attributable to depression. That is, the construct of depression is very heterogeneous [27,28] consisting of cognitive, affective and somatic symptoms [29–31]. The somatic symptoms of depression may overlap with the somatic symptoms of diabetes (e.g. fatigue, weight loss), making it difficult for individuals with diabetes to differentiate whether their complaints originate from the disease or from depression. Indeed, previous research has shown that the presence of somatic symptoms is poorly recognized as being part of depression by the physician but also by patients themselves due to the tendency to attribute physical complaints more to a physical illness than to a psychological cause [32]. Moreover, a study in primary care found that the presence of somatic symptoms resulted in a decreased likelihood of initiating depression treatment [33]. Possibly, persons with somatic symptoms of depression believe that receiving psychological care may not be helpful for alleviating somatic symptoms and therefore decline psychological help. Therefore, it could be hypothesized that persons with high cognitive-affective symptoms, with or without additional somatic symptoms, are more likely to recognize their depressive symptoms and perceive a need for psychological care than those with lower levels of cognitive-affective symptoms.

To our knowledge, this study is the first to explore whether type of depressive symptoms is related to a need for psychological care among individuals with diabetes. We hypothesized that individuals with high levels on cognitive-affective symptoms are more likely to perceive an unmet need for psychological care, compared to those with low levels of these symptoms. No such association is expected for individuals with high levels of somatic symptoms.

Method

Sample and procedure

Participants in this study were recruited as part of the screening procedure for a multicenter RCT on the effectiveness of treating depressive symptoms in individuals with diabetes [34]. The study was approved by the Medical Ethical Committee of the University Medical Center Groningen. Persons in treatment for diabetes (both type 1 and type 2) at one of the participating outpatient clinics were approached from June 2011 to February 2013 and invited to fill in a self-report screening questionnaire including age, gender and BDI-II. Inclusion criteria for the current study were: aged between 18 and 70 years, being able to read/write Dutch and having elevated depressive symptoms (as indicated by BDI-II score of ≥ 14). Exclusion criteria were: pregnancy, severe psychiatric comorbidity, acute suicidal ideation and unstable treatment with an antidepressant in the last 2 months prior to inclusion in the study.

Persons with elevated depressive symptoms were contacted by phone and consequently invited for a face-to-face intake. They were first informed about their elevated depressive symptoms on the questionnaire and then asked whether this reflected their actual mood. Consequently, we asked whether they were currently receiving psychological help and if not, they were asked: *“Are you interested in receiving psychological help for your depressive complaints?”*. Answers to this question were summarized and written down. If participants declined psychological help, they were asked for the reason for this (by using an open question). Those who accepted psychological help were given more information about the participation in the RCT or were referred for further treatment. More detailed information about the RCT procedure is described elsewhere [34].

Measures

The main outcome is depressive symptoms, measured by BDI-II. This is a self-report questionnaire with 21 items. Each item contains 4 answer categories scaled from 0 to 3, resulting in a total score between 0 and 63, with higher scores indicating higher levels of depressive symptoms. Cronbach's alpha in our sample was 0.83. For the purpose of our study, we divided 21 items into cognitive-affective domain comprising of item 1-14 (e.g. worthlessness or loss of pleasure) and somatic domain with items 15-21 (e.g. fatigue or concentration difficulty), based on previous models [29,35]. To verify these domains in our diabetes sample, principal component analysis was executed and suggested two components. With the exception of the item "irritability" (scoring on both domains), the principal component analysis displayed a close-to-perfect fit regarding the above-described two domains. For perceived need for psychological care, data were retrieved from the written summary regarding the need question during the interview. Answers of those who declined psychological help were later divided into three different categories by two of the authors (i.e. LJD and KAT). In total, four groups were created based on participants' need for psychological care as displayed in Figure 1: (1) unmet need for psychological care, (2) no need, (3) met need, (4) unclear need. The 'unmet need' group consists of individuals who desired psychological help for their complaints. The 'no need' group involved those not perceiving a need. The 'met need' group comprised persons that already received psychological help. The 'unclear need' group were individuals with inconsistent or lacking information regarding their need (e.g. those who reported that they maybe have a need but not at the moment or those reporting to have no time for help).

Figure 1. Flowchart of 519 depressed persons with diabetes categorized into four perceived care need groups.

Statistical analyses

For statistical analyses, SPSS 23.0 was used. Descriptive statistics for demographic variables were calculated (i.e. means and standard deviation) by means of ANOVAs and chi-square tests. Post-hoc tests were used to reveal possible differences among the groups. In addition, the four care need groups were compared on total BDI-II scores and subscales (i.e. cognitive-affective and somatic) using ANOVAs. Because we were interested in the difference between those with an unmet need versus those with no need, a logistic regression was executed to examine both domains as predictors for unmet need for care (versus no need) with adjustment for covariates. Interaction terms between the two domains were also added. All predictors were standardized prior to analysis by subtraction of the mean and dividing this by the standard deviation.

Results

In total 2,266 individuals with diabetes were consecutively screened, with 562 eligible persons having elevated depressive symptoms (24.8%). Additionally, 6 individuals were referred by their physician resulting in 568 depressed patients with diabetes. Of those 568, 49 individuals could not be reached for the telephonic interview after several attempts. Therefore 519 participants remained (all Caucasian), which were divided in four groups based on their need for care (see Figure 1). Mean age was 55.2 years with 50.4% being male.

Sample characteristics

Of the 519 participants, 102 had an ‘unmet need’ (19.7%), 293 had ‘no need’ (56.5%), 77 had a ‘met need’ (14.8%) and 47 had an ‘unclear need’ (9.1%). In general, the ‘no need’ group was significantly older compared to the ‘unmet need’ group and the ‘met need’ group. No differences in gender were found between the four groups (Table 1).

Table 1. Sample characteristics of 519 depressed persons with diabetes categorized into four groups based on their perceived need for psychological care.

	Unmet need	No need	Met need	Unclear need	P-value
N	102	293	77	47	
Age (years)	53 ±11.9	57 ±11.0	51 ±12.9	54 ±11.8	<0.001
Gender (% male)	51.0	51.5	42.9	55.3	0.499

For age, P-value is derived from ANOVA; for gender, P-value is from χ^2 -test. Data are means and $\pm$ standard deviation for age and percentages of individuals for gender.

Comparison between four care need groups

The ‘unmet need’ group had higher total depression scores compared to the ‘no need’ group ($p<0.001$) and scored also higher on the cognitive-affective domain ($p<0.001$). No significant differences were found on the somatic domain between the four groups ($p=0.232$) (Table 2).

Table 2. Comparison of 519 depressed persons with diabetes on total BDI-II scores and subscales divided in four groups based on perceived need.

	Unmet need	No need	Met need	Unclear need	<i>P</i> - value
BDI score-II	23.8 ±8.5	20.3 ±6.6	23.9 ±9.7	24.4 ±10.3	<0.001
Cognitive-affective subscale	14.5 ±6.4	11.5 ±5.5	15.0 ±7.3	14.7 ±8.6	<0.001
Somatic subscale	9.3 ±3.4	8.8 ±2.8	9.0 ±3.4	9.7 ±3.2	0.232

BDI-II = Beck Depression Inventory-II

Comparison between unmet need and no need for care

Logistic regression was conducted with demographic variables (i.e. age and gender) as covariates. Table 3 shows regression coefficients, Wald Statistics, odds ratios, and 95% confidence intervals for odds ratios for each predictor. A test of the full model against a constant only model was statistically significant, indicating that predictors reliably distinguished between having an unmet need versus having no need ($\chi^2=22.98$, $p<0.001$ with $df=4$). Wald criterion indicated that only the cognitive-affective subscale significantly contributed to the prediction ($p=0.001$), after adjustment for age and gender. The odds ratio of 1.579 indicates that for one standard deviation increase in cognitive-affective score, a 58% increase in odds of having an unmet care need is expected. The somatic subscale was not significant in predicting unmet need ($p=0.400$) and neither was the interaction ($p=0.582$).

Table 3. Logistic regression predicting (no) need for care in the subgroup of 395 depressed persons with diabetes who endorsed 'unmet need' or 'no need'.

Variables	B	Wald Chi-Square	Odds ratio	95% Confidence Interval for Odds Ratio		P-value
				<i>Lower</i>	<i>Upper</i>	
<i>Step 1</i>						
Age	-0.322	6.214	0.725	0.563	0.934	0.013
Gender	0.074	0.359	1.077	0.845	1.372	0.549
Cognitive-affective subscale	0.457	10.938	1.579	1.204	2.070	0.001
Somatic subscale	0.116	0.709	1.123	0.857	1.473	0.400
<i>Step 2</i>						
Cognitive-affective * somatic	0.071	0.303	1.074	0.833	1.384	0.582

Nagelkerke's R^2 of 0.086 indicated that little variance is explained in the model. Prediction success overall of the model was 74.1% (96.5% for no need and 7.3% for unmet need), suggesting that the model with predictors has good specificity properties (i.e. detecting no need cases), but very low sensitivity in terms of correctly predicting an unmet need case. Interestingly, the overall prediction success of the null model (without predictors, in which all cases are assigned to the largest group) was 74.9% which is almost similar to the prediction model. In other words, adding these predictors to the model did not result in an overall better predictive capacity.

Discussion

The current study examined whether need for care in depressed individuals with diabetes is related to the type of depressive symptoms (i.e. cognitive-affective and somatic) they are experiencing. As hypothesized, individuals with diabetes reporting higher levels of cognitive-affective symptoms were significantly more likely to report an unmet need for psychological care, compared to those

reporting lower levels of these symptoms. Somatic symptoms were not significantly associated with perceiving an unmet need for psychological care. Possibly, individuals with high levels of somatic symptoms are less likely to recognize and link these somatic symptoms to being depressed and the need for psychological care. It could also be the case that they think the offered psychological treatment would not meet their somatic complaints and/or is not effective for treating somatic symptoms. Alternatively, it can be reasoned that those individuals who scored high on somatic items were not depressed and therefore did not report a greater need for psychological care. Rather they were experiencing somatic complaints related to their physical health condition [13,27]. It has been debated whether somatic symptoms should be included in the measurement of depressive symptoms in those with a somatic condition. A study on depression screening in diabetes patients using the BDI concluded that “somatic items did not interfere with the screening utility of the total BDI” [36]. In fact, the ROC curve based on the total BDI was slightly better than that based on the cognitive-affective symptoms alone. In addition, it may be useful to also take into account the specific nature and type of depressive symptoms when relating to diabetes outcomes, as research has shown that different subtypes of depression differentially affect diabetes outcomes [37]. With respect to need for care, our results suggest that such a need is mainly related to the presence or absence of cognitive and affective symptoms.

Even though our hypotheses are supported, it should be noted that the predictive capacity of the model indicated that overall, type of depressive symptoms is not a strong predictor for need for psychological care. Two other studies have drawn similar conclusions. A recent study among cancer patients found that distress, anxiety and depression predicted only little variance of the need for care, suggesting that having an unmet need might be explained by other variables [23]. For instance, stigmatization for receiving professional psychological care may form a barrier for accepting help. Another study in the general population did not find evidence that type of

depressive symptoms was a good predictor for treatment seeking either [38]. In our study only one in five of the depressed individuals with diabetes had an unmet need for psychological care. This is an important finding, as it gives information about the efficiency of depression screening to identify patients with a need for care. Interestingly, similar percentages have been found in other patients groups such as cancer patients [12,20–24]. These low uptake rates question the utility of routine screening on depressive symptoms among individuals with diabetes. Considering the importance of identifying individuals with psychological symptoms who are in need of psychological care and may benefit from such care, alternative ways for efficiently identifying those with an unmet need for care should be considered.

One possible way may be complementing a distress or symptom questionnaire with a list of problems such as the Problem Areas in Diabetes (PAID) [39]. The PAID is a diabetes specific questionnaire and may give additional insights into determinants of need for care, because research in oncology has shown that (in particular practical and emotional) problems are a strong predictor for referral wish [22]. Another alternative, already introduced in the oncology setting, involves a simple help question in order to identify care needs among distressed individuals [23]. Both the PAID and the help question might be beneficial in terms of better revealing care needs in individuals with diabetes.

Nevertheless, we would like to point out that merely focusing on those with an unmet need for care is insufficient, since depression is a severe condition with patients experiencing high levels of distress and comorbid negative health outcomes including poor glycemic control [5]. It is essential that individuals not expressing a need for psychological care are also taken into account. For instance, it might be beneficial to create more awareness (e.g. psychoeducation) about the symptoms these individuals are experiencing and how to interpret these symptoms (e.g. providing insight that somatic complaints may also arise from a depressed mood). Otherwise, strategies may

be implemented aimed at enhancing motivation in individuals with no need for psychological care such as Motivational Interviewing (MI). MI has already been found to increase health screening uptake [40] and may therefore also have the potential to increase motivation among those who were earlier unwilling to accept psychological help.

Despite our finding of little predictive value for somatic symptoms regarding need for care, somatic symptoms should not be overlooked. Instead, it should be considered that somatic symptoms can originate from diabetes-related complaints as well as depression. In general, our results stress the importance of a multidisciplinary approach, given the fact that it is not always possible to distinguish for patient or doctor whether complaints originate from diabetes or depression.

Our study contains several limitations. First, it should be taken into account that some individuals with elevated depressive symptoms included in this study are false positives, meaning they were not depressed and therefore did not report a need for treatment. This was also concluded by a systematic review [13], but this problem cannot be addressed by the current design of our study. However, a study in people with diabetes found that the positive predictive value of the BDI-II was fairly good (0.80 with prevalence of 37%) [36]. As a total BDI-II score is used in screening practice to further discuss the problems and possibly refer someone for additional help, we were interested in examining whether type of depressive symptoms is related to a need for care in all patients with elevated BDI-II scores. Secondly, the measure of need for psychological care was dichotomized into “unmet need” versus “no need” whereas it is more likely to be a continuous construct. Besides, when an individual indicated to perceive no need for psychological treatment, the underlying reason for this was not specified. In addition, other psychological measures such as anxiety, quality of life or distress were not taken into account. All of these variables might determine whether an individual perceives a need for care. Regarding

the sample description, information is missing about marital status (or social support), educational level and type of diabetes. These could not be obtained since the data were collected as part of a screening procedure.

More research is needed to better understand why people with depressive symptoms generally have a low need for care. It seems that the quantity of symptoms or the type of (depressive) symptom is not conclusive to determine whether one perceives an unmet need. Alternatively, possibly the way individuals perceive the meaning and impact of the symptoms on their life and the way they are able to cope adaptively with these symptoms or not, has a greater impact on their need for care. More insight into determinants for care needs may be gained by conducting qualitative research on this topic. This future research should reach beyond the reasons for declining help as identified by previous (cancer) research, including a wish to cope with symptoms on their own [20,23–25]. Instead, it should rather focus on the appraisal and coping of the depressive symptoms. Such knowledge can be used to optimize screening in individuals with diabetes and the uptake of psychological care.

Our results suggest that a greater experience of cognitive-affective symptoms was associated with perceiving an unmet need. Yet overall, the level and type of depressive symptoms were poor predictors of persons' need for psychological care. Other yet to be discovered factors might influence whether or not individuals perceive a need for additional psychological care. Ultimately, more research is needed in order to determine the underlying reasons and mechanisms for participants' unwillingness to accept psychological help.

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Supporting Information

S1 Dataset. SPSS data file.

Funding Statement

This work was supported by the University of Groningen/University Medical Center Groningen. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. No additional external funding received for this study.

Chapter 5:

The Value of Distinct Depressive Symptoms (PHQ-9) to Differentiate Depression Severity in Cancer Survivors: an Item Response Approach

van der Donk, L. J., Bickel, E. A., Krijnen, W. P., Tovote, K. A., Sanderman, R., Schroevers, M. J., & Fleer, J. The Value of Distinct Depressive Symptoms (PHQ-9) to Differentiate Depression Severity in Cancer Survivors: an Item Response Approach.

Psycho-Oncology, 2019;1-4. <https://doi.org/10.1002/pon.5192>

Key points

- The Patient Health Questionnaire-9 (PHQ-9) is frequently used for detecting depressive symptoms in the general population as well as in an oncology setting
- Screening for depressive symptoms among cancer survivors is challenged by the overlap of somatic depression symptoms with symptoms of cancer and its treatment
- No study has examined the discriminative capacities of distinct PHQ-9 depressive symptoms
- We found that all PHQ-9 items (both cognitive-affective and somatic) have excellent discriminative capacities for measuring depressive symptoms among cancer survivors
- Somatic symptoms, in particular Fatigue and Sleep problems, seem to best discriminate for mild depression, whereas cognitive-affective symptoms discriminate best for moderate to severe depression

Introduction

Depressive symptoms are common among cancer patients and may persist after finishing curative treatment. Typical depressive symptoms include cognitive-affective symptoms, such as having a depressed mood and somatic symptoms such as fatigue (1). It is well known that somatic symptoms of depression may overlap with symptoms of the illness and its treatment, hereby increasing the risk of false-positive diagnoses (1,2). Whether or not to include somatic symptoms in the assessment of depressive symptoms in cancer patients has therefore been an on-going debate over the past decades (1,2), with recent studies suggesting to include somatic symptoms also in persons with a somatic condition (1–5).

A limitation of previous studies addressing the in- or exclusion of somatic symptoms in the assessment of depressive symptoms, is that they focused on *domains* of symptoms, that is, to include or exclude *all* somatic symptoms and *all* cognitive-affective symptoms. By doing so, they overlooked the role of *distinct* depression symptoms as was recommended more recently (2,6), given the heterogeneity within the somatic or cognitive/affective domain (6). Another limitation is the focus on ‘depressed’ versus ‘not depressed’ (1,5), with a call for more research addressing the continuum of depression severity (4).

Following these recommendations to focus on distinct depressive symptoms and the continuum of depression severity, we examined how distinct cognitive-affective and somatic symptoms of depression are related to the continuum of depression severity and how these symptoms discriminate different levels of depression severity, using an Item Response Approach.

Method

Procedure

For the current paper, we used data collected during routine depression screening in clinical practice, which was part of a larger intervention trial on the effectiveness of depression treatment among cancer survivors (7). Patients were routinely screened on depressive symptoms using the PHQ-9. Those eligible and willing to participate, were asked to fill in an informed consent form prior to trial participation. Inclusion criteria were any cancer diagnosis except for breast cancer, age 18-75 at time of diagnosis, no active cancer and having completed curative cancer treatment at least one year ago up to five years ago. The study was approved by the Medical Ethical Committee of the University Medical Center Groningen.

Measures

The PHQ-9 is a valid self-report instrument based on the DSM-IV diagnosis of a depressive disorder (8), consisting of nine items that can be scored from 0 to 3, resulting in a total score between 0 and 27. Depression severity categories are: no (0-4), mild (5-9), moderate (10-14), moderately-severe (15-19) and severe depression (20-27) (8). Reliability was good ($\alpha = 0.87$ and $\omega = 0.89$) in our study.

Statistical analysis

For demographic and clinical variables, means and percentages were calculated using SPSS 23.0. The R programming language was used for conducting Item Response Theory analyses using package KernSmoothIRT. To examine how distinct cognitive-affective and somatic symptoms of depression are related to the continuum of depression severity, we used polyserial correlation

coefficients to estimate the association between ordinal items and the continuous overall depression trait. To examine how distinct symptoms discriminate different levels of depression severity, we plotted Expected Item Scores against the expected values on the overall depression trait, in order to localize the most discriminative areas.

Results

In total, 2,099 cancer survivors (74.6% of the approached 2,814) returned the questionnaire. Mean age was 63.39 years (± 10.27) of which 62% was male. Average years since diagnosis was 3.32 (± 1.31) and years since treatment was 2.99 (± 1.25). Most common cancer types were gastrointestinal (39.6%) and urological tumors (19.2%) with surgery only (21.7%) or radiotherapy only (20.4%) as most received treatments. The response distributions of the nine PHQ-9 items differed considerably among items (see Table 1), with most commonly reported symptoms being ‘Sleep problems’ (39.2%) and ‘Fatigue’ (45.9%), whereas ‘Suicidality’ was only endorsed by 5.5% of the cancer survivors.

Associations of distinct depressive symptoms (PHQ-9) with depression severity

Polyserial correlations were computed to estimate the association between the nine items and the continuous overall latent depression trait (Table 1). Largest correlations were found for ‘Fatigue’ (0.80), ‘Depressed mood’ (0.79) and ‘Anhedonia’ (0.77), indicating that these symptoms are most strongly associated with the latent depression trait. The weakest correlation was found for ‘Suicidality’ (0.59).

Table 1. Descriptive statistics and polyserial correlation coefficients for the nine Patient Health Questionnaire-9 (PHQ-9) items.

PHQ-9 Item	Mean $\pm$ SD ^a	Answer categories (%)				Polyserial Correlations	
		Not at all	Several days	More than half the days	Nearly every day	Coefficients	CI ^b
Item 1 (Anhedonia)	0.33 $\pm$ 0.69	76.3	16.9	4.0	2.8	0.77	0.74-0.80
Item 2 (Depressed mood)	0.23 $\pm$ 0.56	82.1	14.1	2.4	1.4	0.79	0.76-0.81
Item 3 (Sleep problems)	0.63 $\pm$ 0.94	60.8	23.7	6.9	8.6	0.73	0.71-0.76
Item 4 (Fatigue)	0.72 $\pm$ 0.95	54.1	28.9	8.0	9.1	0.80	0.78-0.82
Item 5 (Appetite change)	0.26 $\pm$ 0.66	83.8	9.5	4.0	2.8	0.70	0.66-0.74
Item 6 (Low self-esteem)	0.18 $\pm$ 0.53	87.4	8.9	2.2	1.5	0.74	0.69-0.77
Item 7 (Concentration difficulty)	0.30 $\pm$ 0.67	79.0	14.6	3.6	2.8	0.71	0.67-0.75
Item 8 (Psychomotor)	0.16 $\pm$ 0.52	89.6	6.3	2.7	1.4	0.63	0.58-0.67
Item 9 (Suicidality)	0.07 $\pm$ 0.33	94.5	4.2	0.9	0.4	0.59	0.54-0.64

^a SD = Standard Deviation

^b CI = Confidence Intervals

Discriminative capacities of distinct depressive symptoms (PHQ-9)

The Expected Item Scores revealed that all items showed monotonicity (Figure 1), with increased item scores being associated with increased depression severity. In general, the complete set of nine items covered the continuum of depression severity reasonably well. Item 3 ‘Sleep problems’ and item 4 ‘Fatigue’ display concave slopes, indicating particularly high discrimination for mild depressive symptoms, whereas item 8 ‘Psychomotor problems’ and item 9 ‘Suicidality’ have more convex slopes, indicating high discrimination for moderately-severe depressed individuals. Item 1 ‘Anhedonia’, item 2 ‘Depressed mood’, item 5 ‘Appetite changes’, item 6 ‘Low self-esteem’ and item 7 ‘Concentration difficulty’ show constant linear slopes, indicating that these items discriminate evenly well for mild, moderate and severe depression levels.

Discussion

Our results showed that the two core symptoms (i.e. Depressed mood and Anhedonia) and Fatigue were most strongly associated with the latent depression trait. Overall, all distinct PHQ-9 symptoms showed excellent discriminative capacities among cancer survivors, with somatic symptoms (i.e. Sleep problems and Fatigue) discriminating best for mild depression and Psychomotor problems and Suicidal thoughts discriminating best for moderate to severe depression.

As such, our findings are in line with recent findings concluding that somatic symptoms should be included in the assessment of depressive symptoms among chronic ill patients (1–5). Our findings also support previous research (9) showing the unidimensionality of the PHQ-9 and therefore warrant using a total score. Previous studies investigating distinct depressive symptoms have mostly dichotomized depression (1,5) and so our study adds

Figure 1. Expected Item Scores as a function of depression severity for all items of the Patient Health Questionnaire-9 (PHQ-9).

to previous research by showing that somatic symptoms Sleep problems and Fatigue mainly discriminate for mild depression, whereas somatic symptoms Appetite changes and Concentration difficulty discriminate evenly across depression severity.

Clinical Implications

Our findings have important clinical implications, as results suggest that the screening purpose determines the utility of items. If a clinician or researcher is interested in

distinguishing moderate to severely (PHQ $\geq$ 10) from not to mildly depressed cancer patients (PHQ<10), the PHQ-2 questionnaire may be a valuable screening tool, consisting of the two (affective) core symptoms ‘Anhedonia’ and ‘Depressed mood’, as these discriminate properly for moderate depression. However, if a clinician or researcher wants more insight into the overall depression levels in cancer patients, then the PHQ-9 questionnaire seems more appropriate, since it has high discriminative properties in terms of differentiating mild, moderate and severe depression.

Study Limitations

A major study limitation involves the absence of a golden standard (i.e. diagnostic interview). Yet, it should be noted that even when applying such an interview, distinguishing whether somatic symptoms originate from depression or from cancer (treatment) remains challenging for patients and professionals, so a possible overlap in some degree is inevitable when assessing depressive symptoms among chronic ill patients. Future research is needed to repeat our analyses in healthy persons, to examine whether our finding of high discriminating value of somatic symptoms for mild depression is (not) caused by an underlying somatic illness.

In conclusion, our study results point out that both somatic and cognitive-affective symptoms of the PHQ-9 are valuable in measuring symptoms of depression in cancer patients and that the screening purpose determines the relative utility of distinct symptoms.

Conflict of Interest

The authors have no potential conflicts of interest to report.

Ethics Statement

The study was approved by the Medical Ethical Committee of the University Medical Center Groningen (METc 2014/214).

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Chapter 6:

Subtypes of Depressive Symptoms among Depressed Cancer Survivors

van der Donk, L. J., Zhu, L., Tovote, K. A., Sanderman, R., Schroevers, M. J., & Fleer, J.
Subtypes of Depressive Symptoms among Depressed Cancer Survivors

Introduction

Cancer patients have an increased risk for depression compared to the general population with rates of depressive symptoms varying between 8% to 24% (1,2), associated with reduced quality of life, less adherence to cancer treatment, prolonged hospitalization and even decreased survival rates (3). It is therefore essential that depressive symptoms among cancer patients are detected early and treated adequately.

Psychological interventions, especially those based on Cognitive Behavioral Therapy and Mindfulness Based Therapy have found to be effective in reducing depressive symptoms (4,5). However, as symptoms of depression are very heterogeneous (6–9) (consisting of cognitive-affective symptoms such as having little interest or pleasure in doing things as well as somatic symptoms such as fatigue or concentration difficulties), it has more recently been argued that depression interventions could be optimized by developing new interventions that specifically target certain types of depressive symptoms. The aim of the current study was to examine whether distinct subtypes of depressive symptoms exist in cancer patients. If so, this could inform future intervention research to develop and test more targeted interventions to treat depressive symptoms.

Different methods exist for detecting depressive symptoms. The DSM-5 outlines the following criteria to diagnose an individual with major depressive disorder (MDD): five or more depressive symptoms (i.e. weight change, sleep disturbance, psychomotor agitation or retardation, fatigue, feelings of worthlessness, diminished ability to concentrate, recurrent thoughts of death) including at least one of the core symptoms: depressed mood or loss of interest or pleasure (10). This results in 227 different symptom combinations, all currently labeled as MDD (6–8,11). A second method for detecting depressive symptoms, often used in research settings, involves summing up self-reported depressive symptoms to a sum score, in order to determine whether an individual has clinically ‘elevated levels of depressive

symptoms' (i.e. above a cut-off score). Although easy to use, several studies have shown that summing up symptoms should also be avoided due to information loss regarding specific symptoms (11,12). Most importantly, both methods (i.e. the DSM-5 and sum score method) assume that all depressive symptoms are equivalent and interchangeable indicators of depression (6–8) and as a consequence all patients are offered the same treatment. Ideally, patients receive a treatment that specifically targets their reported symptoms instead of a one-size-fits-all approach (13,14). Indeed, two reviews recommended that due to non-specificity of major depression, the diagnosis 'major depression' should be avoided and instead subtypes of depression need to be studied (7,15).

So far, several studies attempted to identify such depression subtypes among depressed persons in the general population, by using a data-driven technique called latent class analysis (LCA) (7,16). This technique classifies individuals with similar depression subtypes based on their observed score. Two systematic reviews on depression subtypes summarized that the findings were very diverse (7,16), with the number of subtypes varying from two to seven and no consistent subtypes identified across studies. In almost 75% of the studies the identified depression subtypes mostly differed on *severity of symptoms* (7,16,17) (such as mild, moderate and severe depression). Only few studies have identified subtypes differing on *type of symptoms*, such as presence of certain symptoms (e.g. suicidality) (17) or symptom clusters (e.g. atypical or melancholic depression) (17,18).

Given the overlap between depressive symptoms and symptoms of cancer and its treatment (19) (so-called somatic overlap), it is important to examine subtypes of depressive symptoms in cancer patients. So far, only a single study has addressed depression subtypes in cancer patients (6). This study screened cancer patients on depressive symptoms, including only those with clinically elevated levels and three subtypes were identified. Yet, similar as

the studies in the general population, the identified subtypes were mainly based on depression severity (i.e. mild depression, slightly higher depression levels, severe depression).

In order to unravel clinically meaningful depression subtypes, previous studies have recommended that LCA should differentiate between *type of symptoms*, instead of differentiate between *severity of symptoms* (7,16,20). One explanation for the distinction between severity could be that in most previous studies conducting LCA, a substantial group of the included sample reported few depressive symptoms (6,7,16,21). This could explain why one subtype, usually a substantial proportion of people, was formed by individuals that reported no or only mild depressive symptoms. Therefore, in the current study, we performed LCA to identify subtypes of depressive symptoms in a group of cancer patients, that were screened on reporting at least moderate levels of depressive symptoms. When comparing the depression subtypes, it is important to differentiate between somatic symptoms and cognitive-affective symptoms of depression, given the somatic overlap (19) but also because these are differently related to health outcomes (22).

The aim of this study is to investigate subtypes of depressive symptoms among depressed cancer survivors. We have data on depressive symptoms from 2,099 cancer survivors which allowed us to select only those reporting at least moderate levels of depressive symptoms. These subtypes will be compared on the presence of somatic symptoms versus cognitive-affective symptoms. In addition, our study will investigate whether the depression subtypes are related to demographic and cancer-related characteristics of the patient, as this may reveal whether depressive subtypes differ in certain individual characteristics (7). For instance, several studies among the general population found depression subtypes to be related to gender, age or race (18,21,23), whereas other studies found no significant associations for these variables in the general population (24,25) or with demographic or cancer variables among cancer patients (6).

Method

Screening procedure and participants

Participants in this study were recruited as part of a multi-center randomized controlled trial on the efficacy of depression treatment for cancer survivors. Cancer survivors were routinely screened for depressive symptoms at several hospitals in the Netherlands, inviting them to complete a mood questionnaire (PHQ-9). Further information on the full screening procedure can be found elsewhere (26). Eligible criteria for this study were: being between 18 to 75 years, having had a cancer diagnosis (except breast cancer), currently no active cancer, completion of curative treatment at least one year and at maximum five years ago and reporting at least moderate levels of depressive symptoms (PHQ-9 ≥ 10). Persons were excluded when they: were not able to read or write Dutch, had severe psychiatric comorbidity, received psychological treatment for depressive symptoms (currently or less than two months ago) or had an instable anti-depressant regimen.

Measures

Socio-demographic variables and medical variables were obtained from the medicals records of the patient. Depressive symptoms were measured using the Patient Health Questionnaire (PHQ-9), a valid self-report screening measure based on the DSM-IV criteria for diagnosis depression (27). The questionnaire contains nine items that can be scored from '0' (indicating not at all) to '3' (indicating nearly every day). This results in a total score varying between 0 and 27, with higher scores indicating more depressive symptoms and a threshold of PHQ-9 ≥ 10 is typically used for determining moderate levels of depressive symptoms (27). Reliability of the questionnaire in the full sample was good ($\alpha = 0.87$).

Statistical analysis

Descriptive characteristics (i.e. mean, standard deviation and percentages) were calculated for demographic and cancer-related variables. To prevent subgroups of patients being formed according to depression severity rather than symptom type, only patients with moderate levels of depression (PHQ-9 ≥ 10) were included. Latent Classes Analysis (LCA) was used to identify subgroups of patients with distinct depressive symptoms. Our study reported on details regarding model selection and a clear description of how depression classes were labeled, following recommendations by two systematic reviews (7,16). In order to investigate which model had the best data fit several parameters were examined including Bayesian information criterion (BIC), Akaike information criterion (AIC), entropy and the bootstrapped likelihood ratio test (BLRT). The four classes were then compared on demographic and cancer-related variables and on endorsed depression symptoms.

Results

Descriptive statistics

In total 2,099 cancer survivors returned the questionnaire, with 175 cancer survivors (8.3%) reporting moderate levels of depressive symptoms (PHQ ≥ 10), see Table 2. Mean age of the 175 survivors was 59.19 years (± 11.63) with 54.9% being male. Average year since diagnosis and since treatment were 3.29 and 2.90, respectively. Most common cancer type was gastrointestinal cancer and radiotherapy treatment the most common treatment type. In total, 20 persons (11.4%) have had a recurrence of cancer.

Table 1. Fit indices and class prevalence for the latent class analysis ($n = 164$).

	AIC	BIC	Entropy	BLRT	VLMR	Class size (%)				
						1	2	3	4	5
2-class	4120.968	4209.582	0.837	-2092.014***	-2092.014*	72%	28%			
3-class	4054.635	4174.896	0.912	-2032.484***	-2032.484*	41%	35%	24%		
4-class	4024.065	4175.974	0.912	-1989.317***	-1989.317	40%	10%	33%	17%	
5-class	4012.287	4195.845	0.921	-1964.032***	-1964.032	33%	40%	4%	15%	8%

*** $p < 0.001$

** $p < 0.01$

* $p < 0.05$

Identification subtypes of depressive symptoms among 175 cancer survivors

First, the fit indices of the LCA models were compared on a statistical ground (Table 1).

Models 3, 4 and 5 were all acceptable. AIC and BIC criteria are indices of model fit, with AIC favoring the five-class model, whereas the BIC criterion favored the three-class model.

Highest entropy was achieved by the five-class model. All models had significant BLRT, but only two-class and three-class models had significant VLMR. Another decision criterion includes that the smallest class of the model should be substantial (preferably at least 5%).

According to this rule, the five-class model is not preferred as it showed a relatively small class (4%) and both the three-class model and the four-class model are acceptable. A final decision rule involves that the addition of an extra class should represent a new pattern compared to the model with fewer classes. Following this rule, both models were investigated and the three-class model had mostly similar patterns, whereas the four-class model had unique patterns regarding depressive symptoms and was therefore selected in this study. For the purpose of transparency, the three-class solution is also presented in the Appendix.

Table 2. Descriptive characteristics of 175 moderately depressed ($PHQ \geq 10$) cancer survivors and comparison of four subgroups based on latent classes of depressive symptoms.

	Total sample	Class 1	Class 2	Class 3	Class 4	P-value
Demographic variables						
N	175	71	18	57	29	
% of total sample		40%	10%	33%	17%	
Gender, male (%)	54.9	49.3	66.7	63.2	44.8	.198
Age (M, SD)	59.19 ±11.63	59.69 ±11.03	60.61 ±9.10	58.23 ±13.27	59.00 ±11.38	.852
Cancer-related variables						
Years since diagnosis (M, SD)	3.29 ±1.24	3.27 ±1.30	3.30 ±1.34	3.29 ±1.23	3.36 ±1.08	.990
Years since diagnosis (%)						.387
≤ 2,5 year	32.0	38.0	33.3	29.8	20.7	
> 2,5 year	68.0	62.0	66.7	70.2	79.3	
Years since end treatment (M, SD)	2.90 ±1.16	2.93 ±1.23	2.93 ±1.15	2.88 ±1.11	2.86 ±1.16	.991
Years since end treatment (%)						.956
≤ 2,5 year	44.6	45.6	50.0	42.9	42.9	
> 2,5 year	55.4	54.4	50.0	57.1	57.1	
Cancer recurrence, yes (%)	11.4	8.5	5.6	14.0	17.2	.460
Cancer type ^a (%)						
Lung	6.9					
Skin	2.3					
Head and neck	20.6					
Endocrine	5.1					
Gastro-intestinal	24.6					
Urological	17.1					
Gynaecological	9.7					
Bone & soft tissue	2.9					
Hematological	9.7					
Other / primary unknown	1.1					
Received treatment ^a (%)						
Surgery	16.6					
Surgery + RT*	18.3					
Surgery + Chemotherapy	5.7					
Surgery + RT* + Chemotherapy	6.9					
RT*	29.7					
RT* + Chemotherapy	14.9					
RT* + Hormone therapy	4.0					
Chemotherapy	2.3					
Other	1.7					

Numbers may slightly differ due to missing variables

*RT = Radiotherapy Treatment

^a = Classes were not compared because minimum expected cell count was below five

Four subtypes of depressive symptoms

The four subtypes of depressive symptoms are depicted in Figure 1. The largest group (class 1, n=71, 40%) had an average total score of 12.03. Highest average item score in this class was ‘Sleep problems’ (2.13). Patients in class 2 (n=18, 10%) had an average total score of 18.45. Highest average scores were found for ‘Fatigue’ (2.93), ‘Suicidality’ (2.42), ‘Depressed mood’ (2.33) and ‘Low self-esteem’ (2.30). Of the two core depression symptoms, in particular ‘Depressed mood’ was high (2.33). In class 3 (n=57, 33%) patients had an average total score of 12.99. Highest average scores in this class were ‘Fatigue’ (2.98) and ‘Sleep problems’ (2.12). The highest reported symptoms in this class were mainly somatic symptoms, whereas neither of the two depression core symptoms was substantially high (1.65 for ‘Anhedonia’ and 1.03 for ‘Depressed mood’). Patients in class 4 (n=29, 17%) had an average total score with 18.94. Highest average scores were found for ‘Fatigue’ (2.93), ‘Sleep problems’ (2.83), but in general all symptoms were highly scored in this class, with the exception of ‘Psychomotor agitation/retardation’ (1.20) and ‘Suicidality’ (0.56) and ‘Concentration difficulty’ in a lesser extent (1.78), suggesting that the component of depression related to behavioral change is less affected in this class. The two core depressive symptoms were both high in this class (2.77 for ‘Anhedonia’ and 2.40 for ‘Depressed mood’), whereas average score of the ‘Suicidality’ item was low (0.56).

The four classes were compared on demographic and cancer-related variables (Table 2). No significant differences were found for demographic or cancer-related characteristics between the four classes. Concerning the two depression core symptoms (i.e. ‘Loss of interest’ and ‘Depressed mood’), people in class 4 reported both core symptoms. In contrast, people in class 1 reported neither one of these two symptoms. In class 2, people were likely to report a ‘Depressed mood’.

Somatic symptoms of depression (9) of the PHQ-9 including ‘Sleep problems’, ‘Fatigue’, ‘Appetite problems’ and ‘Concentration problems’ were reported in all 4 classes, but the relative contribution varied significantly ($p<.0001$): in class 3 most reported symptoms were somatic (63.0%), then class 1 and class 4 (54.7% and 52.8%, respectively) and finally class 2 (44.3%). Regarding suicidality, only patients in class 2 reported on average high scores on ‘Suicidality’ compared to the other 3 classes.

Figure 1. Mean PHQ-9 item scores of the four latent classes among 175 moderately depressed ($PHQ\geq 10$) cancer survivors.

Discussion

In order to optimize depression treatment among cancer patients and deliver targeted (i.e. symptom specific) treatment, it has been suggested to investigate whether depressive subtypes exist among cancer survivors. Although we aimed to differentiate mainly between *type of symptom* instead of *severity of symptom* (by only including moderately depressed patients), differences in depression levels in some extent between the subtypes are inevitable. Our study identified four distinct subtypes of depressive symptoms among moderately depressed (PHQ-9 ≥ 10) cancer survivors. Persons in class 1 (40%) reported mainly Sleep problems and scored moderate levels of depression. In class 2 (10%) mainly Fatigue, Suicidality, Depressed Mood and Low self-esteem were endorsed, with moderate-severe depression levels. Class 3 (33%) consisted of persons scoring high on most somatic symptoms (Fatigue and Sleep problems in particular), with moderate depression levels. Persons in class 4 (17%) scored high on all symptoms (in particular Fatigue and Sleep problems), except for Agitation/Retardation and Suicidality and with moderate-severe depression levels. The four subtypes did not significantly differ on demographic or cancer-related variables.

The finding that all four subtypes had high levels of Fatigue or Sleep problems (and thus did not differentiate between subtypes) can be explained by evidence from studies investigating distinct depression symptoms in cancer patients. These studies found that mainly somatic symptoms are endorsed in mild depression (particularly Fatigue and Sleep problems (9)), whereas more severe depression levels are characterized by cognitive-affective symptoms in addition to somatic symptoms (6). Since we included only moderately depressed patients in our analyses, all our subtypes scored high on Fatigue and Sleep problems. In addition, due to the potential risk of somatic overlap in cancer patients (19), items Fatigue or Sleep problems are more likely to be endorsed because of cancer treatment-related symptoms irrespective of the presence of depressive symptoms.

Two subtypes in our sample scored only high on somatic symptoms (i.e. class 1 on Sleep problems and class 3 on all somatic symptoms). The two other subtypes (i.e. class 2 and class 4) reported additional symptoms, including at least one of the two core depression symptoms. Moreover, in class 2 persons had high scores on Suicidality. For this reason, it is important that urgent care is warranted for these individuals due to increased suicide risk. In our study, the four subtypes did not differ on demographic or cancer-related variables, which is in line with another study among cancer patients (6). Yet, studies in the general population did find subtypes to be related to demographic characteristics (18,21,23). A possible explanation for this discrepancy is that the studies in the general population used large cohorts (such as national surveys) (18,21,23) for samples and thus in our study and the other study among cancer patients statistical significant differences could simply not be detected due to relatively small sample sizes.

In general, apart from the differences between the subtypes, it should be noted that there was also substantial overlap between symptoms of the four subtypes (e.g. all four classes reported high scores on Fatigue and/or Sleep problems). It can therefore be questioned whether our analysis (i.e. latent class analysis) was appropriate for detecting different subtypes of depressive symptoms. That is, some studies suggest that in literature depression subtypes are not consistently found because other methods than latent class analysis are required (16) such as a more dimensional approach (28,29). Regarding these dimensions, some studies recommend using depression severity indicators, such as mild, moderate and severe depression (29), but although this is preferable to a sum score (or dichotomizing depressed versus non-depressed due to information loss), this solution is suboptimal because within these dimensions the variety in symptoms can still be substantial (11,12). Alternatively, other studies used dimensions such as melancholic or atypical depression but this may also be undesirable, because these dimensions have little practical value (7) and the

overlapping dimensions did not differentiate in depression treatment outcomes (28). One study in fact suggested the possibility that subtypes in literature are not consistently found simply due to the absence of patterns to be found (7). Another possibility is that patterns are not detected because two factors are not taken into account: 1) the daily fluctuations of depressive symptoms 2) the fact that depressive symptoms are inter-related (i.e. suffering from fatigue may cause concentration difficulties). Therefore, a promising method for elucidating patterns of depressive symptoms may be a network-approach, as it offers future research the possibility for longitudinally investigating distinct depressive symptoms and take hereby the inter-relatedness of symptoms into account (30).

Clinical implications

Our findings have several clinical implications. Dependent on the most frequent endorsed symptoms, more tailored treatment options can be offered to an individual. For instance, individuals belonging to subtypes characterized by Fatigue (both depression-related and treatment-related) as the main complaint, may benefit from interventions addressing physical exercise as these have proven to be effective in reducing fatigue in cancer patients (31,32). On the contrary, subtypes characterized by predominantly cognitive complaints, may benefit from therapies addressing cognitions such as Cognitive Behavioral Therapy or Mindfulness-Based Cognitive Therapy (4,5). Future research may either optimize these conventional methods by enhancing specific treatment components in order to make them more tailored (and effective) or develop new interventions targeting specific symptoms.

Study limitations

Our study has several limitations. Individuals in our sample had no official diagnosis of major depression, but were instead selected because they had elevated levels of depressive symptoms in a self-report measure. In addition, because our sample comprised cancer

patients, the somatic symptoms of depression may not necessarily indicate depression but may be treatment-related complaints. Moreover, the cross-sectional nature of our study does not allow to investigate the daily fluctuations in symptom severity. Fourth, the sample size of this study was relatively small, especially in comparison to the large national cohorts. For this reason, caution is warranted when drawing conclusions from our findings. Future research needs to replicate our study in a larger sample, preferable with an official MDD diagnosis. In conclusion, our study identified four subtypes of depressive symptoms among moderately depressed cancer survivors. Despite some overlap between the subtypes, they also have different, unique features, which can be valuable for clinical practice as it may give rise to the development of targeted treatment options. However, future research is first needed to replicate our findings in a broader context, both in cancer patients and in the general population.

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Appendix

Appendix 1. Mean PHQ-9 item scores of the three-class solution among 175 moderately depressed ($PHQ \geq 10$) cancer survivors.

Chapter 7:

General Discussion

7.1 General Discussion

After completing curative treatment, many cancer survivors still suffer from depressive symptoms. The initial aim of this thesis was to test the efficacy of different interventions for treating depression among cancer survivors by means of a multi-center randomized controlled trial, thereby strictly following high-quality standards. Cancer survivors who reported depressive symptoms on a depression screening questionnaire were invited to participate in the trial, in which two different types of psychological treatments were tested for their efficacy: Cognitive Behavioral Therapy (CBT) and Mindfulness-Based Cognitive Therapy (MBCT). However, due to low patients' participation and uptake of treatment, we were unable to draw conclusions regarding the efficacy of these interventions.

This situation, low uptake of care in a trial conducted according to high methodological standards, raised several fundamental questions, on the one hand about the utility of screening for emotional distress and depressive symptoms of cancer survivors as currently recommended (1–4) and on the other hand about the seemingly low care needs of cancer survivors for psychological treatment. We therefore shifted the focus of our research to reflect on the feasibility of screening for depressive symptoms in clinical practice, patients' need for psychological care and the psychometric properties of the used screening tool (i.e. PHQ-9). In the following paragraphs, we will summarize our main findings, reflect on our chosen methodology, and describe implications for future research and clinical practice.

7.2 Summary of main findings

Clinical guidelines currently recommend to routinely screen cancer patients on distress throughout the illness and treatment trajectory in order to detect distress and refer patients accordingly to additional care (1–4). In this context, we set up a randomized controlled trial (**Chapter 2**) for testing different depression treatment options in cancer survivors, with those

reporting elevated levels of symptoms offered psychological care as part of the trial. Of the 1,937 cancer survivors who returned a depression screening questionnaire (74.3%), only 147 cancer survivors (7.6%) reported at least moderate depressive symptoms. Of this group with depressive symptoms, 49 survivors (33.3%) were found to be ineligible (including 26 survivors already receiving treatment) and another 44 survivors (30.0%) reported no need for treatment. In the end, only 25 of the 1,937 cancer survivors (1%) were eligible and interested in receiving psychological care as part of our trial. Four major reasons for non-participation were: non-response to depression screening, no elevated levels of depressive symptoms, no need for care, or already receiving psychological care. Hereby, our findings strongly question the efficiency of using consecutive depression screening (i.e. approaching all potentially eligible patients and inviting them to fill in a depression questionnaire, see Box 1) for intervention research in cancer survivors and, in a broader sense, whether to spend the limited resources in psycho-oncological care on following screening guidelines.

As one of the interventions we tested was based on mindfulness, we were interested in understanding how mindfulness and a related concept, self-compassion, were associated with the report of depressive symptoms in cancer survivors. In **Chapter 3**, we examined whether mindfulness and self-compassion are always beneficial for psychological functioning or only/mainly under stressful circumstances. Specifically, we investigated whether distinct facets of mindfulness and self-compassion are equally or more strongly related to depressive symptoms and affect in cancer survivors, compared to matched healthy controls without somatic comorbidity. Results clearly suggest that mindfulness and self-compassion are basic resources that are beneficial for well-being, regardless of the presence of stress. The mindfulness facets ‘Act with awareness’ and ‘Non-judgment’ were most strongly related to depressive symptoms and negative affect as well as the negative self-compassion factor, which involves the negative components of self-compassion (e.g. self-judgment, over-

identification). In contrast, the mindfulness facets ‘Describe’ and ‘Observe’ were most strongly related to positive affect as well as the positive self-compassion factor, consisting of the positive components of self-compassion (e.g. self-kindness, common humanity). Above-mentioned facets may in particular be targets for future interventions that aim to reduce depression or increase positive affect.

With our research, we were also curious what may explain whether patients have or do not have a need for psychological care. Specifically, given the heterogeneity in depressive symptoms (5,6), we were interested in the question whether the type of depressive symptom is related to having (no) need for psychological care. In **Chapter 4** we therefore examined whether patients with distinct types of depressive symptoms differed in their need for psychological care, using data of an intervention trial in depressed patients with diabetes. We hypothesized that especially patients with cognitive-affective symptoms of depression (e.g. depressed mood, lack of interest) would be more likely to perceive an unmet need for psychological care, with no strong association for somatic symptoms of depression (e.g. fatigue) and need for care. Although results showed that patients with an unmet need for care reported higher levels of cognitive-affective symptoms, the results overall indicated that the predictive capacity of type of depressive symptoms on psychological care needs was weak.

For our intervention trial, we used the questionnaire PHQ-9 to measure depressive symptoms. This questionnaire assesses the nine symptoms of depression as formulated by the DSM-V classification of disorders. We were also interested in gaining more insight into the psychometric properties of the used screening tool (i.e. PHQ-9). Specifically, we tested the role of somatic symptoms in the measurement of depressive symptoms in cancer patients. That is, for three decades it has been debated whether somatic symptoms should be included when assessing depressive symptoms among chronic ill patients, as these somatic depression symptoms like fatigue may also be related to the medical illness and its treatment (7,8). Most

recent studies on this debate (7,8) concluded that somatic symptoms should remain included. A limitation of these previous studies is that they examined whether to include or exclude *all* somatic symptoms, hereby overlooking the role of *distinct* symptoms. Furthermore, they often simplified depression severity, by classifying ‘depressed’ versus ‘not depressed’, rather than examining a continuum of depression severity, as recommended (9). In **Chapter 5** we examined whether distinct depressive symptoms of our screening tool, the Patient Health Questionnaire-9 (PHQ-9) (10) should be included when measuring depression among cancer survivors. Results showed that all distinct nine depressive symptoms had excellent discriminative capacities among cancer survivors, with somatic symptoms (particularly ‘Fatigue’ and ‘Sleep problems’) discriminating best for mild depression and cognitive-affective symptoms discriminated best for moderate-severe depression (‘Psychomotor’ and ‘Suicidality’ in particular indicating severe depression). Based on these results, it seems warranted to include all PHQ-9 symptoms when assessing depressive symptoms in cancer survivors (so also somatic symptoms), with the utility of distinct items depending on the screening purpose (i.e. which depression severity level is to be distinguished).

Patients with distinct types of depressive symptoms (e.g. cognitive-affective, somatic) are currently offered the same depression treatment. Ideally, patients receive a treatment that specifically targets their reported symptoms instead of a one-size-fits-all approach (11,12). In **Chapter 6** it was investigated whether distinct depressive subtypes exist. When only including moderately depressed persons, we identified four subtypes of depressive symptoms: class 1 mainly reported Sleep problems and Fatigue, class 2 mainly Suicidality, Self-blame and Fatigue, class 3 mainly somatic symptoms and class 4 mainly the two depression core symptoms, Sleep problems, Fatigue and Eating problems. These findings suggest that different subgroups of patients exist that differ in their type of depressive symptoms. These different subgroups may benefit from different types of treatment. Future research can

investigate whether patients reporting especially fatigue may benefit more from interventions that explicitly address balancing physical activity and rest and whether patients reporting mainly or additional cognitive-affective complaints may benefit particularly from cognitive behavioral therapy or mindfulness-based cognitive therapy.

7.3 Implications for clinical practice and research

7.3.1 Screening for trial recruitment: *Consecutive versus convenience sampling*

In our multi-center randomized controlled trial (Chapter 2), we approached participants by means of screening. This means that people received a letter and brief depression questionnaire at home, which they could fill in and send back. Those reporting elevated levels of depressive symptoms were then called to discuss these symptoms and a possible need for care. In total, 2,608 cancer survivors were approached, with only 25 cancer survivors (1.0%) included in the trial, suggesting that 99.0% of all cancer survivors who were approached, did not benefit from the screening in terms of receiving adequate psychological care. For this reason, we conclude that this kind of screening procedure is not effective. Screening is commonly used for trial recruitment (13) and is in the research context also referred to as sampling. The screening procedure in our trial involved *consecutive sampling* (see Box 1). In short, this means that all patients that may be eligible are approached by the researcher and are then selected on eligible criteria for participating in the trial. Another type of screening is *convenience sampling* (see Box 1), in which patients can enroll themselves and are then

Box 1. Defining consecutive sampling and convenience sampling

Different sampling strategies exist for recruiting participants for a trial. The selection of an appropriate sampling strategy involves a proper balance between on the one hand available resources, costs and time and on the other hand a minimal sampling bias. A commonly used sampling strategy involves *consecutive sampling*, in which every subject that meets the inclusion criteria is approached until the required sample size is achieved (56). Practically, in our study this involved that by examination of the medical records, every non-breast cancer patient between 18 and 75 years was selected and approached for trial participation that had: completed curative treatment one to five years ago and currently has no active cancer. All these eligible patients were invited to fill in the screening questionnaire, selecting only those with an elevated score. An alternative recruitment strategy may be *convenience sampling*, in which persons (meeting certain criteria) can enroll themselves in the trial. An example in the psycho-oncological context would involve that through advertising via newspapers and/or social media, cancer survivors meeting above-mentioned criteria could enroll themselves into a trial. Ideally, this procedure is automated in a sense that a website link is provided inviting all eligible patients to fill in the screening questionnaire. In this way, those with an elevated score can be distinguished automatically from the whole sample of self-enrolled patients.

selected on eligible criteria for participating in the trial. Conventionally, the *consecutive sampling* strategy, although often very time-consuming, is seen as the golden standard because it offers the possibility to all persons (meeting certain criteria) to participate in the study and thereby reduces the risk of sampling bias (14). Consecutive screening also has the advantage that it gives insight into characteristics of those who (not) responded and it offers the opportunity to calculate useful ratios including eligibility rates, enrollment rates and recruitment rates that allow comparison of uptake ratios between RCTs (15). An interesting side note is that the CONSORT guidelines (for setting up high-quality RCTs) do not postulate consecutive sampling to be superior to convenience sampling (16).

More recently consecutive sampling has also been criticized. A study using consecutive sampling found that this approach may still be prone to selection bias, as it was found that particularly young and highly educated patients were selected (17). Given the huge efforts and resources required for obtaining sufficient participants when using consecutive sampling, studies plead for greater pragmatism when recruiting participants for a trial (17,18) and recommend using convenience sampling (e.g. referral by health care professionals or self-

referral by patients). Major advantages of a convenience sampling strategy include high motivation among participants and relatively low costs and required resources (18). In addition, convenience sampling may be ideal for bridging the gap from research to practice, as a study found that consecutively sampled participants were not representative to those persons recruited via routine care (18).

Previous studies using either consecutive or convenience sampling both have shown selection bias (i.e. patients' characteristics more likely associated with participation including young, highly-educated women) (17,19) and it seems that individuals who are willing to participate in trials and receive care are not representative for the whole sample (19), irrespective of the used sampling strategy. As both consecutive sampling and convenience sampling result in (some) selection bias, neither of these strategies seems superior. Instead, considerations to be made regarding consecutive or convenience sampling may depend upon the context, the purpose of the study and time and resources available.

7.3.2 Screening for clinical practice, adhering the guidelines?

Another application of depression screening is in clinical practice, as recommended by guidelines (1–4), in order to detect persons in clinical practice with elevated levels of depressive symptoms and refer those patients for appropriate treatment. This so-called routine screening was also included in our trial, with cancer survivors being screened as part of standard care. When reporting elevated levels of depressive symptoms, they were informed about the possibility to receive psychological care as part of an intervention trial.

7.3.2.1 International and Dutch guidelines

It should be noted that international guidelines differ regarding whether routine screening for depression should be implemented. Whereas the United States Preventive Services Task

Force recommends routine screening for depression in primary care, the United Kingdom National Screening Committee does not recommend this. The Canadian Task Force on Preventive Health Care even recommends against depression screening (20) due to lack of direct trial evidence of screening effectiveness. Regarding Dutch guidelines, the Netherlands Comprehensive Cancer Organization has formulated specific screening guidelines for cancer patients. Regarding depression screening among cancer patients, only guidelines are present for depression in palliative care (2), which recommend doctors to actively inform patients about their mood and when in doubt, a screening tool can be used such as the Hospital Anxiety and Depression Scale (HADS). In the broader population of cancer patients, guidelines recommend to screen cancer patients on distress in order to detect care needs (21). A short screening tool is recommended, consisting of the Distress Thermometer and the Problem List (22). In this paragraph we elaborate on the Dutch recommendations, in light of our findings, and discuss whether routine depression screening should be advocated in psycho-oncology practice in the Netherlands.

7.3.2.2 Screening assumptions and efficacy

The purpose of screening is to identify persons that are in need of psychological help and refer them for effective treatment that may benefit them. The justification of routine screening underlies several assumptions (23), including that those reporting distress will need and accept psychological care and that without detection, distress will progress and result in worse health outcomes if untreated. However, recent studies in cancer patients (24,25), including our research, showed that the report of distress is not a good predictor of a need for care. In addition, it has been found that the majority of depressed persons will remit within a year without any intervention (26,27). Another assumption of routine screening is that screening may reveal depressed persons that otherwise would not be identified by individuals

themselves or by health care professionals. However, our results clearly demonstrated that a substantial group of depressed cancer survivors had already found psychological help themselves. Two systematic reviews demonstrated that screening on depression or distress did not result in improved patient outcomes (28,29) and other studies also emphasized the lack of evidence for routine screening (30,31). Based on existing research (20,23,28,29,31), it can be argued that routine screening on depressive symptoms among cancer survivors may not be worth the limited resources, at least not in high-income countries (32) with an adequate health insurance and health care system available.

7.3.2.3 Alternatives to routine screening?

Altogether, previous research, including our findings, suggest that the limited resources available in psycho-oncology may be better spent on alternative options to routine screening. In the light of shared decision making, it seems logical to support patient's autonomy and self-management in the process of offering psychological care. In this process of close collaboration, patients may be offered psycho-education by a nurse or social worker, providing them information about the psychological impact of cancer, types of psychological symptoms, their prevalence, treatment options, and possible barriers in accepting psychological care, in order to facilitate the recognition and discussion of these issues with the healthcare provider. No clinical cut-off is then needed and patients may simply be asked whether they may be interested in receiving help (i.e. help question) (24) or are given the opportunity to contact the medical team, if they wish to receive psychological support. This psychological support should also relate to other domains, such as anxiety (e.g. fear of recurrence) (24), disease- and treatment-related information needs (33), and financial problems (34). In our trial, we focused on needs for psychological care for depressive symptoms only. It is very likely that cancer survivors have other needs as well, such as health

system/information needs (33) or needs related to the practical domain (e.g. financial, work), family domain (e.g. raising children) or physical domain (e.g. nausea, pain) (22,24,33). For instance, a systematic review found that not per se depression, but anxiety (i.e. fear of recurrence) was persistent after having finished curative treatment (35).

7.3.3 Low uptake; the role of low depression levels and low unmet care needs

7.3.3.1 Low depression levels and protective factors in adaptation to cancer

As reported in Chapter 2, the group of cancer survivors reporting depressive symptoms was lower than we had expected. Partly, these low levels could be related to characteristics of the sample, including cancer type and gender (36,37). Still, the relatively large group of cancer survivors reporting low levels of depressive symptoms may also suggest that the majority of cancer survivors is able to adapt to having had cancer and regain a sense of psychological well-being. In Chapter 3, we found that being able to be more mindful and compassionate towards oneself is related to lower levels of depressive symptoms and higher positive affect. Our results are in line with other research showing that an attitude of observing thoughts and feelings by means of a nonjudgmental and accepting way and being kind to oneself instead of self-judging (38,39) is beneficial for cancer patients (40). As we found similar beneficial associations for mindfulness and self-compassion with psychological functioning in healthy persons, it seems that mindfulness and self-compassion are basic universal resources for maintaining psychological well-being.

7.3.3.2 Low care needs

Simply having depressive symptoms does not automatically mean that one wants to receive psychological help for their complaints, as we noticed in our trial. In fact, 30% of the depressed cancer survivors who were offered the possibility to receive free psychological

treatment as part of the trial, refused because they had ‘no need or time for treatment’.

Perhaps, for these persons, the burden of the complaints was not high enough for them to warrant treatment. Another option is that they lack knowledge about the possible benefits of treatment, and think that they will not benefit from it.

According to Leventhal’s Self-Regulatory Model of Illness Representations (41,42), in order to be willing to receive psychological support, several steps are required: people first need to be aware, recognize, and perceive symptoms, based on these symptoms they need to believe that they might be ill, perceive negative consequences and they need to believe that treatment is effective. In Chapter 4, we found that patients who perceived and reported more cognitive-affective symptoms of depression (but not somatic) reported higher care needs than those perceiving and reporting these symptoms less. It can be reasoned that somatic symptoms are not thought of as being a problem for which psychological treatment is needed or beliefs may exist that psychological treatments are ineffective for treating somatic symptoms (of depression). A second reason for low care needs is low burden, which could be related to persons having resources to deal with symptoms on their own, or ignoring/denying the impact of these symptoms.

A lack of symptom recognition may be tackled by psycho-education (provided by the nurse), with more awareness created for the occurrence of depressive symptoms during the cancer trajectory. In addition, in order to tackle barriers for help seeking such as stigmatization for receiving help or beliefs that the therapy may not help, information can be handed to patients about treatment options and benefits in order to normalize the receipt of psychological care. We believe, however, that first, more information is needed about cancer survivors’ perceptions of depressive symptoms and barriers to treatment, before rigorously setting up psycho-educational programs to get patients to accept psychological care, in order to acknowledge a need for the patient’s autonomy and let them make their own choices.

7.3.3.3 Alternative ways of offering help

Future research should investigate what are optimal ways for addressing psychological problems and care needs in cancer survivors. During our intakes for trial recruitment, we noticed that many cancer survivors felt relieved that they could discuss their problems with someone by telephone, with very few interested in receiving an additional 8-week intervention at the hospital. More flexible ways for offering treatment are therefore needed such as a 1-session telephonic conversation in which encountered problems are discussed and if needed, referral for additional help is provided. Another possibility for future interventions may be the use of eHealth (i.e. internet) and/or mHealth (i.e. mobile phones) applications (43,44). Both ways have the potential to deliver care that is adapted to individual needs (as it can cover psychological as well as informational needs) which can be accessed 24 hours a day. For these reasons, such applications are promising treatment options for delivering tailored help to cancer survivors.

7.3.4 *Depression assessment in chronic ill patients*

A final topic of discussion involves how to handle potential somatic overlap of depression symptoms with symptoms of the chronic illness and corresponding treatment. Currently, a persistent paradigm exists in clinical practice where somatic symptoms are avoided in depression assessment among chronic ill patients and questionnaires using only cognitive-affective symptoms are advocated (2), such as the Hospital Anxiety Depression Scale (HADS). However, an abundance of research has shown that somatic symptoms should remain included in depression assessment among chronic ill patients (7–9,45–51) and it is therefore important that such scientific findings are translated to and actually implemented into clinical practice.

In general, given the heterogeneity of depressive symptoms (5,6), it can be questioned whether different depression items are exchangeable. That is, whether an item score of 3 (on a scale from 0 to 3) for fatigue is evenly indicative of depression as an item score of 3 for suicidal ideation. The current way of summing up distinct items to a total score implies that this is the case. However, findings from Chapter 5 indicate, in line with previous research (49,52,53), that item fatigue mainly discriminates for mild depression and item suicidal ideation for moderate-severe depression. An option for taking this into account is to use computerized adaptive testing, in which a person receives an adaptable (digital) questionnaire that offers them the most informative question based on their answers to previously administered questions (54,55). Practically, following our findings, this means that at first somatic items are presented to the person in order to detect whether (at least) mild depressive symptoms are present. If these symptoms are present, subsequently cognitive-affective items can be presented in order to detect more severe levels of depression. It is very unlikely that severe depression symptoms (such as psychomotor agitation) are present in the absence of mild depressive symptoms (such as fatigue) and so in computerized adaptive testing, the psychomotor item is not presented if the fatigue item is not scored on. This way of depression assessment provides two advantages: it results in more individualized and precise measurement and it requires shorter assessments periods (and thus reduced burden for the chronic ill patient). Future research is needed in order to establish whether this is a feasible option for measuring depressive symptoms among cancer survivors.

7.4 Methodological considerations: strengths and limitations

7.4.1 *Study designs*

The results of the present thesis should be considered in the light of some strengths and limitations. The strict adherence to the CONSORT criteria for setting up a high-quality multi-

center randomized controlled trial is a major strength in this thesis. This set-up resulted in the risk of potential biases being reduced to a minimum and thus the preservation of internal validity. Additionally, other strengths of this thesis include the use of the case-control design in Chapter 3, which enabled us to draw firm conclusions about potential differences between cancer patients and a healthy control group regarding mindfulness and self-compassion levels and associations. Moreover, in Chapter 5 continuous depression severity rather than dichotomization was used to compare distinct depression items, making these findings very practical to implement into clinical practice and a valuable contribution to the existing literature. Similarly, in order to avoid depression subtype formation based on depression severity, in Chapter 6 only moderately depressed persons were included in the study, so the presence of distinct depression subtypes could be identified.

Concerning limitations, it should be noted that all the studies in this thesis used cross-sectional designs and for this reason causal inferences cannot be established. For instance, in Chapter 3, we assumed that being mindful and holding a non-judgmental attitude reduces depressive symptoms, but it could be the other way around since depression is characterized by judgmental thinking. Another remark involves that the influence of somatic overlap in our study cannot be ruled out. Practically, this may have resulted in a possible overestimation of depression, although findings of Chapter 5 suggested that this somatic contamination is minimal.

7.4.2 Sample (characteristics)

A major strength of this thesis was the large sample size of cancer survivors approached and participating in screening for the trial (Chapter 2), that included different cancer diagnoses. In addition, as we used consecutive sampling for trial recruitment, insight was gained into characteristics of non-responders and the flow of patient through the study could be

thoroughly monitored. This is in fact a very valuable contribution to the current literature, because in most studies non-responders are not considered as being a part of the studied population, due to lack of information. Similarly, sample sizes in other studies of this thesis including the case control design (Chapter 3), the study with depressed persons with diabetes (in Chapter 4) and IRT analyses (Chapter 5) were also substantial, which increases the reliability of these findings.

A limitation is that in our trial no breast cancer survivors were included (as requested by the Dutch Cancer Foundation), and given that breast cancer is the second most common cancer type among women, generalizability of findings on this sample (i.e. Chapter 2, Chapter 5 and Chapter 6) are limited to non-breast cancer patients. In addition, although demographic characteristics were available about non-responders, it is unknown whether these persons were depressed and/or were interested in receiving psychological help. This may have resulted in an underestimation of depressive symptoms and care needs in our trial. Moreover, our trial set-up was based on the assumption that the depressive symptoms among cancer survivors were a consequence of the cancer trajectory. However, this may be too simplistic and many other related factors are involved that were not taken into account. For instance, somatic comorbidities, lack of social support and a history of depression are all known to be strongly related to depression but these data were not measured during our screening procedure. Similarly, in Chapter 3 cancer patients may have received extra social support during the cancer trajectory or they may have followed a mindfulness training, which makes a proper comparison with a matched control group challenging. In general, such information is pivotal in order to allow a fair comparison between cancer patients and a healthy control group and gain a better sense of why some patients develop depressive symptoms following a cancer diagnosis whereas others do not.

7.5 References

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Chapter 8:

Appendix

Summary in English

Summary in Dutch

About the author

Acknowledgements

List of previous SHARE dissertations

Summary in English

As survival after cancer has improved, more people are now living with the possible psychological burden of having (had) cancer. Throughout the cancer trajectory, psychological complaints such as feelings of anxiety and depression are commonly reported. Our aim was to investigate the efficacy of two psychological interventions (i.e. Cognitive Behavioral Therapy and Mindfulness-Based Cognitive Therapy) for treating depressive symptoms among cancer survivors in a high-quality multi-center randomized controlled trial (RCT). We approached approximately 3,000 cancer survivors by means of screening for depressive symptoms. During the process of recruitment, we encountered a low uptake, with a large group of patients not willing to take part in the trial to receive one of the interventions. We have therefore shifted the focus. This thesis now evaluates and reflects on the chosen procedures, recruitment strategies, patient flow, and the challenges when setting up a randomized controlled trial. In addition, we examined the nature and assessment of depressive symptoms in cancer survivors, by examining the psychometric properties of our screening tool, the Patient Health Questionnaire (PHQ-9).

In **Chapter 2** we discussed the setting up and conduction of the trial and the flow of patient participation. Our trial was set up following the CONSORT guidelines, which are strict high-quality methodological standards for setting up an RCT. In total, 2,608 cancer survivors were approached for screening using a depression questionnaire, the PHQ-9, with 1,937 cancer survivors returning the questionnaire (74.3%). Of this group, 147 cancer survivors reported moderate depressive symptoms (7.6%). Among these 147 cancer survivors with depressive symptoms, 49 cancer survivors were ineligible for trial participation, including 26 cancer survivors who were already receiving psychological treatment and overall 44 cancer survivors reported no need for receiving professional psychological treatment. In total, only 25 cancer survivors participated in the trial (1.0%), with four major reasons for non-participation (99.0%): not responding to screening, low levels of depressive symptoms, no need for psychological treatment or already receiving psychological treatment. This finding points out a potential gap between methodological guidelines (i.e. following strict methodological standards for setting up an RCT) and actual uptake in clinical practice.

As one of the interventions was focused on cultivating mindfulness as a mean to reduce depressive symptoms in cancer survivors, we were interested in the question to what extent mindfulness plays a more important role in the level of depressive symptoms in cancer survivors, compared to healthy individuals. In **Chapter 3** we investigated to what extent distinct facets of mindfulness and the related concept of self-compassion, are associated with psychological well-being and whether this association is stronger under stressful circumstances (i.e. having received a cancer diagnosis) compared to healthy controls (i.e. without any chronic somatic condition). In our study, we matched 245 cancer patients to 245 healthy controls (without chronic somatic comorbidities) on age, gender and educational level. We found that mindfulness and self-compassion were equally strong related to depressive symptoms and affect in cancer patients and healthy controls. We conclude that having the resources mindfulness and self-compassion available is always beneficial for psychological functioning irrespective of the presence of stressful life circumstances such as having received a cancer diagnosis.

Another central concept in our research is depressive symptoms. Both interventions had the aim to reduce depressive symptoms and in order to gain more insight into the nature of depressive symptoms and how this might affect a need for psychological care, we investigated in **Chapter 4** whether the type of depressive symptoms was associated with a perceived need for psychological care among depressed persons with diabetes. Previous research suggests that among depressed patients the need for care is low and this may be related to the type of depressive symptoms. The construct of depression can be divided into two domains: cognitive-affective symptoms and somatic symptoms. In the case of a chronic illness, somatic symptoms may be attributed to the chronic illness and its treatment side-effects instead of to depression. Given this potential overlap, we hypothesized that persons with high levels of cognitive-affective symptoms are more likely to perceive an unmet need for psychological care compared to persons with low levels of these symptoms. We expected no significant differences in care needs between those with high or low levels of somatic symptoms. In a sample of 519 depressed persons with diabetes, we found that 102 persons had a care need (19.7%), 293 had no care need (56.5%), 77 had a met care need (14.8%) and 47 had an unclear care need (9.1%). As hypothesized, results showed that levels of cognitive-affective symptoms differed between the four groups, whereas no significant differences in levels of somatic symptoms were found among the groups. Further analyses revealed a significant but weak association showing that levels of cognitive-affective symptoms significantly predicted a psychological care need.

In **Chapter 5**, we continued our research into the nature and assessment of depressive symptoms in persons with a somatic illness. In this chapter, we investigated distinct depressive symptoms. Given that somatic symptoms may be related to depression and/or the illness and its treatment, as mentioned earlier, it has been debated for decades whether somatic symptoms should be included in depression screening tools among cancer survivors. As an attempt to reach more clarity in this debate, we focused in Chapter 5 on distinct depressive symptoms (using the PHQ-9) and compared the discriminative capacities for distinct somatic symptoms and distinct cognitive-affective symptoms. In total, 2,099 cancer survivors returned the PHQ-9. Most commonly reported symptoms were ‘Sleep problems’ (39.2%) and ‘Fatigue’ (45.9%) whereas ‘Suicidality’ (5.5%) was the least commonly reported. Our results showed that all nine depressive symptoms had excellent discriminative capacities. This finding confirms recent research suggesting that somatic symptoms should be included in the assessment of depressive symptoms in somatically ill persons. Another important finding of our study was that somatic symptoms (in particular ‘Sleep problems’ and ‘Fatigue’) discriminated best for mild depression, whereas the cognitive-affective symptoms ‘Psychomotor problems’ and ‘Suicidality’ discriminated best for moderate to severe depression. This finding suggests that the screening purpose determines the utility of the PHQ-9 items. For instance, if one is interested in distinguishing moderate to severely from not to mildly depressed cancer patients, the PHQ-2 questionnaire, consisting of the two core symptoms (i.e. Depressed mood and Anhedonia) is a valuable screening tool, as both symptoms discriminate properly for moderate depression.

In our final study, in **Chapter 6** we investigated whether subtypes of depressive symptoms exist among cancer survivors with depressive symptoms. As previously mentioned, depressive symptoms tend to be very heterogeneous (i.e. cognitive-affective and somatic symptoms). Still, persons with different depressive symptoms generally receive the same

depression treatment. A first step in exploring whether tailored depression treatment options should be offered, is to examine whether subtypes of depressive symptoms exist among depressed persons. In order to differentiate mainly between the type of depressive symptoms instead of the severity of depressive symptoms, we only included 175 moderately to severely depressed persons. We found four subtypes of depressive symptoms: class 1 (40%) and class 3 (33%) reported moderate overall depression levels, with class 1 mainly reporting Sleep problems and class 3 reporting high on all somatic symptoms (in particular Fatigue and Sleep problems). Persons in class 2 (10%) and class 4 (17%) reported moderate-severe overall depression levels, with class 2 mainly reporting Fatigue, Suicide, Depressed mood and Low self-esteem and class 4 reporting high on all symptoms except for Agitation/Retardation and Suicidal ideation. The identification of these subgroups enables the development and testing of more tailored treatment options. For instance, persons mainly reporting fatigue may benefit more from treatments that address physical exercises or cognitive-behavioral interventions that focus on reducing fatigue. On the other hand, those persons reporting cognitive-affective symptoms may benefit more from cognitive therapies such as cognitive restructuring or mindfulness exercises.

To conclude, this thesis focused on cancer survivors that have finished curative cancer treatment at least one year ago and that experience depressive symptoms. One of the most striking findings was the low levels of depressive symptoms in our group of cancer survivors, suggesting that the majority of cancer survivors have regained a sense of psychological well-being. Another key finding was that a substantial group of those cancer survivors who reported elevated depressive symptoms, did not want to receive professional psychological help for their symptoms. More research is needed for a better understanding of how cancer survivors perceive and cope with depressive symptoms and reasons for (not) seeking care. Such insights are required in order to optimally guide the cancer patient throughout the illness trajectory.

Summary in Dutch

De overlevingskansen van kanker zijn de afgelopen decennia sterk toegenomen. Als gevolg hiervan leven er tegenwoordig steeds meer mensen die te maken hebben (gehad) met de mogelijke psychische gevolgen van een kankerdiagnose. Rond de tijd van diagnose en de medische behandeling en controles worden psychologische klachten zoals gevoelens van angst of depressie veelvuldig gerapporteerd. Het doel van ons onderzoek was om de werkzaamheid te onderzoeken van twee psychologische interventies (te weten Cognitieve Gedragstherapie en Mindfulness-Gebaseerde Cognitieve Therapie) om depressieve symptomen te behandelen bij ex-kankerpatiënten. Hiervoor hebben we een gecontroleerde multicenter studie opgezet, een zogenaamde randomized controlled trial (RCT) die voldeed aan de strikte criteria voor hoogstaande methodologische kwaliteit. Wij hebben ongeveer 3.000 ex-kankerpatiënten benaderd door middel van een screeningsvragenlijst voor depressieve symptomen.

Gedurende het wervingsproces viel ons het lage deelnamepercentage op: een grote groep patiënten gaf aan niet deel te willen nemen aan de studie en een van de interventies te ontvangen. Om deze reden hebben we de focus van het proefschrift verlegd. Dit proefschrift heeft zich daarom voornamelijk gericht op de evaluatie van en de reflectie op de gekozen procedures, de wervingsstrategieën, de patiëntenstroom en -uitval, en de uitdagingen behorende bij het opzetten van een randomized controlled trial. Daarnaast hebben wij ons gericht op de aard en het meten van depressieve symptomen bij ex-kankerpatiënten, door de psychometrische eigenschappen van ons screeningsinstrument, de Patient Health Questionnaire (PHQ-9), te onderzoeken.

In **Hoofdstuk 2** hebben we de opzet en uitvoering van de trial besproken en de stroom van patiënten in de studie beschreven. Onze trial was opgezet volgens de CONSORT richtlijnen, dit zijn strikte criteria bij het opzetten van een RCT om methodologische kwaliteit te waarborgen. In totaal zijn er 2.608 ex-kankerpatiënten benaderd voor screening middels een depressie vragenlijst (de PHQ-9), waarbij 1.937 ex-kankerpatiënten de vragenlijst teruggestuurd hebben (74.3%). Van deze groep rapporteerden 147 mensen verhoogde depressieve symptomen, waarvan er 49 mensen niet konden deelnemen aan de studie vanwege de in- en exclusiecriteria (waaronder 26 mensen die al psychologische hulp ontvingen). Een andere reden voor mensen met verhoogde depressieve symptomen om niet mee te doen was dat 44 mensen aangaven geen behoefte te hebben om professionele psychologische hulp te ontvangen. In totaal namen slechts 25 ex-kankerpatiënten deel aan de trial (1%).

Een van de interventies was gericht op het cultiveren van mindfulness om depressieve symptomen te verminderen. Om deze reden waren we geïnteresseerd in de vraag in welke mate mindfulness een belangrijkere rol speelt in het niveau van depressieve symptomen bij ex-kankerpatiënten ten opzichte van gezonde personen. In **Hoofdstuk 3** onderzochten we daarom het verband tussen mindfulness en een gerelateerd concept, zelf-compassie, enerzijds en psychologisch welbevinden anderzijds en of dit verband sterker is onder stressvolle omstandigheden. Om dit laatste te onderzoeken hebben we een groep personen die een diagnose kanker heeft gehad vergeleken met gezonde controlepersonen (mensen zonder een chronische somatische aandoening). We hebben dit onderzocht in 245 kankerpatiënten en 245

gezonde controlepersonen die wat betreft leeftijd, geslacht en opleiding overeenkwamen. We vonden dat mindfulness en zelf-compassie even sterk gerelateerd waren aan welbevinden (in termen van depressieve symptomen en affect) in kankerpatiënten als in gezonde controlepersonen. Onze conclusie was dat het beschikken over meer vaardigheden als mindfulness en zelf-compassie altijd samenhangt met een hoger welbevinden, onafhankelijk van de aanwezigheid van stressvolle levensomstandigheden zoals een diagnose kanker.

Een ander concept dat centraal stond in ons onderzoek is depressieve symptomen. Om meer inzicht te krijgen in de lage behoefte aan hulp, hebben we in **Hoofdstuk 4** onderzocht of de behoefte aan psychologische hulp samenhangt met het type depressieve symptomen. Dit hebben we onderzocht bij diabetespatiënten met depressieve klachten. Wat betreft het type symptomen, kan er onderscheid gemaakt worden tussen cognitieve-affectieve symptomen (zoals een sombere stemming) en somatische symptomen (zoals vermoeidheid). In het geval van een chronische ziekte, kunnen somatische symptomen namelijk te maken hebben met de chronische ziekte en de (bijwerkingen van de) behandeling, in plaats van of naast de depressieve symptomen. Onze hypothese was dat personen met veel cognitieve-affectieve symptomen meer behoefte aan psychologische hulp hebben, vergeleken met personen met weinig cognitieve-affectieve symptomen. We verwachten geen significante verschillen in hulpbehoefte tussen personen met veel of weinig somatische symptomen. In een steekproef van 519 depressieve personen met diabetes, vonden we 102 personen met een hulpbehoefte (19.7%), 293 met geen hulpbehoefte (56.5%), 77 met een vervulde hulpbehoefte (14.8%) en 47 met een onduidelijke hulpbehoefte (9.1%). In lijn met onze hypothese, vonden we inderdaad een significant maar zwak verband, met een hogere mate van cognitieve-affectieve symptomen gerelateerd aan meer hulpbehoefte. Zoals verwacht vonden we deze verschillen niet met betrekking tot somatische symptomen.

In **Hoofdstuk 5** vervolgden wij ons onderzoek naar het meten van depressieve symptomen bij personen met een somatische aandoening. Gegeven het feit dat somatische symptomen zowel gerelateerd kunnen zijn aan een depressie als aan een chronische aandoening en de bijbehorende behandeling, is het al decennia lang een punt van discussie of somatische symptomen geïnccludeerd dienen te worden in depressie (screenings)instrumenten bij ex-kankerpatiënten. In een poging om meer helderheid te scheppen in deze discussie, hebben we ons gericht op de depressieve symptomen zoals gemeten door de PHQ-9, welke overeenkomen met de depressie symptomen volgens de Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V). We hebben de discriminatieve capaciteiten (d.w.z. het vermogen om onderscheid te maken in depressie ernst) voor somatische symptomen vergeleken met die van cognitieve-affectieve symptomen. In totaal hebben 2.099 ex-kankerpatiënten de PHQ-9 vragenlijst teruggestuurd. De meest gerapporteerde symptomen waren ‘Slaapproblemen’ (39.2%) en ‘Vermoeidheid’ (45.9%), terwijl Suïcidaliteit (5.5%) het minst gerapporteerd werd.

Onze resultaten lieten zien dat alle negen depressieve symptomen excellente discriminatieve capaciteiten hadden, wat wil zeggen dat zowel cognitieve-affectieve als somatische symptomen goed onderscheid maken in depressie ernst. Deze bevindingen bevestigen recent onderzoek en suggereren dat somatische symptomen geïnccludeerd kunnen (blijven) worden in een screeningslijst voor het meten van depressieve symptomen bij somatisch zieke personen. Een andere belangrijke bevinding was dat somatische symptomen (vooral ‘Slaapproblemen’ en ‘Vermoeidheid’) het best discrimineren voor milde depressie,

terwijl de cognitieve-affectieve symptomen ‘Psychomotorische problemen’ en ‘Suïcidaliteit’ het best discrimineren voor gemiddelde tot ernstige depressie. Dit suggereert dat het doel van screening bepalend is voor het nut van de PHQ-9 items. Als iemand bijvoorbeeld gemiddeld tot ernstige depressieve patiënten van niet tot milde depressieve patiënten wil onderscheiden, dan is de PHQ-2 vragenlijst een waardevol screeningsinstrument. Deze bestaat namelijk uit de twee cognitieve-affectieve kernsymptomen van depressie (te weten ‘Depressieve stemming’ en ‘Anhedonie’) en beide symptomen discrimineren goed rondom depressies van gemiddelde ernst. Als iemand juist meer een totaalbeeld wil schetsen van depressie bij een patiëntengroep, dan is de PHQ-9 vragenlijst meer geschikt, omdat deze lijst goed discrimineert over het gehele spectrum: bij zowel milde, gemiddelde als ernstige depressie.

In onze laatste studie (**Hoofdstuk 6**), hebben we onderzocht of er subtypes van depressieve symptomen bestaan onder ex-kankerpatiënten met depressieve symptomen. Zoals eerder genoemd, kunnen depressieve symptomen erg heterogeen zijn (bestaande uit zowel cognitieve-affectieve als somatische symptomen). Toch ontvangen mensen met verschillende combinaties van depressieve symptomen over het algemeen dezelfde depressiebehandeling. Een eerste stap om te verkennen of meer gepersonaliseerde depressiebehandeling aangeboden moeten worden (welke meer gericht zijn op de combinatie van symptomen die iemand ervaart), is om te onderzoeken of subtypes van depressieve symptomen bestaan onder depressieve personen. Dit hebben we onderzocht in 175 mensen die kanker hebben gehad en die gemiddeld tot ernstig depressief waren.

We hebben vier subtypes van depressieve symptomen gevonden: type 1 (40%) en type 3 (33%) rapporteerden depressies van gemiddelde ernst, waarbij type 1 vooral ‘Slaapproblemen’ rapporteerde en type 3 vooral hoog scoorde op verschillende somatische symptomen (vooral ‘Vermoeidheid’ en ‘Slaapproblemen’). Personen in type 2 (10%) en type 4 (17%) rapporteerden depressies van gemiddeld-ernstige ernst, waarbij type 2 vooral ‘Vermoeidheid’, ‘Suïcidaliteit’, ‘Depressieve stemming’ en ‘Laag zelfbeeld’ en type 4 op alle symptomen hoog scoorde, behalve ‘Agitatie/Retardatie’ en ‘Suïcidaliteit’. De identificatie van deze subgroepen met depressie symptomen faciliteert mogelijk de ontwikkeling en het testen van de effectiviteit van meer gepersonaliseerde behandelmogelijkheden. Zo kunnen personen die vooral vermoeidheidsklachten rapporteren, mogelijk meer profiteren van behandelingen die zich specifiek richten op fysieke oefeningen of cognitieve-gedraginterventies gericht op het verminderen van vermoeidheid. Personen die daarentegen ook cognitieve-affectieve symptomen rapporteren, kunnen meer profijt hebben van cognitieve therapie zoals cognitieve herstructurering of mindfulness oefeningen.

Samengevat heeft dit proefschrift zich gericht op ex-kankerpatiënten die minstens 1 jaar geleden een curatieve kankerbehandeling hebben afgerond en die depressieve symptomen ervaren. Een van de meest belangrijke bevindingen was de lage niveaus van depressieve symptomen in onze groep van ex-kankerpatiënten. Een andere belangrijke bevinding was dat een substantiële groep met verhoogde depressieve symptomen geen professionele psychologische hulp wilde ontvangen voor hun symptomen. Er is meer onderzoek nodig om beter inzicht te krijgen in hoe mensen die kanker hebben gehad, aankijken tegen depressieve klachten en depressiebehandeling, de manieren waarop ze met deze klachten omgaan in hun dagelijks leven en de redenen om (geen) professionele hulp hiervoor te zoeken. Dergelijke inzichten zijn vereist om de kankerpatiënt optimaal te begeleiden door het gehele ziekte traject.

About the author

Loek van der Donk was born on the 3rd of November 1989 in Loon op Zand, the Netherlands. In 2013 he received his Bachelor's degree in Health Psychology at Tilburg University. He continued his studies at Tilburg University and graduated from the Research Master Medical Psychology in 2015 in which he followed the track Biological Psychology, with a special interest in psycho-physiology. In September 2015, Loek started his PhD project at the department of Health Psychology at the University Medical Center Groningen, resulting in this thesis. During his PhD project, he was the coordinator of a multi-center

RCT regarding the efficacy of depression treatment in cancer survivors and was also involved in the web editorial team for the Dutch Society of Psychosocial Oncology (NVPO). Due to a growing interest in Epidemiology and big data in specific, he started as a data scientist since June 2019 combined with a postmaster education in Business Analytics and Data Science at the Vrije Universiteit (VU), where he is continuing conducting research for several companies, using predictive modeling and machine learning techniques.

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Acknowledgements

53.223433, 6.572884 - maandag 14 september 2015, 09:00 uur, (CET)

Wat een avontuur is het geweest sinds mijn eerste werkdag in Groningen: een nieuwe baan als onderzoeker aan de andere kant van het land. En wat heeft dit avontuur mij veel bijgebracht. Niet alleen wat betreft vaardigheden gerelateerd aan mijn PhD traject, maar ook in de vorm van persoonlijke ontwikkeling. Dat dit gehele traject, met zijn ups maar zeker ook zijn downs, uiteindelijk heeft kunnen uitmonden in een succesvolle afronding, was onmogelijk geweest zonder de onvoorwaardelijke steun van een aantal mensen die ik dan ook van harte wil bedanken.

Om te beginnen, **Maya**. Als co-promotor heb je me heel erg veel steun gegeven met je optimisme, je geduld en de fijne brainstormsessies. Naast het feedback geven op papers, rebuttals, posters en abstracts (etc. etc.), kon ik ook voor persoonlijke zaken altijd bij je aankloppen. Hetzelfde geldt voor **Joke**: bedankt dat je mij behoedde als de RCT teveel dreigde te worden. Verder heb ik ook heel erg veel steun gehad aan jouw kritische blik, om voor het submitten van een paper, nog kritische kanttekeningen te plaatsen (en daarmee rejection te voorkómen?). Daarnaast ben ik **Robbert** ook enorm dankbaar. De rust die jij voortdurend uitstraalde, heeft mij geleerd dat ook na een belangrijke congrespresentatie de wereld niet vergaat en bovendien heb ik meer ‘academisch zelfvertrouwen’ gekregen door de zelfstandigheid die je mij hebt gegund in het begeleiden van studenten. **Annika**, ook jij heel erg bedankt! Bij de start van mijn traject heb ik de kneepjes van het vak (hoe een RCT op te zetten en alles wat daar bij komt kijken!) meteen van een excellente onderzoeker mogen leren. Verder wil ik graag mijn dank uitspreken aan **Ans** voor al haar hulp bij het uitvoeren van de RCT met honderden telefoongesprekken en duizenden enveloppen. **Hendrikje** en **Corry** ook bedankt voor jullie inzet! Verder dank aan mijn (PhD) collega's: **Esmée**, **Birte**, **Yvette**, **Angélica**, **Fabiola**, **Monica**, **Simon**, **Rodrigo**, **Tyas**, **Joost** en **Margreet**.

Ook wil ik graag mijn dank uitspreken aan mijn roomie, steun en toeverlaat: **Alicia**. Waar zou ik toch zijn geweest als wij niet eindeloos samen hadden zitten sparren over correcte hypothese formuleringen of alternatieve verklaringen voor onderzoeksbevindingen. Daarnaast wil ik je graag persoonlijk bedanken, want je stond altijd paraat of het nou persoonlijk of zakelijk was. Wat heb ik een geluk gehad dat ik bij jou op de kamer mocht zitten! Verder, beste lezer, sta ook even stil bij de mooie omslag van dit boekje, ontworpen door **Jesse Meeusen**, bedankt! Een andere collega die ik graag wil bedanken is **Anne**. Naast de interessante academische gesprekken, ga ik ook zeker de Groningse spelletjes-, pubquiz- en stapavonden missen (als jij midden in de nacht over ‘logistische regressie’ begon). Dat wordt trainen! Ook wil ik nog iemand bedanken die technisch gezien geen collega was, maar er vaker te vinden was dan menig collega: **Roland**. Wat heb ik veel baat gehad bij de vele gesprekken over Neff's snode plannen. En wat ga ik ze missen, de Noorderplantsoen-BBQ's, GPS tochten per step, AH-maaltijdsalades en (misschien wat minder) de gesprekken over Bayesiaanse statistiek, incommensurabiliteit en je paradigma dat alles in het leven te herleiden is tot materie of concept (jammer dat de Oblomov jury daar anders over dacht). En bedankt dat je mij overtuigd hebt dat programmeren / Data Science veel spannender is dan dat het klinkt! Daarnaast wil ik graag nog de Brugte Broekies bedanken voor alle gezellige borrel/quiz/stapavonden: **Bart** en **Jesper** bedankt (ook voor de keren dat ik op visite mocht

komen of kon blijven logeren). Another special person I am very grateful to is: **Jhonatan**. Muchas gracias for all daghapjes, biertjes, sinterklaasjes, drankjes en feestjes that we shared together. Also many thanks to the fellow musicians I collaborated with in Groningen!

Als laatste wil ik graag mensen bedanken die niet in Groningen wonen, maar er toch voor me waren. Lieve **mama**, wat ben ik ontzettend blij dat jij voortdurend mijn verhalen over mijn traject wilde aanhoren. Het ene moment was ik in een dipje vanwege rejections en project tegenslagen en het andere moment sprong ik een gat in de lucht vanwege een publicatie; maar jij hebt altijd 100% vertrouwen gehouden in me, bedankt! Verder wil ik ook graag mijn dank uitspreken aan **papa**. Na een drukke werkweek in Groningen was het een verademing dat we lekker samen muziek konden maken, of onder het genot van een speciaal biertje erover konden praten. **Iris** en **Viola**, ook jullie bedankt: jullie hebben helemaal gelijk gehad met: “Nog even volhouden!”, zie hier het resultaat. Verder ben ik ook **Riph** ontzettend dankbaar. Wat een toewijding om op donderdagavond voor een gourmet-voor-twee op en neer te komen vanuit Brabant. Daarnaast herinner ik me de geweldige stapavonden samen met **Peter** om nooit te vergeten, deze waren perfect om PhD stress te relativeren. Verder ook **Bjorn** bedankt voor je steun en de leuke muzikale projectjes die we samen hebben gedaan (onthoud dat ‘ons pensioen’ - de muzikale wereldhit “Procrastinatie” voltooid is in Groningen). Daarna heeft mijn weg zich vervolgd naar Utrecht, en daar wil ik graag **Arten** en **Jordi** bedanken. Door voldoende ontspanning met jullie heb ik de moed er weten in te houden in lastige situaties. Vrienden van de **BBV, Wimpies, de Reünie en de Carnavalsgroep**, ook bedankt voor de gezellige afleidingen! Tenslotte wil ik nog één speciaal persoon bedanken, die ik pas tegen het eind van mijn traject heb leren kennen. Lieve **Suzanne**, ontzettend bedankt dat je mij hebt gesteund bij de laatste loodjes, door enerzijds mijn tegenslagen aan te horen en anderzijds samen leuke uitstapjes als afleiding te plannen. Ik ben ontzettend blij dat het einde van mijn PhD avontuur een nieuw begin met jou heeft betekend (en wat een moed om met een op papier ‘werkloos’ persoon te gaan daten). Bedankt allemaal voor jullie steun!

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